Medicinrådet

Bilag til Medicinrådets anbefaling vedr. setmelanotid til behandling af svær overvægt og appetitkontrol i forbindelse med genetisk bekræftet Bardet-Bields syndrom (BBS)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. setmelanotid
2. Forhandlingsnotat fra Amgros vedr. setmelanotid
3. Ansøgers endelige ansøgning vedr. setmelanotid

Radarweg 29,
1043 NX Amsterdam, Netherlands
www.rhythmtx.com

Attn: Danish Medicines Council (DMC)

We appreciate the DMC for the opportunity to comment on the assessment report of Imcivree® for treating obesity and control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above.

We acknowledge that the DMC recognizes hyperphagia as a feature of BBS disease and the role of the MC4R pathway as a known mechanism leading to hyperphagia. This understanding is crucial for fully appreciating the potential of Imcivree® in improving the quality of life for affected patients.

In order to contribute constructively to the evaluation process, we wish to address the following key aspects related to the content of the assessment reports:

1. Rationale for study design and its significance in demonstrating Imcivree's Efficacy

The DMC report points to uncertainties on the efficacy and patient benefits of Imcivree® related to the pivotal trial design. This design was the result of discussions with regulatory bodies and reflects a balance between the need to demonstrate patient benefits within methodological constraints.

A 14-week randomized period was considered appropriate, allowing demonstration of benefits on hyperphagia through the proxy endpoint of hunger measurement. Regulatory authorities advised against a longer randomized period due to the very small target population, the need to provide a therapeutic option to patients with high unmet need and no alternative therapy, and the potential risk of unblinding / loss of patients in the placebo group due to lack of effect on hyperphagia and lack of hyperpigmentation.

The primary endpoint of weight loss is assessed after 52 weeks of treatment vs. baseline, as data from the largest historical cohort of patients with BBS and obesity (CRIBBS registry) show that very few patients achieve spontaneous weight loss. For statistical purposes, a null hypothesis of 10% was chosen based on historical data of 6.4% of patients achieving the target 10% weight loss (153 patients for 313 patient years). Data at 52 weeks in the study are compared to that historical cohort leading to a positive p-value for the Imcivree® treated population. A 10% weight loss is at the high end of regulatory recommendations for assessing weight loss therapies (5 to 10%) is highly challenging in a trial that includes 50% of children and adolescent patients who are going through natural growth.

As pointed out by DMC there is no validated tool for the treatment of hyperphagia in patients with BBS. Thus, hunger was used as a measure of the effect of Imcivree® on satiety signals, but hunger is an imperfect measure as it is affected by food intake. However, reduction in hunger is only one element supporting reduction in hyperphagia. As pointed earlier, patients with obesity and BBS do not lose weight spontaneously. Weight loss can only result from a major change in eating habits that is itself resulting from a significant reduction in hyperphagia. This combination of reduction in hunger and reduction in weight is the best possible demonstration of reduction in hyperphagia given the lack of specific tool.

The DMC report also refers to the fact that trial patients did not receive treatment meeting Danish clinical practice: diet and exercise. In order to assess a single variable, the trial did not include specific diet and exercise counselling. But the very large majority of patients had been on diet and exercise at baseline for several years, being treated in large academic and specialized centers offering full multidisciplinary care.

Rhythm understands the limitation associated with study design but believes that the trial design was the best possible given regulatory, operational, clinical and ethical constraints and demonstrates the value of Imcivree® in patients with BBS and obesity and no alternative treatment options.

Radarweg 29,
1043 NX Amsterdam, Netherlands
www.rhythmtx.com

2. Exclusion on modeling effect of Imcivree® on hyperphagia

We acknowledge the DMC's rationale for excluding the modelling effect of Imcivree® on hyperphagia from their main analysis due to the lack of specific hyperphagia data, and the measure of hunger instead.

Nevertheless, this approach significantly underestimates Imcivree's therapeutic benefits. The targeted mechanism of action on the MC4R pathway, identified as the primary root of hyperphagia, joined with clinical experiences and testimonials from patients and their families, shows that reduction in hyperphagia is essential for patients to achieve the weight loss documented in clinical trials and is felt by patients within days of therapy initiation. Hyperphagia also returns almost immediately in case of therapy interruption.

Such evidence and insights underpin our emphasis on a response-based model, with responders to treatment experiencing a considerable reduction in hyperphagia levels, as this would be necessary to drive a clinically meaningful improvement in their BMI/BMI Z-score.

Therefore, we request that DMC reconsiders the broader therapeutic benefits of Imcivree® beyond measurable weight-related outcomes. The impact of Imcivree® on hyperphagia has been recognized by most HTA bodies, including NICE, GBA, HAS and AIFA.

3. Imcivree® addresses a major unmet need for patients in Denmark

A positive recommendation for Imcivree® would address a significant unmet for patients with hyperphagia and obesity associated with BBS in Denmark, as no other approved drugs are available for this condition.

BBS is a rare and disabling genetic disorder with multiple clinical features, exacerbated by the obesity resulting from hyperphagia [1,2] This condition severely affects patients' quality of life, daily functioning, and mental health, resulting in a significant burden that negatively impacts the lives of both patients and their caregivers [3]. It is widely recognized that obesity is associated multiple related complications and an increase in mortality [4], with the risks being even greater in cases of early-onset obesity [5,6].

Current strategies in Denmark focus on lifestyle changes, but these are limited by BBS symptoms, including impaired vision and cognitive function. Adherence to restrictive diets is challenging due to insatiable hunger. A Danish study demonstrates that children with MC4R mutations did not show improvement in obesity lifestyle treatment, highlighting the need for personalized treatment approaches [7].

Setmelanotide is the first and only approved therapy targeting the MC4R pathway impairment, addressing the root cause of the obesity and hyperphagia. It offers a potential reversal of the patients' weight gain trajectory. The unique value of Setmelanotide is not just in its ability to reduce hyperphagia and body weight but in its prevention of the weight gain and associated complications such as metabolic syndrome severity [8,9] that would inevitably occur without intervention [10,11]. We trust the DMC, will consider the innovative nature of Imcivree® to allow Danish patients to benefit from therapy.

4. Plans for resubmission

The current assessment does not recognize the impact of hyperphagia and its effects on patients within the *Cost-Effectiveness Model* (CEM). We believe this significantly underestimates the value of Imcivree® for both patients and the healthcare system. As a result, we plan to resubmit a revised application that includes an *Alternative agreement Model* designed to ensure the inclusion of hyperphagia in the CEM. We expect this to lead to a substantial reduction in the Incremental Cost-Effectiveness Ratio (ICER), more accurately reflecting the benefits of Imcivree®.

References

1. CARE-BBS, CARE-BBS study report. Caregiver burden in Bardet-Biedl syndrome (CARE-BBS): A survey of BBS-related obesity and hyperphagia impacts in the United States, United Kingdom, Canada, and Germany. 2022.
2. Forsythe, E., et al., Managing Bardet–Biedl syndrome—now and in the future. Frontiers in pediatrics, 2018. 6: p. 23.
3. Burden in Bardet-Biedl syndrome: findings from the CARE-BBS study. Orphanet J Rare Dis. 2023;18(1).
4. Bhaskaran, K., et al., Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. Lancet Diabetes Endocrinol, 2018. 6(12): p. 944-953.
5. Lindberg, L., et al., Association of childhood obesity with risk of early all-cause and cause-specific mortality: A Swedish prospective cohort study. PLoS Med, 2020. 17(3): p. e1003078.
6. Emerging Risk Factors Collaboration. "Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation." The lancet. Diabetes & endocrinology vol. 11,10 (2023): 731-742. doi:10.1016/S2213-8587(23)00223-1
7. Trier, C., et al., *Obesity treatment effect in Danish children and adolescents carrying Melanocortin-4 Receptor mutations.* Int J Obes (Lond), 2021. **45**(1): p. 66-76.
8. Haqq, A.M., et al. , *Impact of Setmelanotide on Metabolic Syndrome Risk in Patients With Bardet-Biedl Syndrome. Accepted for "oral presentation"*, in *Obesity Society's Obesity Week*. 2023: Dallas, USA.
9. Haqq, A.e.a. *Impact of Setmelanotide on Future Metabolic Syndrome Risk in Pediatric Patients With Bardet-Biedl Syndrome. Accepted for "oral presentation"*. in *Annual Meeting of the European Society for Paediatric Endocrinology*. 2023. The Hague, The Netherlands.
10. Katsanis N, Lupski JR, Beales PL. Exploring the molecular basis of Bardet–Biedl syndrome. Hum Mol Genet [Internet]. 2001 Oct 1 [cited 2022 Nov 10];10(20):2293–9. Available from: https://academic.oup.com/hmg/article/10/20/2293/559356
11. Forsythe E, Beales PL. Bardet–Biedl syndrome. European Journal of Human Genetics 2013 21:1 [Internet]. 2013 Jun 20 [cited 2022 Oct 20];21(1):8–13. Available from: https://www.nature.com/articles/ejhg2012115

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

22.02.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	20.03.2024
Leverandør	Rhythm Pharmaceuticals
Lægemiddel	Imcivree (setmelanotide)
Ansøgt indikation	Behandling af svær overvægt og appetitkontrol associeret med bekræftet Bardet-Biedl syndrom hos voksne og børn ≥ 6 år
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Imcivree (setmelanotide):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Imcivree	10 mg/ml	1 ml	20.502,33	[redacted]	[redacted]

Prisen er IKKE betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har indgået en aftale med leverandøren som gælder fra den 20.03.2024 til 31.03.2025. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Imcivree (børn)	10 mg/ml	1 ml	2,7 ml dagligt (SC)*	[redacted]	[redacted]
Imcivree (voksne)	10 mg/ml	1 ml	2,9 ml dagligt (SC)*	[redacted]	[redacted]

*jf. Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering

Konklusion

[redacted]

Version log

Version log		
Version	**Date**	**Change**

Application for the assessment of Imcivree® for treatment of obesity and control of hunger associated with genetically confirmed Bardet-Biedl Syndrome in adults and children aged ≥6 years in Denmark

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

Contact information	
Name	**Charles Savoie**
Title	General Manager Nordics & Head of International Operations
Phone number	+33 6 71 00 72 72
E-mail	csavoie@rhythmtx.com
Name (External representation)	**Eva Calvo**
Title	International Market Access Director
Phone number	+34 605 360 713
E-mail	ecalvo@rhythmtx.com

Table of contents

Version log **1**

Tables and Figures **8**

Abbreviations **11**

1. Regulatory information on the pharmaceutical **14**

2. Summary table **15**

3. The patient population, intervention, choice of comparator(s) and relevant outcomes **17**

3.1 The medical condition 17
3.2 Patient population 21
3.3 Current treatment options 25
3.4 The intervention 26
3.4.1 The intervention in relation to Danish clinical practice 28
3.5 Choice of comparator(s) 28
3.6 Cost-effectiveness of the comparator(s) 29
3.7 Relevant efficacy outcomes 29
3.7.1 Definition of efficacy outcomes included in the application 30

4. Health economic analysis **33**

A cost-utility analysis was performed for this submission. 33
4.1 Model structure 33
4.2 Model features 36

5. Overview of literature **38**

5.1 Literature used for the clinical assessment 38
5.2 Literature used for the assessment of health-related quality of life 41
5.3 Literature used for inputs for the health economic model 44

6. Efficacy **47**

6.1 Efficacy of setmelanotide compared to best supportive care for genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above 47
6.1.1 Relevant studies 47
6.1.2 Comparability of studies 50
6.1.3 Comparability of patients across studies 50
6.1.3.1 Comparability of the study population(s) with Danish patients eligible for treatment 52
6.1.4 Efficacy – results per Study RM-493-023 53

6.1.4.1 Proportion of pivotal patients aged ≥12 years who achieved a ≥10% reduction in body weight after 52 weeks of setmelanotide treatment 55
6.1.4.2 Change in body weight after 52 weeks of setmelanotide treatment 56
6.1.4.3 Change in body weight after 14 weeks of setmelanotide treatment compared with placebo 57
6.1.4.4 Change in BMI Z-score after 52 weeks of setmelanotide treatment in patients <18 years 58
6.1.4.5 Change in BMI 95th percentile after 52 weeks of setmelanotide treatment in patients <18 years 59
6.1.4.6 Change in BMI after 52 weeks of setmelanotide treatment 60

7. Comparative analyses of efficacy 62
7.1.1 Differences in definitions of outcomes between studies 62
7.1.2 Method of synthesis 62
7.1.3 Efficacy – results per [outcome measure] 63

8. Modelling of efficacy in the health economic analysis 63
8.1 Presentation of efficacy data from the clinical documentation used in the model 63
8.1.1 Patient characteristics 63
8.1.2 Setmelanotide treatment effect 63
8.1.3 Discontinuation rate 66
8.1.4 Extrapolation of efficacy data 66
8.1.5 Calculation of transition probabilities 66
8.2 Presentation of efficacy data from additional documentation 66
8.2.1 Best supportive care treatment effect 66
8.2.2 Mortality 67
8.3 Modelling effects of subsequent treatments 67
8.4 Other assumptions regarding efficacy in the model 67
8.5 Overview of modelled average treatment length and time in model health state 68

9. Safety 68
9.1 Safety data from the clinical documentation 68
9.2 Safety data from external literature applied in the health economic model 73

10. Documentation of health-related quality of life (HRQoL) 73
10.1 Presentation of the health-related quality of life 75
10.1.1 Study design and measuring instrument not applicable 75
10.1.2 Data collection not applicable 75
10.1.3 HRQoL results not applicable 75
10.2 Health state utility values (HSUVs) used in the health economic model 76
10.2.1 HSUV calculation 76
10.2.1.1 Mapping 77
10.2.2 Disutility calculation 78

10.2.3 HSUV results 78
10.3 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy 78
10.3.1 Study design TTO vignette study 78
10.3.2 Data collection TTO vignette study 79
10.3.3 HRQoL Results TTO vignette study 79
10.3.4 HSUV and disutility results TTO vignette study 79
10.3.5 Study design EQ-5D and EQ-5D-Y 80
10.3.6 Data collection EQ-5D 80
10.3.7 HRQoL Results EQ-5D 80
10.3.8 HSUV and disutility results EQ-5D 80
10.3.9 Study design EQ-5D-3L 83
10.3.10 Data collection EQ-5D-3L 83
10.3.11 HRQoL results EQ-5D-3L 83
10.3.12 HSUV and disutility results EQ-5D-3L 83
10.3.13 Study design Standard gamble 86
10.3.14 Data collection Standard gamble 86
10.3.15 HRQoL results Standard gamble 86
10.3.16 HSUV and disutility results Standard gamble 86

11. Resource use and associated costs 87
11.1 Pharmaceutical costs (intervention and comparator) 87
11.2 Pharmaceutical costs – co-administration – not applicable 89
11.3 Administration costs 89
11.4 Disease management costs 89
11.5 Costs associated with management of adverse events- not applicable 95
11.6 Subsequent treatment costs – not applicable 96
11.7 Patient costs 96
11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost) – not applicable 97

12. Results 97
12.1 Base case overview 97
12.1.1 Base case results 98
12.2 Sensitivity analyses 99
12.2.1 Deterministic sensitivity analyses 99
12.2.2 Probabilistic sensitivity analyses 105

13. Budget impact analysis 106

14. List of experts 107

15. References 107

Appendix A. Main characteristics of studies included 114

Appendix B. Efficacy results per study 125
B.1 Results per study RM-493-023 125
B.1.1 Additional endpoints RM-493-023 147
B.2 Results per study RM-493-022 150
B.2.1 Additional endpoints RM-493-022 153

Appendix C. Comparative analysis of efficacy - not applicable 154

Appendix D. Extrapolation – not applicable 155

Appendix E. Serious adverse events 156

Appendix F. Health-related quality of life 156

Appendix G. Probabilistic sensitivity analyses 158

Appendix H. Literature searches for the clinical assessment 169
H.1 Efficacy and safety of the intervention and comparator(s) 169
H.1.1 Search strategies 173
H.1.2 Systematic selection of studies 178
H.1.2.1 Results 182
H.1.3 Quality assessment 196
H.1.4 Unpublished data 197

Appendix I. Literature searches for health-related quality of life 197
I.1 Health-related quality-of-life search 197
I.1.1 Search strategies 198
I.1.2 Quality assessment and generalizability of estimates 201
I.1.3 Unpublished data 201

Appendix J. Literature searches for input to the health economic model -not applicable 202
J.1 External literature for input to the health economic model 202
J.1.1 Ex. Systematic search for […] 202
J.1.2 Ex. Targeted literature search for [estimates] 202

Appendix K. Early Onset of Obesity Model: Initial situation 203
K.1 Summary 203
K.2 Initial situation 204
K.2.1 Methodical approach 206
K.3 Sources and Data Extraction 207
K.3.1 T2DM Prevalence 209
K.3.2 Cardiovascular Event Prevalence 210
K.3.3 NAFLD Prevalence 210
K.3.4 Cancer Prevalence 211

K.3.5 Asthma Prevalence 211
K.3.6 Sleep Apnea Prevalence 212
K.3.7 T2DM Mortality Risk 212
K.3.8 Cardiovascular Event Mortality Risk 213
K.3.9 NAFLD Mortality Risk 213
K.3.10 Cancer Mortality Risk 214
K.3.11 Asthma Mortality Risk 214
K.3.12 Obesity Duration impact on Mortality Risk 215
K.3.13 Obesity Duration impact on T2DM Risk 215
K.3.14 Obesity Duration impact on Cardiovascular Event Risk 215
K.3.15 Obesity Duration impact on Cancer Risk 216
K.3.16 Irreversible Risk Accumulation Integration 216
K.4 Model Framework 216
K.4.1 Methodology of modelling outcomes of obesity and weight development 216
K.4.2 Model Step-by-Step assembly 218
K.5 Case example 219
K.6 Model conclusions 220
K.7 Model Graphics 221
K.7.1 Graphic 1: T2DM Prevalence 221
K.7.2 Graphic 2: Cardiovascular Event Prevalence 221
K.7.3 Graphic 3: NAFLD Prevalence 221
K.7.4 Graphic 4: Cancer Prevalence 222
K.7.5 Graphic 5: Asthma Prevalence 222
K.7.6 Graphic 6: Sleep Apnea Prevalence 222
K.7.7 Graphic 7: T2DM Mortality Risk 223
K.7.8 Graphic 8: Cardiovascular Event Mortality Risk 223
K.7.9 Graphic 9: NAFLD Mortality Risk 223
K.7.10 Graphic 10: Cancer Mortality Risk 224
K.7.11 Graphic 11: Asthma Mortality Risk 224
K.7.12 Graphic 12: Obesity Duration impact on Mortality Risk 224
K.7.13 Graphic 13: Obesity Duration impact on T2DM Risk 225
K.7.14 Graphic 14: Obesity Duration impact on Cardiovascular Event Risk 225
K.7.15 Graphic 15: Obesity Duration impact on Cancer Risk 225
K.7.16 Graphic 16: Irreversible T2DM Risk Accumulation 226
K.7.17 Graphic 17: Irreversible CV Risk Accumulation 226
K.7.18 Graphic 18: Irreversible NAFLD Risk Accumulation 226
K.7.19 Graphic 19: T2DM Risk adjustment 227
K.7.20 Graphic 20: CV Risk adjustment 227
K.7.21 Graphic 21: Cancer Risk adjustment 227
K.7.22 Graphic 22: NAFLD Risk adjustment 228
K.8 Literature Overview 228
K.8.1 Studies included 228
K.8.2 Studies assessed but not included in the modelling 230

Tables and Figures

Table 1. Primary and secondary diagnostic features of BBS and their frequency (Forsythe 2018) [3] 19
Table 2 Proportion of BBS patients impacted 'moderately' or 'a great deal' by hunger as assessed by the caregiver 21
Table 3 Proportion of BBS caregivers reporting being affected either 'moderately' or 'a great deal' by their child's hunger 21
Table 4. Relevant baseline characteristics in Study RM-493-023 23
Table 5. Incidence and prevalence in the past 5 years 24
Table 6. Estimated number of patients treated with estimated Imcivree®) 25
Table 7. Overview of the intervention 26
Table 8. Overview of comparator 28
Table 9 Efficacy outcome measures relevant for the application 30
Table 10. Methodology for mapping BMI Z-score to BMI 34
Table 11 Features of the economic model 36
Table 12 Relevant literature included in the assessment of efficacy and safety 40
Table 13 Relevant literature included for (documentation of) health-related quality of life 41
Table 14 Relevant literature used for input to the health economic model 44
Table 15 Study RM-493-023 analysis sets 48
Table 16 Overview of study design for studies included in the comparison 49
Table 17 BBS patient characteristics on inclusion (Study RM-493-023, pivotal and supplemental patients) 50
Table 18 Baseline BMI and BMI Z-score categories for BBS patients (Study RM-493-023, pivotal patient SAS) 51
Table 19 Characteristics in the relevant Danish population and in the health economic model 52
Table 20 Pivotal ≥12-year-old Full Analysis Set, after last enrolled patient in the pivotal cohort has completed period 2 (W52) 54
Table 21 Pivotal ≥12-year-old Placebo Controlled Analysis Set (not cognitively impaired for hunger-bases SE 2), after last patient completes the 14 Week Double Blind Placebo Controlled period (W14)* 54
Table 22 Proportion of BBS or AS patients aged ≥12 years who achieved a ≥10% reduction in body weight (Study RM-493-023, pivotal BBS and AS patient FAS) 56
Table 23 Proportion of BBS patients aged ≥12 years or ≥18 years with a 10% reduction in body weight (Study RM-493-023, pivotal patient FAS) 56
Table 24 Change in body weight from baseline after 52 weeks of setmelanotide treatment in patients aged ≥18 years (Study RM-493-023, pivotal patient FAS) 56
Table 25 Change in body weight from baseline after 14 weeks of setmelanotide treatment in patients aged ≥18 years (Study RM-493-023, all patient PCAS) 57
Table 26. Change in BMI Z-score from baseline after 52 weeks of setmelanotide treatment in patients aged <18 years (Study RM-493-023, pivotal patient FAS) 58
Table 27. Proportion of patients aged <18 years achieving a BMI Z-score reduction from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal patient FAS) 59

Table 28 Change in BMI 95th percentile from baseline after 52 weeks of setmelanotide treatment in patients aged <18 years (Study RM-493-023, pivotal patient FAS) 59
Table 29 Change in BMI from baseline after 52 weeks of setmelanotide treatment in patients aged <18 years or aged ≥18 years (Study RM-493-023, pivotal patient FAS) 60
Table 30. Results from the comparative analysis of setmelanotide vs. placebo for genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above 62
Table 31. BMI Z-score shift data for individual BBS patients aged <18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients), considering BMI-Z class intervals of 0.5 64
Table 32. Modelled treatment effect of setmelanotide on the BMI Z-score category (paediatric treatment initiation). 64
Table 33. Modelled treatment effect of setmelanotide on the BMI category (Adult treatment initiation). 65
Table 34 Overview of modelled average treatment length and average time spent in each BMI Z-score/BMI category, undiscounted and not adjusted for half cycle correction (paediatric treatment initiation) 68
Table 35 Overview of safety events (14 weeks) 69
Table 36 Overview of safety events (52 weeks) 70
Table 37 Serious adverse events (14 weeks) 70
Table 38 Serious adverse events (52 weeks) 71
Table 39 Adverse events used in the health economic model 72
Table 40 Overview of included HRQoL instruments 74
Table 41 Pattern of missing data and completion not applicable 75
Table 42 HRQoL [instrument 1] summary statistics N/A 75
Table 43 The ordinary least squares regression algorithm used to map BMI Z score category utility values 77
Table 44 Overview of health state utility values [and disutilities] N/A 78
Table 45 Overview of health state utility values [and disutilities] 79
Table 46. Overview of HSUV (utility values by BMI Z-score and BMI category and age) 80
Table 47. Comorbidity-specific disutilities 84
Table 48. Disutility values by BMI/BMI Z-score category for each comorbidity 84
Table 49. Disutility associated with adverse events. 86
Table 50 Pharmaceutical costs used in the model 88
Table 51 Annual treatment cost with setmelanotide for paediatric and adult patients in Denmark (DKK) 88
Table 52 Monitoring resource use unit costs used in the model 89
Table 53 Annual monitoring costs per patient (paediatric treatment initiation) in DKK for setmelanotide plus BSC and BSC alone for year 1 and year 2+ 90
Table 54 Average annual healthcare costs per person for adult treatment initiation by BMI category in Denmark 91
Table 55 Average annual healthcare costs per person for paediatric treatment initiation by BMI Z-score category 91

Table 56 Average annual healthcare costs per adult treatment initiation by BMI category 92
Table 57. BMI-based prevalence values for osteoarthritis 92
Table 58. Osteoarthritis prevalence for pediatric patients 93
Table 59. Average annual comorbidity costs per person 94
Table 60 Cost associated with management of adverse events - not applicable 95
Table 61 Pharmaceutical costs of subsequent treatments – not applicable 96
Table 62 Patient costs used in the model 96
Table 63. Use of time per year, number of trips per year and total indirect costs per year per treatment arm 97
Table 64 Base case overview 98
Table 65 Base case results, discounted estimates (DKK) 98
Table 66 One-way sensitivity analyses results 99
Table 67 Scenario analyses results 103
Table 68. Number of patients expected to be treated over the next five-year period if the pharmaceutical is introduced and not introduced (adjusted for market share) 106
Table 69. Expected budget impact of recommending setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS, in adults and children 6 years of age and above with obesity and severe hyperphagia. 107
Table 70 Main characteristic of study RM-493-023 114
Table 71 Main characteristic of study RM-493-022 120
Table 72 Main characteristic of study RM-493-014 122
Table 73 Results per study 125
Table 74. BMI shift data for individual patients aged ≥18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients) 147
Table 75. BMI Z-score shift data for individual patients aged <18 years who were classified as 52-week responders (Study RM-493-023, pivotal patients) 147
Table 76. Symptom improvement in patients with BBS aged ≥18 years after 52 weeks of setmelanotide treatment (Study RM-493-023) 148
Table 77 Symptom improvement in patients with BBS aged <18 years after 52 weeks of setmelanotide treatment (Study RM-493-023) 149
Table 78 Results per study 150
Table 79 BMI shift data for individual patients aged ≥18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients) 153
Table 80 BMI Z-score shift data for individual patients aged <18 years who were classified as 52-week responders (Study RM-493-023, pivotal patients) 153
Table 81 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] – not applicable 154
Table 82. Impact of setmelanotide in adult participants with BBS (≥18yo) with available baseline and 52-week health related quality of life data 156
Table 83. Impact of setmelanotide in paediatric participants with BBS (8-17 yo; self-reported) with available baseline and 52-week HRQoL data 156
Table 84. Effect of setmelanotide on EQ-5D-5L score in patients aged ≥16 years without cognitive impairment (Study RM-493-023, pivotal patients) 157

Table 85. Mean EQ-5D-5L utility by weeks using setmelanotide in patients ≥12 years old. 157
Table 86. Overview of parameters in the PSA 158
Table 87 Bibliographic databases included in the literature search 170
Table 88 Other sources included in the literature search 170
Table 89 Conference material included in the literature search 171
Table 90. Electronic literature search strategies (2 June 2023) 173
Table 91. Conferences search strategies (2 June 2023) 175
Table 92. Electronic literature search strategies (15 February 2023) 176
Table 93. PICOS selection criteria for the systematic literature review (June 2021 and August 2022 Search) 178
Table 94 PICOS selection criteria for the systematic literature review (January 2023 and February 2023 Search) 180
Table 95. Outcomes by study 184
Table 96. Overview of study design for studies included in the technology assessment 185
Table 97 List of excluded studies at full-text screening 187
Table 98 Bibliographic databases included in the literature search – not applicable 197
Table 99 Other sources included in the literature search – not applicable 197
Table 100 Conference material included in the literature search – not applicable 198
Table 101 Search strategy for [name of database] – not applicable 198
Table 102. Characteristics of studies informing on health-related quality of life in patients with BBS 199
Table 103 Sources included in the search – not applicable 202
Table 104 Sources included in the targeted literature search – not applicable 202

Abbreviations

ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AGRP	Agouti-related peptide
AHI	Apnoea-hypopnea index
ALMS1	Alström syndrome protein 1
ALT	Alanine transaminase
AS	Alström syndrome
ASAT	Aspartate aminotransferase
AST	Aspartate aminotransferase
ATB	Treatment baseline
ATC	Anatomical therapeutic chemical code
BBS	Bardet-Biedl syndrome
BBS1	BBS-associated gene 1
BBS10	BBS-associated gene 10
BBSx	BBS-associated genes

BIA	Bioelectrical impedance
BIM	Budget impact model
BMI	Body mass index
BP	Blood pressure
BSC	Best supportive care
CDSR	Cochrane database of systematic reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane central register of controlled trials
CI	Confidence interval
COVID	Coronavirus disease
CRD	Centre for reviews and dissemination
C-SSRS	Columbia suicide severity rating scale
CTCAE	Common terminology criteria for adverse events
CV	Cardiovascular
CVD	Cardiovascular disease
DARE	Database of abstracts of reviews of efficacy
DK	Denmark
DKK	Danish krone
DMC	Danish medicines council
DRG	Diagnosis-related group
DSM-V	Diagnostic and statistical Manual of Mental Disorders fifth edition
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
EMA	European medicines agency
ESRD	End-stage renal disease
EUR	Euro
FAS	Full analysis set
FDA	United States food and drug administration
FSH	Follicle-stimulating hormone
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GP	General practitioner
HDL	High-density lipoprotein
HRQoL	Health-related quality of life
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IV	Intravenous
IWQOL	Impact of weight on quality of life-lite
KOL	Key opinion leader
LDL	Low-density lipoprotein
LEP	Leptin hormone
LEPR	Leptin receptor
LY	Life years
MC1	Melanocortin 1

MC3	Melanocortin 3
MC4R	Melanocortin-4 receptor
MSH	Melanocyte stimulating hormone
MWPC	Meaningful within-patient change
NA	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHGRI	National Institutes of Health
NHS EED	National health service economic evaluation database
NICE	The National Institute for Health and Care Excellence
NPR	Danish national patient register
NR	Not reported
OS	Overall survival
PCAS	Placebo-controlled analysis set
PCPB	Placebo-controlled period baseline
PEDsQL	Paediatric quality of life inventory
PFS	Progression free survival
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PHQ-9	Patient health questionnaire-9
PICOS	Populations, interventions, comparators, outcomes, and study design
POMC	Pro-opiomelanocortin
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSP	Pharmacy selling price
PWS FPD	Prader-Willi syndrome food problem diary
QALY	Quality adjusted life years
QD	"Quaque die", once a day
QoL	Quality of life
RGDO	Rare genetic disease of obesity
SAE	Serious adverse events
SAS	Safety analysis set
SD	Standard deviation
SDS	Standard deviation score
SE	Standard error
SEK	Swedish krona
SG	Standard gamble
SH2B1	Src homology 2B adaptor protein 1
SLR	Systematic literature review
SMD	Standardized mean difference
SMR	Standardized mortality ratio
SoC	Standard of care
SRC1	Steroid receptor coactivator-1
T2DM	Type 2 diabetes mellitus

TEAE	Treatment emergent adverse events
TSH	Thyroid-stimulating hormone
TTO	Time trade-off
UK	United kingdom
US	United States
VAT	Value added tax
WHO	World health organization

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical [1]	
Proprietary name	Imcivree®
Generic name	setmelanotide
Therapeutic indication as defined by EMA	Imcivree® is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above.
Marketing authorization holder in Denmark	Rhythm Pharmaceuticals Netherlands B.V.
ATC code	A08AA12
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	Imcivree® was issued a marketing authorization for a group of variations, to add the new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome throughout the European Union on 02 September2022
Has the pharmaceutical received a conditional marketing authorization?	N/A
Accelerated assessment in the European Medicines Agency (EMA)	N/A
Orphan drug designation (include date)	On 21 August 2019, orphan designation (EU/3/19/2192) was granted by the European Commission, for setmelanotide for the treatment of Bardet-Biedl syndrome [2]. The Committee for Orphan Medicinal Products has recommended that Imcivree®,

Overview of the pharmaceutical [1]	
	setmelanotide for treatment of Bardet-Biedl syndrome (EU/3/19/2192) is not removed from the Community Register of Orphan Medicinal Products [2]
Other therapeutic indications approved by EMA	Imcivree® is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed, loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR/NBS
Packaging – types, sizes/number of units and concentrations	1 x 1ml multidose vial (10mg/ml)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Imcivree® is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above. The population relevant for this assessment and the health economic analysis are individuals initiating treatment as paediatrics at an age 6 years.
Dosage regiment and administration:	Imcivree® should be injected once daily, subcutaneously in the abdomen. For dosing see section 3.4
Choice of comparator	Best supportive care (BSC) without setmelanotide
Prognosis with current treatment (comparator)	Given that BBS is a genetically heterogenous disease, its prognosis varies with symptoms and severity. There is no recent published evidence on the life expectancy of the individuals with obesity due to BBS. However, general obesity has been associated with life-long complications, such as diabetes mellitus, cardiovascular disease, and kidney diseases, that result in an increase in mortality risk. Early onset obesity (starting from 2 years of age) is associated with a nearly three times greater risk of all-cause mortality compared to the normal population showing that obesity is associated with both increased risk of all-cause as well as the risk of cause-specific mortality.

Summary	
Type of evidence for the clinical evaluation	Placebo controlled randomised trial RM-493-023 (NCT03746522), extension Study RM-493-022 (NCT03651765) and Phase 2 Study RM-493-014 (NCT03013543).
Most important efficacy endpoints (Difference/gain compared to comparator)	Setmelanotide is a clinically-effective treatment for hyperphagia and obesity in patients with BBS. In RM-493-023, over 52 weeks of treatment, reductions in hunger and weight loss were sustained. The mean % change in maximal hunger in patients treated with setmelanotide was -30.9% (p = 0.0001) , 47% of patients with BBS aged ≥18 years of age achieved a ≥10% reduction in body weight from the active-treatment baseline, which was statistically significant (p=0.0003) compared with a historical control rate of 10%. In patients < 18 years of age, 86% achieved a ≥0.2 reduction from baseline in BMI Z-score over 52 weeks (95% CI 57.2, 98.2), with a ≥0.2 reduction considered clinically significant. The reductions in body weight and BMI/BMI-Z in adults and paediatrics are assumed to be due to reductions in hunger and hyperphagia following setmelanotide treatment.
Most important serious adverse events for the intervention and comparator	The main treatment emergent adverse events experienced by patients receiving setmelanotide during study RM-493-023 were skin hyperpigmentation (59.1%), injection site erythema (45.5%), nausea (22.7%) and vomiting (27.3%). These treatment emergent adverse events were transient (e.g., nausea, injection site reaction) or reversible (e.g., skin hyperpigmentation).
Impact on health-related quality of life	Clinical documentation: Participants in RM-492-023 with BBS treated with setmelanotide experienced and maintained substantial improvements in measures of quality of life at 1 year. See further Appendix F Health economic model: In the health economic assessment, the model predicts better quality of life in the paediatric initiated population with [redacted] incremental QALYs for Imcivree compared to BSC
Type of economic analysis that is submitted	Cost-utility analysis
Data sources used to model the clinical effects	Setmelanotide treatment effect (response rate at 52 weeks) and discontinuation rate was based on a post hoc analysis from study RM-493-023. Patients receiving BSC without setmelanotide (lifestyle, dietary interventions, and behavioural therapy) are assumed to have no treatment effect in terms of BMI/BMI Z-score or hyperphagia state, as previous evidence shows that BSC is an ineffective approach for managing genetic obesity. As impairment of the MC4R pathway is the root cause of hyperphagia and obesity in BBS patients, management with diet and exercise (BSC) has no impact on hyperphagia and as a consequence is unlikely to have a meaningful effect on obesity for this population. Comorbidity and mortality inputs was

Summary	
	implemented using a early onset model (see section Appendix K.
Data sources used to model the health-related quality of life	A vignette study was deemed to provide the most accurate to base utility values for mild, moderate, and severe hyperphagia., as EQ-5D captured in the RM-493-023 trial was not deemed sufficiently sensitive to capture the impact of hyperphagia on quality of life.
Life years gained	[redacted] years
QALYs gained	[redacted] QALY
Incremental costs	[redacted] DKK
ICER (DKK/QALY)	4,453,966 DKK/QALY
Uncertainty associated with the ICER estimate	The parameters that had the greatest impacts on the ICER were the baseline hyperphagia category distribution, the setmelanotide QALY multiplier and the baseline BMI Z-score category distribution.
Number of eligible patients in Denmark	Incidence: 1-2 Prevalence: [redacted]
Budget impact (in year 5)	[redacted] DKK

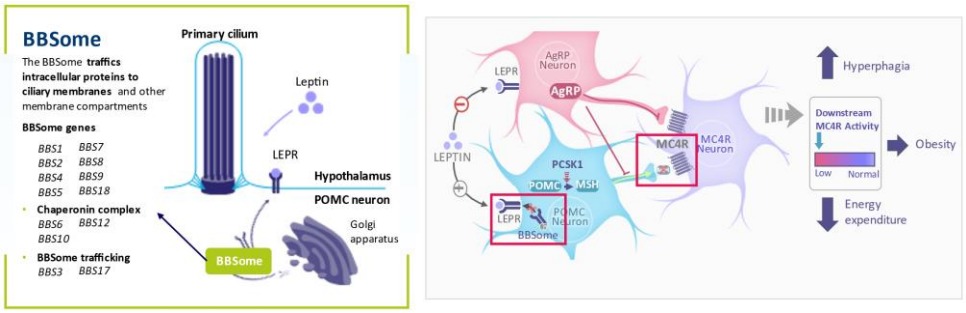
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disease, which in many cases is characterised by hyperphagia (an overwhelming, heightened, and relentless hunger mimicking feelings of starvation) that leads to marked obesity. Obesity affects 72% to 92% of patients with BBS [3]. While most have normal birth weight, by 2 years of age it is estimated that >55% of children with BBS are overweight or obese, and by the age of 5 obesity rates exceed 90% [4]. The mechanisms of obesity in BBS are believed to involve disruption of the hypothalamic leptin-melanocortin (MC4R) signalling pathway [4] responsible for regulation of appetite and satiety illustrated by Figure 1. Consequently,

patients with BBS often have severe hyperphagia, a complex condition incorporating insatiable hunger, longer time to reach satiety, shorter duration satiety, and distress if denied food [5], leading to excess energy intake and resulting in continual weight gain throughout the patients' lifetime.

Figure 1. Dysregulation of the MC4R pathway by disrupted leptin signalling contributes to hyperphagia and obesity in patients with BBS



Abbreviations: AGRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; BBSome, complex of 8 BBS proteins; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, pro-opiomelanocortin. Sources: [6-16].

Other symptoms of BBS include rod-cone dystrophy, which affects approximately 93% of patients [3] . It initially presents as night blindness at around the age of 7 to 8 years, and by the age of 16 years a significant proportion of BBS patients are legally blind [17]. Polydactyly is often present at birth, with other symptoms of BBS presenting variably and progressively throughout childhood (Figure 2).

Figure 2. Development of characteristic BBS symptoms

Source: 1 Forsythe 2013 [18], 2 Castro-Sanchez 2015 [19], 3 Katsanis 2001 [20], 4 Forsyth 2003 [21], 5 Agrawal 2018 [22], 6 Khan 2019[23], 7 Putoux 2012 [24], 8 Pomeroy 2021 [4], 9 Sherafat-Katzemzadeh 2013 [25], 10 Beales 1999 [26], 11 Weihbrecht 2017[27].

Diagnosis of BBS relies on the presence of clinical symptoms, which can be categorised as primary or secondary features (Table 1). Obesity is one of six potential primary features and results from uncontrollable hunger/hyperphagia. It is widely accepted that the presence of four primary features or three primary features and two secondary features is clinical diagnostic of BBS. Whilst hyperphagia is not a diagnostic feature of BBS, it is increasingly accepted as an important disease feature that directly relates to obesity.

Table 1. Primary and secondary diagnostic features of BBS and their frequency (Forsythe 2018) [3]

Primary features (frequency)	Secondary features (frequency)
• Rod-cone dystrophy (93%) • Polydactyly (63% to 81%) • Obesity (72% to 92%) • Genital anomalies (59% to 98%) • Renal anomalies (53%) • Learning difficulties (61%)	• Speech delay (54% to 81%) • Developmental delay (50% to 91%) • Diabetes mellitus (6% to 48%) • Dental anomalies (51%) • Congenital heart disease (7%) • Brachydactyly (46% to 100%) /syndactyly (8% to 95%) • Ataxia/poor coordination (40% to 86%) • Anosmia or hyposmia (60%)

Following clinical diagnosis, BBS is confirmed in approximately 80% of patients using genetic testing [28]. To date, 22 BBS-associated genes have been identified; BBS1 and BBS10 are most commonly involved and account for approximately 23% and 20% of cases respectively [28]. Patients with BBS1 mutations generally experience later onset visual deterioration and are less likely to develop renal disease than those with other BBS mutations; however, the number and severity of symptoms is highly variable even between patients of the same genotype [3].

There is currently no published evidence informing on the life expectancy of BBS patients. UK experts experienced in the treatment of BBS, estimate that patients have approximately a 10-year reduction in life expectancy compared with the general population; however, this will vary depending on the severity of the individual's symptoms. Renal failure is historically a major cause of mortality; a third of BBS patients develop renal failure and approximately 10% progress to end-stage renal failure requiring dialysis and/or transplant [29]. It is widely accepted that increasing levels of obesity lead to higher mortality rates [30], however there is now a growing appreciation that obesity that begins in childhood further increases mortality risk. A recent Swedish study demonstrated that individuals who were obese in childhood had a 3-times higher risk of mortality in early adulthood compared with a population-based comparison group [31].

The impact of obesity on quality of life is well documented. Individuals with obesity are affected by numerous discriminations that impact on all dimensions of life [32]. Children with obesity are three times more likely than others to be victims of bullying, they have poorer school performance and find it more difficult to complete higher education [33]. Adults with obesity (BMI ≥30 kg/m2) are at increased risk of developing major depressive disorder [34]and some other mental disorders (low self-esteem, mood disorders, motivational disorders, eating problems, impaired body image and interpersonal communication issues)[35]. Adults with obesity are less likely to have a job, and when they do work they are more likely to be absent and be less productive [33]. Being obese also puts people at increased risk of comorbidities such as hypertension, T2DM, non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnoea, all of which contribute to reduced quality of life [35].

In addition to obesity, patients with BBS also have to deal with severe hyperphagia which can distract from activities of daily life [5]. Hyperphagia can be defined as the most extreme form of overeating, a relentless, overwhelming force, which due to the extreme level of food seeking behaviour causes not just obesity, but constant stress and frustration to the people experiencing it and the ones around them [36].

In 2022, Rhythm Pharmaceuticals conducted the real-world study CAREgiver Burden in BBS (CARE-BBS) [5]. This study was a multi-country, cross-sectional survey involving 242 adult caregivers of patients with BBS who have had hyperphagia and obesity. The survey consisted of questionnaires including Symptoms of Hyperphagia, Impacts of Hyperphagia, Impact of Weight on Quality of Life (IWQOL)-Kids Parent Proxy, and Patient-Reported Outcome Measurement Information System (PROMIS) v1.0-Global Health 7. In addition, clinical characteristics, medical history, and weight management questions were included [5].

The newly developed Impacts of Hyperphagia questionnaire consisted of two components, observer- and self-reported, with 10 total items measuring the extent of how hunger behaviour affects multiple aspects of life in patients and caregivers, respectively. The Impacts of Hyperphagia caregiver observer-reported version asked caregivers five questions on the extent to which hunger negatively affected the person in their care's sleep, mood or emotions, school, leisure or recreational activities, and relationships with family or friends over the past 7 days. The Impacts of Hyperphagia self-reported version asked caregivers 5 questions on the extent to which the person in their care's hunger negatively affected their own sleep, mood or emotions, work, leisure or recreational activities, and relationships with family or friends over the past 7 days. The item responses were "not at all," "a little," "moderately," or "a great deal." The questionnaire components are scored separately for patient impact and caregiver impact, with a score range from 0 to 15, where higher scores indicate greater impacts of hyperphagia [5].

Most caregivers reported numerous disruptive behaviours related to uncontrollable hunger occurring over the previous 24 hours. These included food negotiation during the day, eating extremely quickly, sneaking food, waking up and looking for food at night, and asking for more food just after finishing a meal or snack [5]. Approximately 80% of caregivers also reported that uncontrollable hunger impacted on the patient's focus at school at least 'sometimes'; 81% of children had missed at least 1 day of school in the previous week due to BBS [5].

In addition to the impact on schooling, other effects of hyperphagia included disruption of the following five domains: 1) sleep, 2) mood and emotions, 3) school, 4) leisure activities, and 5) relationships with friends and family. When asked about the impact of hyperphagia over these 5 domains, 96.3% of caregivers reported that the patient they cared for had been affected either 'moderately' or 'a great deal' in at least one domain over the previous 7 days and 15.7% were affected either 'moderately' or 'a great deal' over all 5 domains (Table 2).

Table 2 Proportion of BBS patients impacted 'moderately' or 'a great deal' by hunger as assessed by the caregiver

Number of domains affected	N=242 carers
5 domains	38 (15.7%)
At least 4 domains	79 (32.6%)
At least 3 domains	134 (55.4%)
At least 2 domains	190 (78.5%)
At least 1 domain	233 (96.3%)
Not affected 'at all' or only 'a little' over all domains	9 (3.7%)

Caregivers of BBS patients with obesity and hyperphagia reported using an average of 8 weight management approaches including healthy meal planning, counting/ restricting calorie and fat intake, tracking weight, counting/restricting carbohydrate intake, and limiting the availability of certain foods. Notably, 44.2% reported locking up food at night and 26.4% reported using fasting with their child [5]. When asked specifically about the effect of the patient's hyperphagia on their own quality of life, caregivers reported the impact to be similar to that on their child; 90.9% of caregivers reported that their child's hyperphagia negatively affected them either 'moderately' or 'a great deal' in at least one domain (sleep, mood or emotions, work, leisure or recreational activities; Table 3).

Table 3 Proportion of BBS caregivers reporting being affected either 'moderately' or 'a great deal' by their child's hunger

Number of domains affected	N=242 carers
5 domains	38 (15.7%)
At least 4 domains	77 (31.8%)
At least 3 domains	130 (53.7%)
At least 2 domains	182 (75.2%)
At least 1 domain	220 (90.9%)
Not affected 'at all' or only 'a little' over all domains	22 (9.1%)

3.2 Patient population

The currently approved indication for Imcivree® for BBS includes a patient population of adult or paediatric patients with genetically confirmed BBS aged ≥6 years.

The relevant population for the base case analysis is a paediatric treatment initation, and include patients. ≥6 years who have obesity and severe hyperphagia. Severe hyperphagia is caused by impairment of the MC4R pathway which leads to overwhelming, heightened, and relentless hunger that mimics feelings of starvation and results in excessive food consumption and a preoccupation with food that interferes with a patient's ability to function in daily life.

This is narrower than the marketing authorisation because this population reflects where Imcivree® provides the most clinical benefit and where the product will likely be used in real life in Denmark.

The future population will be comprised mainly of paediatric patients, identified through screening and genetic testing, which will promote the early diagnosis of BBS and, consequently, the treatment initiation, aiming to reduce or prevent the long-term consequences of childhood obesity on various aspects of health and mental well-being. While most individuals with BBS have a normal birth weight, it is estimated that by age two, over 55% of BBS children are overweight or obese, with obesity rates exceeding 90% by age 5 [4]. As a result, it is expected, and was confirmed by Danish clinical experts [37, 38], that most individuals will receive a diagnosis and will initiate treatment during early childhood. The treatment with Imcivree® is lifelong.

Although in the future most BBS patients will start Imcivree® treatment as children, the current population of BBS patients with hyperphagia and obesity could include adults, and reimbursement is sought for both adult and paediatric patients. The health economic base case analysis considered paediatric initiated patients with BBS in Denmark, aged ≥6 years who had severe hyperphagia and assumed starting treatment at the age of 6 years. As currently, treatment initiation with Imcivree® in the BBS population could include adults, a scenario analysis was, therefore, conducted to reflect the current setmelanotide-treatable population, which comprised 60% paediatric patients and 40% adult patients.

In Denmark, all children with BSS should be monitored and treated at one of the two Centres for Rare Diseases [38]. As described before, while most patients with BBS have normal birth weight, by two years of age it is estimated that >55% of children with BBS are overweight or obese and by the age of five years obesity rates exceed 90% [4]. This type of very early onset, dramatic weight gain is considered to be atypical, which should lead to early consideration, screening and diagnosis for BBS in childhood [4]. Early screening and genetic testing for BBS being implemented would contribute to early diagnosis and consequently, early treatment initiation. Of the patients with BBS with hyperphagia and obesity, approximately 20% are expected to have end stage renal disease (ESRD) and will be unsuitable for treatment with Imcivree.

The baseline characteristics of the modelled cohort relevant for this application were based on evidence from the pivotal Phase 3 trial Study RM 493-023 of patients with BBS aged ≥6 years, considered representative for the Danish population based on inputs from two Danish clinical experts (see Table 4) [37, 38]. Hyperphagia is the driving force behind the onset of obesity in BBS patients. Fifteen of 16 adult patients in trials had a BMI of ≥35 kg/m^2 and 12 of 16 paediatric patients had a BMI Z-score of ≥3. These are representative of patients with severe obesity. It was assumed that a high frequency of severe obesity

was the result of severe hyperphagia. This assumption was made because baseline hunger score cannot be directly used as measurement of baseline hyperphagia i.e., hunger is a key component of hyperphagia but hyperphagia cannot be quantified by hunger alone. BBS patients with obesity often eat multiple times per day (up to 7-8 meals with additional snacking) and often wake up at night to eat. Due to the very high frequency of food intake, especially for patients who are not in a highly controlled environment, it is possible for patients to suffer from severe hyperphagia with only limited hunger. Nonetheless, the baseline maximal hunger score was 7.0 [39], and when combined with a mean BMI of 41.6 reflecting strong overeating, this is considered by clinical experts as representative of severe hyperphagia in the large majority of patients.

Table 4. Relevant baseline characteristics in Study RM-493-023

Demographics			Source
Treatment initiation:	Paediatric	Adult	
Age at treatment initiation	6 years	20 years	Clinical trial NCT03746522 data [40]
% Female:	50%	56%	Clinical trial NCT03746522 data [40]
Baseline BMI Z-score or BMI/Patient count	0.0-1.0/0 1.0-2.0/1 2.0-2.5/1 2.5-3.0/2 3.0-3.5/3 3.5-4.0/ 3 ≥4.0/6	20-25/ 0 25-30/0 30-35/1 35-40/2 40-45/6 45-50/ 3 ≥50/4	Clinical trial NCT03746522 data [40]
Baseline Hyperphagia level (%) Mild Moderate Severe	 0% 0% 100%*		Assumption describing a study baseline characteristic (used in the model) and validated with two Danish clinical experts.

Note: *Corresponds to the expected patient population the will receive Imcivree® treatment,

BBS is a rare autosomal recessive disease which affects males and females equally. It has an estimated prevalence globally of 1 in 100,000. In Denmark the estimated prevalence is shown to be higher, 1 in 59,000 due to consanguinity [3, 41]. According to two Danish clinical experts it is likely that both adult and paediatric people are underdiagnosed.

Based on available literature of disease prevalence and the population size of Denmark, it is estimated that there are approximately 110 patients with BBS in Denmark [41-44] of

which approximately 30-38 are eligible for Imcivree® treatment as per label. These patient estimates were validated with Danish clinical experts [37, 38].

The eligible population in Denmark was calculated as follows:

- It was estimated that there are 110 people with BBS in Denmark.
- 72% to 92% (79-101) of the people with BBS are estimated to have obesity [18].
- 80% (63-81) of these patients with BBS have had their diagnosis genetically confirmed, as required by the setmelanotide license [45].
- Approximately 20% of patients are expected to have end stage renal disease and will be unsuitable for treatment, as estimated by treatment centres. Thus, 80% (50-65) do not have end-stage renal disease (ESRD).
- 95% of patients are aged >6 years, as estimated at by treatment centres, which is estimated to be 48-62 individuals.
- Of these approximately 30-38 (~60%), are estimated to have severe hyperphagia, the population relevant for this assessment.

Not all eligible patients are expected to get Imcivree® the first years when the product is on the Danish market. Both paediatric patients and adults are eligible for Imcivree® treatment , but it is expected that all future patients will start Imcivree® treatment in the paediatric setting, which is why only paediatrics are considered in the patient estimates. In addition, these estimates may be conservative as clinical experts recognize that the condition is underdiagnosed. Table 5 below presents prevalence of BBS in the past five years in Denmark as well as the estimated number of eligible patients in the past five years. As pointed out before, according to Danish clinical expert input, it is likely that patients are underdiagnosed. Therefore, the budget impact calculations assume [redacted] patients eligible for treatment. Table 6 present the estimated numbers of patients expected to be treated with Imcivree® over the next five years in Denmark.

Table 5. Incidence and prevalence in the past 5 years

Year	2018	2019	2020	2021	2022
Prevalence in Denmark BBS	98	99	99	99	100
Prevalence in Denmark with confirmed genetic BBS with obesity, above 6 years of age with severe hyperphagia and no ESRD	30	31	31	31	31
Incidence in Denmark with confirmed genetic BBS with obesity, above 6 years of age with severe hyperphagia and no ESRD	1-2	1-2	1-2	1-2	1-2
Global prevalence *	See note				

*For small patient groups, also describe the worldwide prevalence. The www.orpha.net state; In the US, the prevalence for BBS is estimated at 1/100,000. Whilst epidemiological data is limited in Europe, a prevalence of 1/59,000 has been estimated in Denmark and 1/45,000-66,000 in the Reunion Island, France (due to a founder effect)
Source: Based on population growth [46] and estimation according to Imcivree® label. Incidence based on KOL input [38].

Abbreviations: BBS: Bardet-Biedl syndrome, ESRD: end-stage renal disease

Table 6. Estimated number of patients treated with estimated Imcivree®)

Year	2023	2024	2025	2026	2027
Number of patients with confirmed genetic BBS with obesity, above 6 years of age with severe hyperphagia and no ESRD, in Denmark who are expected to use the pharmaceutical in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

Denmark does not have national guidelines for treating and monitoring BBS. The Danish handbook for physicians (Lægehåndbogen) available at sundhet.dk [47] presents general recommendations for BBS that include follow-up and monitoring based on the individual symptoms that are present, highlighting the importance of an interdisciplinary coordination [18]. The current treatment for patients with BBS focuses on management of presenting features from different clinical services including ophthalmology, nephrology, urology, dietetics, endocrinology, clinical genetics and gynaecology [48]. Weight management is particularly important for patients with BBS as excess weight contributes to development of comorbidities such as T2DM, hypertension and metabolic syndrome [3].

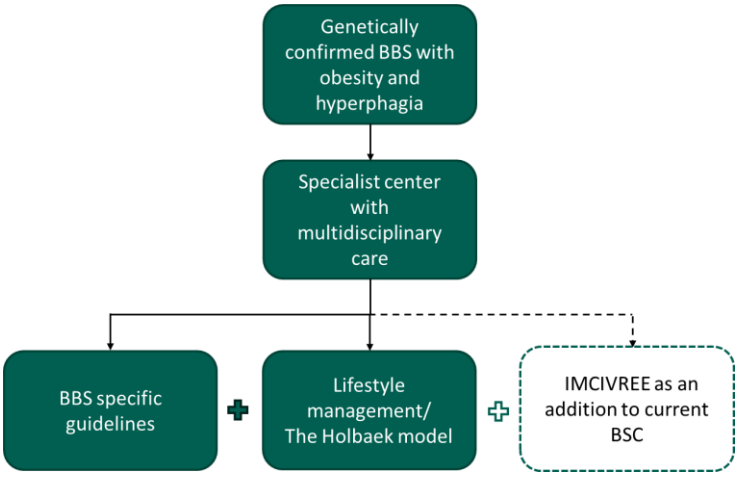
There is currently no drug therapy approved for the management of hyperphagia and obesity associated with BBS. Rather, hyperphagia and obesity are managed symptomatically mostly through lifestyle modification. The Danish paediatric society recommend Holbaek model that currently is under development. The Holbaek model is based on lifestyle modification and reducing appetite, which are particularly important for the QoL and impact on the patients' social life. It is estimated that the Holbaek model is used by approximately 80% of municipalities in Denmark [37]. Whilst diet and exercise advice can be effective in the short term, it does not address the underlying mechanism of impaired MC4R pathway signalling and the resulting severe hyperphagia that drives the patient to overeat [3]. A study conducted to evaluate the effect of obesity treatment in Danish children and adolescents with genetic impairments in the MC4R pathway revealed that individuals carrying damaging or unresolved MC4R mutations failed to reduce their BMI SDS during obesity treatment, highlighting the need of personalized treatment approaches [49]. Imcivree® has potential to re-establish a healthy appetite and energy expenditure and thus aid body weight regulation [1]. In the RM-493-023 study patients were not subject to diet or lifestyle modification. With the current BSC it is anticipate

better results in real life than in the study since the “system” is in place to support patients once their hyperphagia is controlled

In addition to reduced hyperphagia and improved quality of life with Imcivree®, meaningful reductions in weight-related outcomes are associated with decreases in MetS-Z-BMI (Metabolic Syndrome severity Z-score employing BMI as its measure of adiposity) score in patients with BBS. These data suggest that early treatment initiation may lead to reduction in future risk of T2DM and cardiovascular disease (CVD) development [50]. Furthermore, Imcivree® treatment response is associated with reductions in metabolic syndrome severity score in paediatric patients with BBS, which are associated with reduced risk of metabolic syndrome, CVD, and T2DM. These data support the broad benefits of Imcivree® beyond weight loss and hunger reduction, thus supporting early initiation of treatment for potentially reducing future risk of CVD and T2DM [51].

Figure 3 presents the treatment algorithm for patients with BBS and how Imcivree® should be used as a part of BBS multidisciplinary care and as an addition to lifestyle management.

Figure 3 Treatment algorithm for BBS with obesity and hyperphagia



3.4 The intervention

Table 7. Overview of the intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	The marketing authorization for the indication in scope for this submission is treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above.
Method of administration	For subcutaneous use. Setmelanotide should be injected once daily, at the beginning of the day (to maximize hunger reduction during awake period), without regard to the timing of meals. Setmelanotide should be injected subcutaneously in the abdomen, alternating the abdominal area each day.

Overview of intervention	
Dosing	Dose in adult and paediatric patients aged ≥16 years: 2 mg once daily subcutaneous injection for 2 weeks. If well tolerated the dose can be increased to 3 mg once daily. If the 2 mg starting dose is not tolerated it can be reduced to 1 mg once daily. If 1 mg once daily is tolerated, dose titration can be resumed. After the starting dose, if a subsequent dose is not tolerated the dose should be reduced to the previous level. If the reduced dose is tolerated, dose titration can be continued. Dose in paediatric patients (children aged 6 to <16 years): 1 mg once daily subcutaneous injection for 1 week. If tolerated after 1 week, the dose can be increased to 2 mg once daily in the second week. If well tolerated, dose can be increased to 3 mg once daily from the third week. If the 1 mg starting dose is not tolerated, it should be reduced to 0.5 mg once daily. If the 0.5 mg once daily dose is tolerated, the dose can be increased to 1 mg once daily and titration continued. For patients with mild or moderate renal impairment, no special dose adjustments are necessary. For details on dosing in the severe renal impairment population, please see the Summary of product characteristics [1].
Dosing in the health economic model (including relative dose intensity)	The starting dose, dose during titration, and an assumption of the post-titration dose are used to calculate the average year 1 dose for paediatric and adult patients with BBS. See section 11.1.
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Imcivree® is a life-long treatment. Weight loss and control of hunger associated with setmelanotide can be maintained as long as the therapy is continued uninterrupted. If treatment is discontinued, or if compliance to the dosing regimen is not maintained, symptoms of obesity and/or hunger in BBS will return.
Necessary monitoring, both during administration and during the treatment period	No special monitoring is required during administration. During the treatment period, monitoring of skin, heart rate and blood pressure, prolonged penile erection, and depression should be performed.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Only patients with genetically confirmed BBS should be offered treatment with Imcivree®. The cost effectiveness model only includes patients with genetically confirmed BBS.

Overview of intervention	
Package size(s)	1 x 1ml multidose vial (10mg/ml).

3.4.1 The intervention in relation to Danish clinical practice

As described in section 3.3, the current treatment for obesity in patients with BBS includes lifestyle management including dietary and physical activity advice. The main approach is based on lifestyle modification by changing diet habits and increasing physical activity. No therapy normalising satiety signals is currently available in Denmark. Whilst diet and exercise advice can be effective in the short-term weight management, it does not address the underlying mechanism of impaired MC4R pathway signalling and the resulting severe hyperphagia that drives the patient to overeat. Imcivree® has potential to re-establish a healthy appetite and energy expenditure and thus aid body weight regulation [1]. Patients with untreated BBS start to gain weight early in life, and the severity of obesity increases with age. Setmelanotide is not only effective in reducing body weight, but also have the potential to reverse the tendency of weight gain [21].

Also, Imcivree® as an addition to current BSC is expected to make the BSC (diet and exercise) more effective. In clinical trials Imcivree® has shown hunger reduction that was maintained throughout the 52 weeks of treatment, and clinically meaningful reductions in body weight and BMI/BMI-Z score [40]. In Danish patients with BBS above 6 years of age with obesity and severe hyperphagia, Imcivree® would offer a new effective treatment option in addition to current BSC.

3.5 Choice of comparator(s)

The relevant comparator to Imcivree® in Denmark is established clinical management/BSC without Imcivree® consisting of a reduced calorie diet and increased physical activity, in accordance with local treatment guidelines and clinical expert opinion [37, 38]. Bariatric surgery is not recommended for MC4R pathway diseases and does not address the genetic impairment and resulting insatiable hunger. It is also not a suitable treatment option for patients with cognitive impairment, and is not considered a comparator [52].

Table 8. Overview of comparator

Overview of comparator	
Generic name	Established clinical management without Imcivree® (lifestyle modifications with reduced calorie diet and increased physical activity)
ATC code	Not applicable
Mechanism of action	Not applicable
Method of administration	Not applicable

Overview of comparator	
Dosing	Not applicable
Dosing in the health economic model (including relative dose intensity)	Not applicable
Should the pharmaceutical be administered with other medicines?	Not applicable
Treatment duration/ criteria for end of treatment	Not applicable
Need for diagnostics or other tests (i.e. companion diagnostics)	Not applicable
Package size(s)	Not applicable

3.6 Cost-effectiveness of the comparator(s)

The comparator has not been evaluated by the DMC as no medicinal intervention has been approved for this indication.

3.7 Relevant efficacy outcomes

The efficacy outcomes considered relevant and necessary to evaluate the effect of setmelanotide plus BSC compared to BSC was based on study RM-493-023 and are included in Table 9 below.

The primary objective of study RM-493-023 was to assess the effect of setmelanotide on the proportion of patients ≥12 years of age at baseline treated with setmelanotide for ~52 weeks who achieve a clinically meaningful reduction from baseline (i.e., ≥10%) in body weight. Study RM-493-023 was conducted in both BBS and AS patients but the marketing authorisation was not sought for AS patients. As the relevant indication for this assessment is in patients with BBS, it is only the primary endpoint that is presented for the full trial population that includes both BBS and AS patients. Other outcomes are presented for pivotal patients ≥12 years of age BBS population only, in accordance with the protocol and SAP, and the study primary, key secondary, and other secondary efficacy analyses.

As previously described, the relevant population in this assessment consist of paediatric treatment initiation. Because children >12 years continue to grow and mature, it was important to examine setmelanotide effect on weight in the subgroup of patients who were largely finished growing, i.e., adults ≥18 years of age. Since reductions in body weight can be masked by concomitant increases in height and overall development in growing children and adolescents, setmelanotide effects in paediatric patients were primarily

assessed using BMI scores which adjust weight for height. As the main population in this assessment consists of paediatric treatment initiation relevant outcomes are presented separately for patients aged ≥18 years and those aged <18 years. In addition, the economic model considered paediatric treatment initiation as the base case analysis and was informed by a post-hoc analysis to determine the proportion of patients who moved from one BMI Z-score category to another.

3.7.1 Definition of efficacy outcomes included in the application

Table 9 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Proportion of patients achieving ≥10% reduction in body weight	Baseline to 52 weeks	Proportion of patients who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment . BBS patients aged ≥12yo and ≥18yo FAS	Weight was measured in triplicate and mean weight calculated at the study visit. Mean weight was utilized for analysis purposes. Binomial proportions were calculated for each of 100 imputed datasets. Outcomes from imputed datasets were combined using Rubin's rule to provide an overall estimate against the null hypothesis with CIs and a corresponding p value. The one sided 0.025 significant level was chosen based on the small sample size due to the rarity of the disease.
Mean and mean percent change in body weight and BMI	Baseline to 52 weeks	Mean percent change from active treatment baseline in body weight and BMI after ~52 weeks of treatment. BBS patients aged ≥12 and ≥18yo FAS	A one-sample t-test for each of 100 imputed datasets, assuming a mean change of 0 from baseline. The outcomes from imputed datasets were combined using Rubin's rule to provide CIs and a p-value (evaluated at a one-sided, 0.025 significance level). If statistical analysis was not performed, descriptive statistics were presented
Mean and mean percent change in BMI Z-score	Baseline to 52 weeks	Mean percent change from active treatment baseline in BMI-Z score after ~52 weeks of treatment. BBS patients aged <18yo FAS	A one-sample t-test for each of 100 imputed datasets, assuming a mean change of 0 from baseline. The outcomes from imputed datasets were combined using Rubin's rule to provide CIs and a p-value (evaluated at a one-sided, 0.025 significance level). If statistical analysis was not performed, descriptive statistics were presented.
Proportion of achieving a BMI-	Baseline to 52 weeks	A percent change from active treatment baseline of point 0.2 or 0.3 point in BMI Z score	A reduction in BMI Z score of at least 0.15 to 0.20 is clinically meaningful in paediatric patients.

Z score reduction from baseline		reduction after ~52 weeks of treatment. BBS patients aged <18yo FAS	
Proportion of patients in the BMI 95th weight percentile	Baseline to 52 weeks	Percentage of the CDC 95th percentile. BBS patients aged <18yo FAS	A one-sample t-test for each of 100 imputed datasets, assuming a mean change of 0 from baseline. The outcomes from imputed datasets were combined using Rubin's rule to provide CIs and a p-value (evaluated at a one-sided, 0.025 significance level). If statistical analysis was not performed, descriptive statistics were presented
Mean and percent change in the weekly average of the daily hunger score	Baseline to 52 weeks	Mean percent change from active treatment baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment. BBS patients aged ≥12yo PCAS population (daily hunger score was not collected in patients with cognitive impairment)	The Daily Hunger Questionnaire was administered to patients with no cognitive impairment (per the Investigator's judgement). Due to the unsuitability of using the hunger score tool in younger patients, this was only administered in patients ≥12 years of age at baseline. The questionnaire assessed 3 aspects of hunger (average hunger in the last 24 hours, most/worst hunger in the last 24 hours, and morning hunger) daily. The responses to the Daily Hunger Questionnaire were recorded in an electronic diary. Each of the 3 items (average hunger, most/worst hunger, and morning hunger) was scored separately (rather than combined) and averaged on a weekly basis. For a week of hunger scores to be considered evaluable, scores needed to be recorded and available for analysis on at least 1 of 7 days to provide sufficient data to determine mean values. The 1 of 7 days algorithm was chosen as acceptable due to experience and learnings from Rhythm's other two Phase III studies (RM-493-012 POMC and RH-493- 015 LEPR), which supported the significant difficulties of obtaining hunger scores on a daily basis over a one-year study. Rhythm believes that the 1 out of 7 days approach will largely prevent missing data and best utilize the data points available. Unless specified otherwise, this will be applicable for all hunger score related analysis.

			This approach was validated with regulatory authorities as the best approach to assess hunger in patients with hyperphagia. A one-sample t-test for each of 100 imputed datasets was done, assuming a mean change of 0 from baseline. The outcomes from imputed datasets were combined using Rubin's rule to provide CIs and a p-value (evaluated at a one-sided, 0.025 significance level). If statistical analysis was not performed, descriptive statistics were presented.
Proportion of patients with a ≥25% improvement in the weekly average of daily hunger score	Baseline to 52 weeks	Proportion of patients who achieve a ≥25% improvement from active treatment baseline in the weekly average of the daily hunger score. Based on an analysis of data from the Clinical Registry Investigating BBS (CRIBBS) ≥12yo FAS population	The p-value after 52 weeks of treatment was analysed using binomial proportions calculated for each of 100 imputed datasets. Outcomes from the 100 imputed datasets were combined using Rubin's rule to provide an overall estimate.
Body weight percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients	Baseline to 14 weeks	Body weight percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients. BBS patients aged ≥12yo PCAS population	Analyses were based on a two-sample t-test for each of the 100 imputed datasets, with an assumed mean percent change from baseline in the select parameter score of zero. Outcomes from the 100 imputed datasets were combined using Rubin's rule to provide CIs and a corresponding p-value, which was evaluated at a one-sided, 0.025 significance level.
Weekly average daily hunger score percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients	Baseline to 14 weeks	Weekly average daily hunger score percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients BBS patients aged ≥12yo PCAS population (daily hunger score was not collected in patients with cognitive impairment)	Analyses were based on a two-sample t-test for each of the 100 imputed datasets, with an assumed mean percent change from baseline in the select parameter score of zero. Outcomes from the 100 imputed datasets were combined using Rubin's rule to provide CIs and a corresponding p-value, which was evaluated at a one-sided, 0.025 significance level.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

The Guideline on clinical evaluation of medicinal products used in weight management by EMA recommends documenting absolute and relative weight loss (kg and percentage), and states that at least 5% placebo-corrected weight loss from baseline after 12 months of treatment is a valid primary efficacy criterion [1]. Responder definitions for adults should include patients with at least 5% and 10% weight loss at the end of a 12-month period. In study RM-493-022 the 10% weight loss was used and considered clinically relevant. For paediatric BMI Z-score is a more commonly accepted standard for characterising obesity in paediatric patients [53]. BMI Z-scores and BMI 95th percentile scores were also examined since BMI is known to vary by age and sex in growing children and these scores are calculated using age and sex matched normative data. A ≥0.2 reduction in BMI-Z score is considered clinically significant. Several studies support this threshold: A study in children (median age 12.4 years) with severe obesity found that a reduction of 0.25 BMI Z-score units was required to improve adiposity and metabolic health [54], while improvements in cholesterol were observed in children (aged 7-17) with obesity with a BMI Z-score reduction of <0.1 units [55], and improvements in insulin and cholesterol were observed in 5 to 19 year-olds with obesity following a BMI Z-score reduction of 0.15 units [56].

Based on many of the above studies, the United States Preventive Services Task Force (USPSTF) has defined clinically important weight loss associated with cardio- metabolic improvements as a reduction in BMI Z-score of ≥0.2 units [57]. Consistent with this, in a large-scale German study to predict weight loss in overweight/obese paediatric patients, weight loss success was defined as a reduction in BMI SDS-score of ≥0.2 [58]. Similarly, a reduction in BMI Z-score of ≥0.2 was used to define success in a recent and relatively large study examining characteristics and lifestyle behaviours associated with achieving clinically important weight loss [59].

Measurements of central adiposity (waist circumference) can be used as a secondary outcome measure, which was used in the extension trial RM-493-022.

4. Health economic analysis

A cost-utility analysis was performed for this submission.

4.1 Model structure

The model was developed to assess the cost-effectiveness of setmelanotide plus standard of care (BSC) compared to best supportive care (BSC) alone for the treatment of patients with BBS, aged ≥6 years who have severe hyperphagia and obesity. This aligns with a sub-population of the licensed indication for setmelanotide. The analysis uses a lifetime model. The analysis follows two patient populations, one with paediatric treatment initiation (at 6 years old) and the other with an adult treatment initiation (at 20 years old). This is because, currently, treatment initiation in the BBS population could include adults

according to setmelanotide label. However, in the future, it is expected that BBS patients with severe hyperphagia and obesity will start setmelanotide treatment as children. This aims to reduce or prevent the long-term consequences of childhood obesity on other aspects of health and on mental well-being. The base case in the current assessment is paediatric treatment initiation. An additional scenario analysis considered the adult population, conducted to reflect the current setmelanotide-treatable population, which comprised 60% paediatric patients and 40% adult patients (see Table 67).

The model is comprised of eight disease states for both treatment arms to reflect the target patient populations (seven BMI Z-score categories along with a 'death' state). The seven BMI Z-score categories are stratified as follows:

- For paediatric patients (base case population) BMI Z-score categories were defined as: BMI Z-score 0.0-<1.0; BMI Z-score 1.0 to <2.0; BMI Z-score 2.0 to <2.5; BMI Z-score 2.5 to <3.0; BMI Z-score 3.0 to <3.5; BMI Z-score 3.5 to <4.0; and BMI Z-score ≥4.0.
- Adult (scenario analysis) BMI categories comprised: BMI <25; BMI 25 to <30; BMI 30 to <35; BMI 35 to <40; BMI 40 to <45; BMI 45 to <50; and BMI ≥50.

At model entry, patients are distributed across BMI/BMI Z-score categories based on clinical trial data [40]. Patients with paediatric treatment initiation transition from their BMI Z-score category to the correspondent BMI category at 18 years old. The mapping process from BMI-Z to BMI was implemented using calculations published by WHO [60]. Table 10 shows the transition matrix derived from the mapping.

Table 10. Methodology for mapping BMI Z-score to BMI

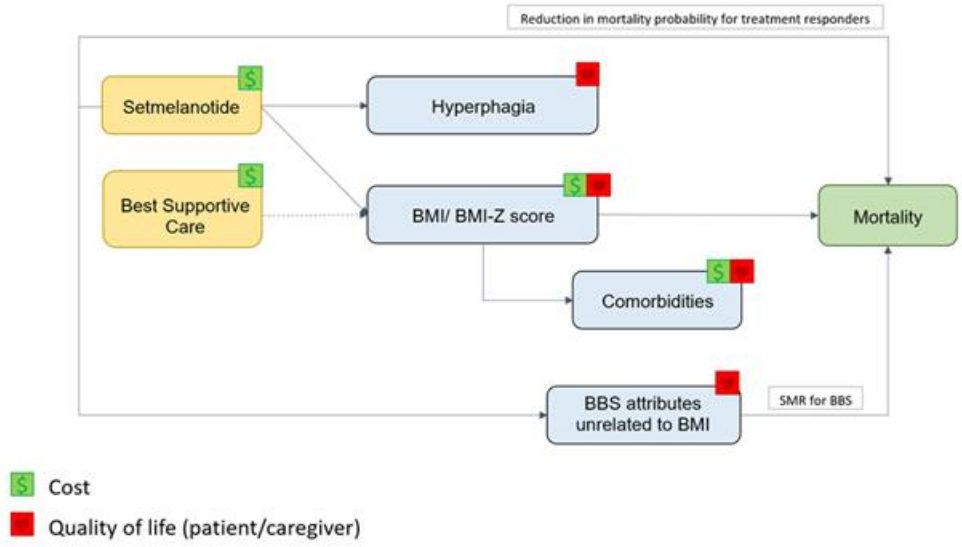
		BMI Z-score						
		0.0 to <1.0	1.0 to <2.0	2.0 to <2.5	2.5 to <3.0	3.0 to <3.5	3.5 to >4.0	≥4.0*
BMI (kg/m²)	20 to <25	100%	0%	0%	0%	0%	0%	0%
	25 to <30	0%	100%	0%	0%	0%	0%	0%
	30 to <35	0%	0%	100%	100%	0%	0%	0%
	35 to <40	0%	0%	0%	0%	100%	0%	0%
	40 to <45	0%	0%	0%	0%	0%	100%	33%
	45 to <50	0%	0%	0%	0%	0%	0%	33%
	≥50	0%	0%	0%	0%	0%	0%	33%

* There are no established curves to map BMI-Z to BMI for a BMI-Z over 4. As a result, the BMI Z-score ≥ 4 was split equally in three BMI categories.

Treatment with setmelanotide is assumed to alter the distribution of patients across BMI/BMI Z-score categories. Treatment with SoC alone is assumed to have no effect on the distribution of patients across the BMI/BMI Z-score categories. Once patients discontinue setmelanotide they revert immediately to their original BMI/BMI Z score category. This is a conservative assumption as, in real life, it will take some time for them to regain the lost weight Additionally, setmelanotide is also modelled to manage the BBS patients' hyperphagia. The model accounts for three different hyperphagia levels (mild, moderate, and severe) that are associated with unique utility multipliers. The influence of treatment with setmelanotide on hyperphagia is modelled separately from that for BMI/BMI Z-score, so that both influence quality of life independently.

Treatment with SoC alone is assumed to have no effect on the BBS patient's hyperphagia. The model considers the costs of treating obesity in patients with BBS, the medical costs and HRQoL impact associated with increased BMI, the HRQoL impact of living with hyperphagia, and the costs and utility decrements of obesity-related comorbidities, including sleep apnoea, osteoarthritis, NASH, T2DM, and cardiovascular events. The BMI/BMI Z-score category also drives mortality risk. Mortality probabilities by BMI/BMI Z score level and age were applied to reflect the higher risk of death for BBS patients compared with the general population. The mortality data was derived from an innovative process used to estimate the effect of early onset of obesity on comorbidities and mortality risk (see Appendix K). A conceptual diagram showing model drivers is presented in Figure 4.

Figure 4. Drivers of the cost-effectiveness model of setmelanotide plus standard of care compared to standard of care alone for the treatment of patients with BBS



BBS: Bardet-Biedl syndrome; BMI: Body mass index; SMR: Standardized mortality ratio

As the model progresses cycle by cycle for the duration of the time horizon, cost and utility data were summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between model arms at model completion. The model approach is flexible and adequately quantifies the primary objectives of treating

individuals with BBS who have severe hyperphagia and obesity, particularly considering the scarcity of disease-specific data. Moreover, it uses clinical trial results [40] to inform baseline and treatment-effect data, which ultimately drives model outcomes.

4.2 Model features

Table 11 shows the features of the economic model.

Table 11 Features of the economic model

Model features	Description	Justification
Patient population	Patients with BBS, aged ≥6 years who have severe hyperphagia and obesity. In the analysis base case, only paediatric treatment initiation is explored.	The patient population in the economic model is aligned with the relevant patient population described in section 3.2. The patient population in the economic model is aligned with the enrolled population in the pivotal trial (Study RM 493-023) [40]. The baseline patient characteristics of the modelled cohort were based on this trial. The patient population in the economic model is aligned with a sub-population of the licensed indication for setmelanotide. The included population reflects where setmelanotide provides the most clinical benefit and where the product is likely to be used in real life in Denmark. The analysis base case only considers paediatric treatment initiation. This is because, in the near future, it is expected that BBS patients with severe hyperphagia and obesity will start setmelanotide treatment as children. This aims to reduce or prevent the long-term consequences of childhood obesity on other aspects of health and on mental well-being.

Model features	Description	Justification
Perspective	Limited societal perspective	According to DMC guidelines.
Time horizon	Lifetime (with a maximum patient age of 100 years)	BBS has a life-long impact on the affected patients. Therefore, a lifetime time horizon (with a maximum patient age of 100 years) is used in the base case analysis, to capture the full benefit of treatment with setmelanotide. Alternative time horizons are explored in scenario analyses.
Cycle length	1 year	
Half-cycle correction	Yes	It allows a better approximation of the area under the curve. For each cycle, instead of using the output calculated for a specific cycle, the average of the output at the current and previous cycles is taken.
Discount rate	0-35 years: 3.5% 36-70 years: 2.5% 70+ years: 1.5%	According to Finansministeriet [61].
Intervention	Setmelanotide + best supportive care	Setmelanotide is not expected to replace diet and exercise advice for the treatment of obese patients with BBS. Rather, it is expected to improve the impact of these interventions thanks to its effect on hyperphagia.
Comparator(s)	Best supportive care	The relevant comparator to setmelanotide in Denmark is established clinical management (lifestyle modifications with reduced calory diet and increased physical activity). The current management, and relevant comparator for patients with BBS with obesity and hyperphagia used in the model is aligned with local

Model features	Description	Justification
		treatment guidelines and was validated by two Danish clinical experts [37, 38].
Outcomes for efficacy	Shift in BMI Z-score class for the paediatric patients who respond to setmelanotide. Shift in the hyperphagia level for the paediatric patients who respond to setmelanotide.	Both represent relevant efficacy outcome measures in the treatment of BBS patients with severe hyperphagia and obesity.

BBS: Bardet-Biedl syndrome; BMI: Body mass index; DMC: Danish Medicines Council

5. Overview of literature

5.1 Literature used for the clinical assessment

This application for Imcivree® concerns the treatment of obesity and the control of hunger associated with genetically confirmed BBS with severe hyperphagia and obesity in adults and children 6 years of age and above. This submission includes data from both publications associated with key studies and the clinical study reports. In addition, a systematic literature review (SLR) was conducted to identify any other data relating to the management of obesity and hyperphagia in BBS patients, see Appendix H. Three articles reported on clinical outcomes comprising Haws 2020, [62] Haws 2021 [63] and Argente 2022 [64]. However, following completion of the SLR, a new article was published relating to trial NCT03746522 that superseded prior publications, Haqq 2022 (trial NCT03746522) [39]. The three clinical studies considering clinical outcomes in patients with BBS investigated the efficacy and safety of setmelanotide are:

- An international, randomized, double-blind placebo controlled followed by an open label treatment period Phase 3 trial, 38 individuals were enrolled with a genetically-confirmed diagnosis of BBS or Alström syndrome (AS) (trial NCT03746522, RM-493-023) [63].
- An open-label long-term extension trial was conducted (trial NCT03651765, RM-493-022) in patients aged ≥6 years who had been treated and shown clinical benefit with setmelanotide in either the Phase 2 or Phase 3 study (described above); outcomes were assessed after ~2 years of setmelanotide treatment (in both the index and extension trial) for change in body weight and various other weight-related measures [64].
- A single-arm, open-label, basket-design, pilot, Phase 2 study, patients with various rare genetic obesity disorders including BBS were enrolled (trial NCT03013543, RM-493-014) [62].

The health-economic model uses baseline and response data from study RM-493-023 which is the main study for efficacy and safety of Imcivree®. In addition, data from the extension study RM-493-022 was used to inform maintenance of efficacy of Imcivree® but is not used to inform the cost effectiveness model. This is because no special dietary counselling was a part of this trial. As a result, maintenance of efficacy in RM-493-022 only reflects the effect of the drug itself but does not reflect the overall real-life impact of treatment on the management of the patient, including the ability to establish an efficacious lifestyle management program following the resolution of hyperphagia. In addition, the number of patients with long-term follow-up is low due to variable inclusion dates in the index trial, weaking the interpretation of data. For example, for adult patients with BBS, patient numbers and maintenance rates are:

- Month 12: 11 of 11 patients (100.0%).
- Month 18: 7 of 11 patients (63.6%).
- Month 24: 6 of 10 patients (60.0%).
- Month 36: 3 of 3 patients (100.0%).

Therefore, it was decided to not use data from this trial in the health economic model, relying on clinical expert opinions instead.

Data from RM-493-014 are not used in the model, as this was a Phase 2 study which was not designed to assess efficacy. As no drug therapy is currently approved for the management of hyperphagia and obesity associated with BBS, the comparator used for modelling is standard management/best supportive care (BSC). No studies were identified by the SLR that compared setmelanotide directly with BSC. The RM-493-023 study was placebo controlled followed by an open label period, and considered to be representative of the efficacy of setmelanotide versus BSC without setmelanotide and of how patients are expected to be treated in the real-world.

Table 12 summarises the relevant literature used for efficacy and safety.

Table 12 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Rhythm Pharmaceuticals Inc, Clinical Study Report: RM-493-023 A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alstrom Syndrome (AS) Patients with Moderate to Severe Obesity. [Data on file]. 2021. [40] Haqq, A.M., et al., Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alstrom syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. Lancet Diabetes Endocrinol, 2022a. 10(12): p. 859-868. [39] Argente, J., Clement, K., Dollfus, H., Han, J., Haqq, A., Martos-Moreno, G., ... & Haws, R., Phase 3 Trial of Setmelanotide in Participants With Bardet-Biedl Syndrome: Placebo-Controlled Results. Hormone Research in Paediatrics 2021. 94: p. 30-31. [65] Haws, R., et al., A Phase 3 Trial in Participants With Obesity Due to Bardet-Biedl Syndrome or Alström Syndrome: Efficacy and Safety of the Melanocortin 4 Receptor Agonist Setmelanotide. 2021d(2472-1972 (Electronic)). [63] Haws, R., Clement, K., Dollfus, H., Haqq, A., Martos-Moreno, G., Chung, W., Mittleman, R., Stewart, M., Webster, M., Yuan, G., Argente, J.. E, Efficacy and safety of open-label setmelanotide in bardet-biedl syndrome: a phase 3 trial. Obesity (Silver Spring, Md.), 2021c. 29: p. 12. [66]	RM-493-023	NCT03746522	Actual study start date: December 10, 2018 Actual study completion date: March 8, 2021	Setmelanotide efficacy (response data) vs BSC

Argente, J., et al., ODP606 Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome. J Endrocr Soc., 2022. 6(A14). [64]	RM-493-022	NCT03651765	Actual study start date: July 15, 2018 Estimated study completion date: December 2024	Setmelanotide efficacy (maintenance) vs BSC
Haws, R., et al., Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. Diabetes, Obesity and Metabolism, 2020. 22(11): p. 2133-2140. [62]	RM-493-014	NCT03013543	Actual study start date: February 10, 2017 Actual study completion date: March 1, 2022	Not used in comparison

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Three (3) studies in the SLR reported on HRQoL or patient-/caregiver-reported outcomes related to obesity in BBS (see Appendix I) but were not relevant to include in the health economic assessment. HRQoL was measured in RM-493-023 using EQ-5D and was measured after 52 weeks of treatment with setmelanotide (presented in Appendix F). However, the EQ-5D was not deemed to capture the impact of hyperphagia (the biggest driver of quality of life in BBS patients) and these data were, therefore, considered inappropriate for use in the cost-effectiveness analysis. The table below presents the literature used for the health state utility values used in this assessment, and the relevant sections in the application where those are described. The results from the HRQoL reported in study RM-493-023 is presented in Appendix F. The literature search for HRQoL is further described in Appendix I.

Table 13 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Forsythe 2021 Quality of life in patients with Bardet-Biedl syndrome in a setmelanotide Phase 3 trial [67]	N/A	Section Appendix F

Appendix F

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Vignette-study [68]	Mild hyperphagia utility multiplier/0.909 Moderate hyperphagia utility multiplier /0.702 Severe hyperphagia utility multiplier /[redacted]	Section 10.3.1
Riazi, A., et al. (2010). "Health-related quality of life in a clinical sample of obese children and adolescents." Health and Quality of Life Outcomes 8(1): 134. [69]	Utility by BIM-Z score	Section 10.3.5
Alsumali, A., et al. (2018). "Cost-Effectiveness Analysis of Bariatric Surgery for Morbid Obesity." Obes Surg 28(8): 2203-2214 [70]	Utility by BMI category and age	Section 10.3.5
Sullivan, P. W., et al. (2011). "Catalogue of EQ-5D scores for the United Kingdom." Med Decis Making 31(6): 800-804. [71]	Myocardial infarction disutility/0.037 Angina disutility/0.063 Stroke disutility/0.117 Transient ischaemic attack disutility/0.033	Section 10.3.9
Søltoft, F., M. Hammer, and N. Kragh, The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. Qual Life Res, 2009. 18(10): p. 1293-9. [72]	Sleep apnoea disutility/0.034	Section 10.3.9

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Søltoft, F., M. Hammer, and N. Kragh, The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. Qual Life Res, 2009. 18(10): p. 1293-9. [72]	Osteoarthritis disutility/0.187 T2DM disutility/0.043	Section 10.3.9
NICE 2016 [73]	NASH disutility 0.000	Section 10.3.9
Sullivan, P. W., et al. (2011). "Catalogue of EQ-5D scores for the United Kingdom." Med Decis Making 31(6): 800-804. [71]	Cardiovascular events disutility/0.066 (weighted based on the proportion of Myocardial infarction 35.65%, Angina 39.81%, Stroke 21.67% and Transient ischaemic attack 6.33%)	Section 10.3.9
Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JM, et al. Utilities and Disutilities for Type 2 Diabetes Treatment-Related Attributes. Quality of Life Research 16(7),1251-65 (2007) [74]	Nausea/vomiting/-0.04	Section 10.3.13
Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. The European journal of	Injection site reaction/ -0.011	Section 10.3.13

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
health economics : HEPAC : health economics in prevention and care 12(3),219-30 (2011) [75]		

5.3 Literature used for inputs for the health economic model

The health economic model is informed by data from RM-493-023 for baseline and response data. Mortality was based on a disease model. Resource use and cost were based on publicly available literature relevant for Denmark. Table 14 summarizes the relevant literature used for input in the health economic model.

Table 14 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Clinical study report RM-493-023 (Data on file) [40]	Baseline data Treatment effect based on Response rates	Pivotal trial for efficacy	Section 8.1.1
Early onset obesity model (see Appendix K)	Mortality for early onset obesity as a proxy for mortality in the BBS population by age and BMI	See Appendix K	Section 8.2.2

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Spanggaard, M., et al (2022) [76]	BMI-related health care costs	Targeted search of Danish cost of BMI related cost	Section 11.4
Jennum, P et al. [77]	Sleep apnoea cost	Targeted search of Danish or Nordic cost of comorbidities	Section 11.4
Salmon, J.H., et al [78]	Osteoarthritis	Targeted search of Danish or Nordic cost of comorbidities	Section 11.4
Hagström, H., et al. [79]	NASH	Targeted search of Danish or Nordic cost of comorbidities	Section 11.4

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Pulleyblank et. al 2021 [80]	Type 2 diabetes	Targeted search of Danish or Nordic cost of comorbidities	Section 11.4
Hallberg, S., et al. [81]	Cardiovascular events	Targeted search of Danish or Nordic cost of comorbidities	Section 11.4
Publicly available literature	Monitoring cost & Patient cost	Targeted search of monitoring cost and patient cost were sourced from the DMC report of valuation of unit costs and Resource use were estimated by clinical experts and not based on literature.	Section 11.4

6. Efficacy

6.1 Efficacy of setmelanotide compared to best supportive care for genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above

6.1.1 Relevant studies

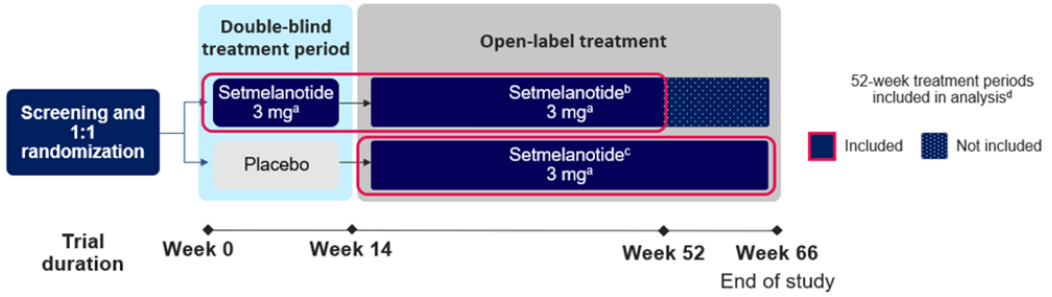
As previously described, three clinical studies considering clinical outcomes in patients with BBS with severe hyperphagia and obesity investigated the efficacy and safety of setmelanotide, RM-493-023 [63], RM-493-022 [64] and RM-493-014 [62]. The main study used in the health-economic model is study RM-493-023, the extension study RM-493-022 was used for providing clinical evidence of the maintenance of efficacy. Data from RM-493-022 and RM-493-014 are not used in the model. Therefore only RM-493-023 [63] are included in the table below. All three studies are further described in Appendix A.

The main study providing data relating to the use and efficacy of setmelanotide in patients with BBS is derived from Phase 3 pivotal Study RM-493-023. Study RM-493-023 had a 2-arm, parallel-group design, with three treatment periods (Figure 5):

- Period 1 was a 14-week, randomised, double-blind, placebo-controlled treatment period. Patients were randomised in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive setmelanotide or placebo once daily via subcutaneous injection.
- Period 2 was a 38-week open-label treatment period in which all patients received setmelanotide.
- Period 3 was a 14-week open-label treatment period in which all patients received setmelanotide. The purpose of this period was to allow patients who received placebo in period 1 to receive 52 weeks of treatment. Those who received setmelanotide in Period 1 continued to receive setmelanotide after assessment of the Week 52 primary endpoint.

The trial was conducted in both AS and BBS patients, however, AS was not included in the setmelanotide marketing authorization and hence this submission focuses on post-hoc analysis of data in BBS patients only (see Figure 5 for an overview). Analysis populations specified for Study RM-493-023 are summarized in Table 15 and the trial profile of pivotal patients in Figure 6.

Figure 5 Study RM-493-023 design schematic



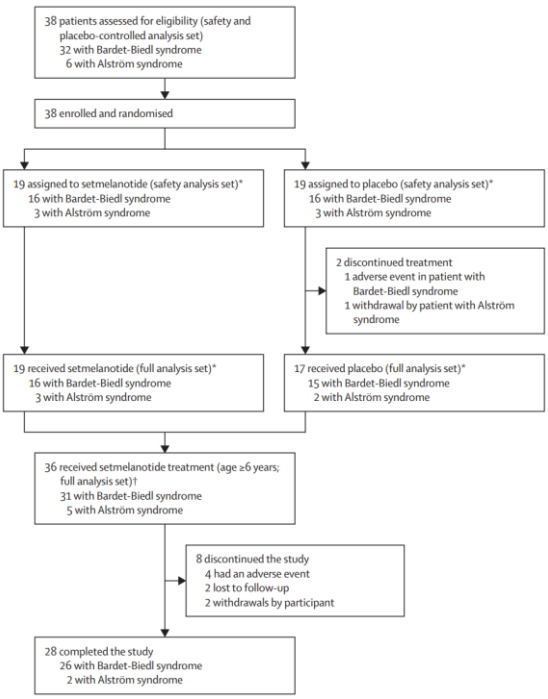
[a] Dose escalation up to 3.0 mg based on age

[b] For patients who received ≥52 weeks of setmelanotide treatment by end of study, the analysis was performed at Week 52.
[c] A multiple imputation model was used to impute data for patients who received <52 weeks of setmelanotide at the primary analysis timepoint
[d] Efficacy outcomes were assessed at 52 weeks of active treatment for each group (i.e. Week 0 to 52 for the setmelanotide group and Week 14 to 66 for the group assigned to placebo during the double-blind treatment period)

Table 15 Study RM-493-023 analysis sets

Analysis set	Definition	Use	Baseline for efficacy analyses
Screening set	All patients who signed informed consent		
Safety analysis set (SAS)	All patients who received at least 1 dose of study drug (placebo or setmelanotide).	Safety endpoints. Patient data were analysed according to the treatment received.	
Full analysis set (FAS)	All patients (irrespective of age) who received at least 1 setmelanotide dose and provided baseline data	Efficacy endpoints	Active treatment baseline (ATB) - the last available measurement prior to the first dose of setmelanotide
Placebo-controlled analysis set (PCAS)	All randomised patients who received at least 1 dose of placebo or setmelanotide and provided baseline data	Data from the 14-week placebo-controlled, double-blind period (Period 1). PCAS analyses were performed based on patients as randomised.	Placebo-controlled period baseline (PCPB) - the last available measurement prior to the first dose of setmelanotide or placebo

Figure 6 Trial profile of pivotal patients



Notes: Safety analysis set includes patients who received at least one dose of setmelanotide or placebo. Placebo-controlled analysis set includes randomly assigned patients who received at least one dose of setmelanotide or placebo and had baseline data. Full analysis set includes randomly assigned patients who received at least one dose of setmelanotide and had baseline data. *Double-blind 14-week period. †Open-label treatment with only setmelanotide

Table 16 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alström Syndrome (AS) Patients With Moderate to Severe Obesity NCT03746522, RM-493-023	international, randomised, controlled, Phase 3 trial, 2-arm, parallel-group design, with three treatment periods	52 weeks Period 1 was a 14-week, randomised, double-blind, placebo-controlled treatment period. Period 2 was a 38-week open-label treatment period in which all patients received setmelanotide. Period 3 was a 14-week open-label treatment period in which all patients received setmelanotide.	Patients with BBS or AS, stratified by age group (≥12 years or <12 years) and disease	Setmelanotide Daily subcutaneous injection in up to 3 mg dosage	Matching placebo at equivalent volume to 3 mg setmelanotide during the placebo controlled period (14 weeks) Daily subcutaneous injection	Effect of Setmelanotide [Time Frame: 52 weeks] The proportion of patients (greater than or equal to 12 years of age at baseline) who achieve a greater than or equal to 10% reduction from baseline in body weight (i.e., are 'responders') after ~52 weeks of treatment with setmelanotide. Effect of Setmelanotide [Time Frame: 52 weeks] Assess the effect of setmelanotide on the proportion of patients treated with setmelanotide for 52 weeks who achieve a clinically meaningful reduction from baseline in body weight.

6.1.2 Comparability of studies

This application is based on a head-to-head study RM-493-023.

6.1.3 Comparability of patients across studies

A summary of demographic and baseline information in the RM-493-023 study is presented for all patients with BBS (pivotal and supplemental) in Table 17. Supplemental patients are the patients added into the protocol in the midcourse of the study. The purpose of the supplemental cohort was to gain more treatment experience. Overall, a total of 52 patients were enrolled in the study, including 38 patients in the pivotal cohort and 14 in the supplemental cohort. With respect to clinical diagnoses, 44 of the 52 patients had BBS and 8 had AS. The supplemental cohort included 12 BBS patients and 2 AS patients. However, unless stated otherwise, all analyses in the SAP refer to the pivotal cohort only.

The mean age of the BBS population at the start of the trial was 20 years of age, across a range of 6 to 46 years. Slightly more females than males were enrolled. Most patients were White. Of note, baseline most/worst hunger scores differed significantly between setmelanotide and placebo groups. Baseline hunger in the setmelanotide arm was 4.7 compared with 6.8 for placebo. Fifteen of 16 adult patients in trial had a BMI of ≥35 kg/m2 and 12 of 16 paediatric patients had a BMI Z-score of ≥3. These are representative of patients with severe obesity. It was assumed that a high frequency of severe obesity was the result of severe hyperphagia. The baseline characteristics of the modelled cohort relevant for this application were based on evidence from the pivotal Phase 3 trial Study RM 493-023 of patients with BBS aged ≥6 years (presented previously in Table 4)

Table 17 BBS patient characteristics on inclusion (Study RM-493-023, pivotal and supplemental patients)

	Setmelanotide (N=22)	Placebo (N=22)	Total (N=44)
Mean (SD) [range] age, years[1]	18.5 (9.7) [6, 42]	21.5 (12.6) [6, 46]	20.0 (11.2) [6, 46]
Age group, n (%)			
≥18 years	10 (45.5)	12 (54.5)	22 (50.0)
<18 years old	12 (54.5)	10 (45.5)	22 (50.0)
Female n (%)	9 (40.9)	15 (68.2)	24 (54.5)
Race, n (%)			
White	15 (68.2)	19 (86.4)	34 (77.3)
Black or African American	1 (4.5)	1 (4.5)	2 (4.5)

Asian	0 (0.0)	1 (4.5)	1 (2.3)
Other	6 (27.3)	1 (4.5)	7 (15.9)
Ethnicity, n (%)			
Non-Hispanic and non-Latin	1 (4.5)	0 (0.0)	1 (2.3)
Hispanic or Latin	18 (81.8)	19 (86.4)	37 (84.1)
Not reported	1 (4.5)	2 (9.1)	3 (6.8)
Unknown	2 (9.1)	1 (4.5)	3 (6.8)
Mean (SD) [range] weight, kg[1]	110.45 (35.8) [46.4, 173.8]	106.5 (31.8) [47.0, 166.0]	108.5 (33.5) [46.4, 173.8]
Mean (SD) [range] BMI, kg/m^2 [1]	41.4 (10.0) [24.4, 61.3]	41.6 (10.1) [24.6, 66.1]	41.5 (9.9) [24.4, 66.1]
Patients aged ≥12 years without cognitive impairment completing the daily hunger questionnaire, n (%)	6 (31.58)	12 (63.16)	18 (94.74)
Most/worst hunger, mean (SD) [n][2]	6.3 (1.6) [26][1]	6.6 (2.0) [12][1]	6.8 (1.8) [18][3]

[1] Placebo-controlled period baseline.

[2] Patients aged ≥12 years without cognitive impairment; self reported. Assessed daily using a numeric rating score from 0 to 10, with 0 = not [hungry] at all and 10 = hungriest possible.

[3] At active treatment baseline.

The baseline distribution of patients by BMI category (adult patients) and BMI Z-score category (paediatric patients) is presented in Table 18.

Table 18 Baseline BMI and BMI Z-score categories for BBS patients (Study RM-493-023, pivotal patient SAS)

Baseline BMI (kg/m^2) / BMI Z-score category	BMI in BBS patients aged ≥18 years (N=16)	BMI Z-score in BBS patients aged <18 years (N=16)
BMI 20 to ≤25 / BMI Z 1 to ≤ 2	[redacted]	[redacted]
BMI 25 to ≤30 / BMI Z 2 to ≤2.5	[redacted]	[redacted]
BMI 30 to ≤35 / BMI Z 2.5 to ≤3	[redacted]	[redacted]
BMI 35 to ≤40 / BMI Z 3 to ≤3.5	[redacted]	[redacted]
BMI 40 to ≤45 / BMI Z 3.5 to ≤4	[redacted]	[redacted]

BMI 45 to ≤50 / BMI Z 4+	[redacted]	[redacted]
BMI 50+	[redacted]	[redacted]

6.1.3.1 Comparability of the study population(s) with Danish patients eligible for treatment

The Danish patient population: The patient population relevant in Denmark consists of adult or paediatric patients with BBS, aged ≥6 years who have severe hyperphagia and obesity; this aligns with the approved market authorisation and indication for Imcivree® and reflects where setmelanotide provides the most clinical benefit and where the product is likely to be used in real life in Denmark. Baseline characteristics in the health economic analysis were based on evidence from study RM 493-023, presented before in section 3.2, Table 4 and are considered representative for the Danish population according to Danish clinical experts. It is estimated that approximately [redacted] patients are eligible for treatment with Imcivree® confirmed by two clinical experts in Denmark [37, 38].

Patient population in the health economic analysis submitted: As previously described, patient characteristics for the modelled population were informed by baseline data from study RM-493- 023 [40] that reflects the Danish patient population[37, 38]. Model inputs related to patient characteristics are age at treatment initiation, % female and baseline BMI Z-score distribution. It was assumed that patients who responded to setmelanotide (i.e. adults who achieved ≥10% weight reduction and paediatric patients who achieved ≥0.2 BMI Z-score reduction) must also have experienced a significant reduction in their hyperphagia levels, sufficient to classify their on-treatment hyperphagia as mild. It was assumed that in order to lose the clinically significant amount of weight required to qualify as a 'responder' that hyperphagia severity was reduced from 'severe' to 'mild'. This assumption was validated with Danish clinical experts [37, 38].

Table 19 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [37, 38]	Value used in health economic model [40]
Age (years) at treatment start	6	6
% Female	50%	50%
BMI Z-score (paediatric)/BMI (adults) distribution		
0 to ≤1 / 20 to ≤25	0 (0.0)/0 (0.0)	0 (0.0)/0 (0.0)
1 to ≤ 2 / 25 to ≤30	1 (6.3)/0 (0.0)	1 (6.3)/0 (0.0)
2 to ≤2.5 /30 to ≤35	1 (6.3)/1 (6.3)	1 (6.3)/1 (6.3)
2.5 to ≤3 / 35 to ≤40	2 (12.5)/2 (12.5)	2 (12.5)/2 (12.5)

3 to ≤3.5 / 40 to ≤45	3 (18.8)/6 (37.5)	3 (18.8)/6 (37.5)
3.5 to ≤4 / 45 to ≤50	3 (18.8)/3 (18.8)	3 (18.8)/3 (18.8)
4+/50+	6 (37.5)/4 (25.0)	6 (37.5)/4 (25.0)
Baseline hyperphagia distribution		
Mild	0%	0%
Moderate	0%	0%
Severe	100%	100%

6.1.4 Efficacy – results per Study RM-493-023

As previously described study RM-493-023 was conducted in both BBS and AS patients but marketing authorisation was not sought for AS patients, and this submission relates only to the use of setmelanotide in BBS patients. However, the primary endpoint is presented for the full trial population (BBS and AS patients) in addition to BBS patients only; all other data are presented for the BBS population only. The summary results for the primary and secondary analysis are presented in Table 20 and Table 21, respectively. Results throughout this section are presented separately for patients aged ≥18 years and those aged <18 years (in contrast with the results from the main trial endpoints that are presented for ≥12 years). In growing children, body weight is heavily influenced by physical development and maturation. Body weight is, therefore, primarily used for patients aged ≥18 years, whilst weight-related parameters that account for differences in height (such as BMI) and those that account for differences in age and sex (such as BMI Z-score and the percentage of the BMI 95th percentile score) are used for patients aged <18 years.

The model considers paediatric treatment initiation as base case and adult treatment initiation is tested in a scenario. in order to inform the economic model, a post-hoc analysis was carried out to determine the proportion of patients aged ≥18 years who moved from one BMI category to another and the proportion of patients aged <18 years who moved from one BMI Z-score category to another. Only data from setmelanotide 'responders' i.e., adult patients who achieved ≥10% weight loss (The response criterion of ≥10% weight loss over a 52 week period is greater than the 5% threshold noted in the FDA and EMA guidance regarding selection of primary endpoints for the development of medicinal products for weight management [82, 83]) or paediatric patients who achieved ≥0.2 reduction in BMI Z-score after 52 weeks of setmelanotide treatment) were used to inform on these transitions, as patients who do not meet such thresholds would not continue setmelanotide treatment in clinical practice. Of the 15 pivotal adult patients in Study RM-493-023, 7 were considered responders; of the 16 paediatric patients, 12 were considered responders.

Table 20 Pivotal ≥12-year-old Full Analysis Set, after last enrolled patient in the pivotal cohort has completed period 2 (W52)

Endpoint	Statistic	≥12yo FAS, pivotal (N = 31)
Primary endpoint: Patients who achieved ≥10% reduction in body weight from baseline after ~52 weeks of treatment compared to a historical untreated proportion of 10%.	Estimated %	32.3
	(95% CI)	(16.7, 51.4)
	p-value (one-sided)	0.0006
Key secondary endpoint 1: Mean percent change from active treatment baseline in body weight after ~52 weeks of treatment	Mean (SD)	-5.21 (7.895)
	(95% CI)	(-9.31, -2.49)
	p-value (one-sided)	0.0007
Endpoint	**Statistic**	**≥12yo FAS, pivotal, not cognitively impaired (N=16)**
Key secondary endpoint 2: Mean percent change from active treatment baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment for patients in the not cognitively impaired ≥12yo pivotal FAS population	Mean (SD)	-30.91 (24.733)
	(95% CI)	(-44.09, -17.73)
	p-value (one-sided)	<0.0001
Key secondary endpoint 3: Proportion of not cognitively impaired ≥12yo patients in the pivotal FAS population who achieve a ≥25% improvement from active treatment baseline in the weekly average of the daily hunger score, versus an historical untreated proportion of 10%.	Estimated %	62.5
	(95% CI)	(35.4, 84.8)
	p-value (one-sided)	<0.0001

Abbreviations: CI, Confidence interval; FAS, Full analysis set; SD, Standard deviation.

Table 21 Pivotal ≥12-year-old Placebo Controlled Analysis Set (not cognitively impaired for hunger-bases SE 2), after last patient completes the 14 Week Double Blind Placebo Controlled period (W14)*

Endpoint	Statistic	Setmelanotide	Placebo
Secondary endpoint 1: Body weight percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients in the pivotal ≥12yo PCAS population	N	16	17
	Mean (SD)	-2.41 (4.752)	-0.32 (2.253)
	Difference	-2.1	
	95% CI	-4.62, 0.42	
	p-value (one-sided)	0.0516	

Endpoint	Statistic	Setmelanotide	Placebo
Secondary endpoint 2: Weekly average daily hunger score percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients in the not cognitively impaired pivotal ≥12 years old PCAS population	N	7	10
	Mean (SD)	-33.38 (15.564)	-13.11
	Difference	-20.27	
	95% CI of difference	-35.72, -4.82	
	p-value (one-sided)	0.0051	

Abbreviations: CI, Confidence interval; FAS, Full analysis set; SD, Standard deviation.

*Differences to placebo after 14 weeks do not impact the health economic analysis. The health economic analysis is based on efficacy at 52 weeks of therapy.

The primary, secondary and exploratory efficacy endpoints in RM-493-023 study are presented in Appendix B. The following sections present the post-hoc analysis used to inform the economic model (response used in the model). For the other endpoints, the results are presented per adults and paediatric to reflect the populations relevant for this assessment.

6.1.4.1 Proportion of pivotal patients aged ≥12 years who achieved a ≥10% reduction in body weight after 52 weeks of setmelanotide treatment

The primary endpoint comprised the proportion of pivotal patients (BBS and AS) aged ≥12 years in the FAS population who achieved a clinically meaningful reduction in body weight (≥10%) from active-treatment baseline after ~52 weeks of setmelanotide treatment. The estimated proportion (32.3%) of pivotal patients ≥12 years of age with BBS or AS who achieved a ≥10% reduction in body weight from the active-treatment baseline was statistically significant (p=0.0006) compared with a historical control rate of 10%; the study, therefore, met its primary efficacy endpoint [40]. Despite the fact that the primary endpoint captures the proportion of patients with a weight change ≥10% vs. baseline, the true value of setmelanotide lies in the difference between the weight reduction achieved with treatment and the weight that would have been gained had treatment not been

initiated. See further details on how the setmelanotide treatment effect was modelled for adult patients in Section 8.1.1.

Table 22 Proportion of BBS or AS patients aged ≥12 years who achieved a ≥10% reduction in body weight (Study RM-493-023, pivotal BBS and AS patient FAS)

	BBS and AS patients aged ≥12 years
N	31
Proportion, % (95% CI) p-value	32.3 (16.7, 51.4) 0.0006

Source: [40].

Analysis of the primary endpoint for BBS patients is presented in Table 23. Approximately [redacted] of BBS patients aged ≥12 years achieved a ≥10% reduction in body weight from the active-treatment baseline after ~52 weeks of setmelanotide along with 47% of patients aged ≥18 years.

Table 23 Proportion of BBS patients aged ≥12 years or ≥18 years with a 10% reduction in body weight (Study RM-493-023, pivotal patient FAS)

	BBS patients aged ≥12 years	BBS patients aged ≥18 years
N	28	15
Proportion, % (95% CI) p-value	[redacted]	46.7 (21.3, 73.4) 0.0003

Source: [40].

6.1.4.2 Change in body weight after 52 weeks of setmelanotide treatment

In pivotal patients aged ≥18 years, 52 weeks of setmelanotide treatment resulted in a significant reduction from active-treatment baseline in body weight compared with the reference value of 0% reduction (Table 24). The reduction in body weight over time is presented in Figure 7. Mean weight loss at Week 52 was -9.42 kg and mean percent change was -7.57%; a change of ≥5% is considered clinically meaningful.

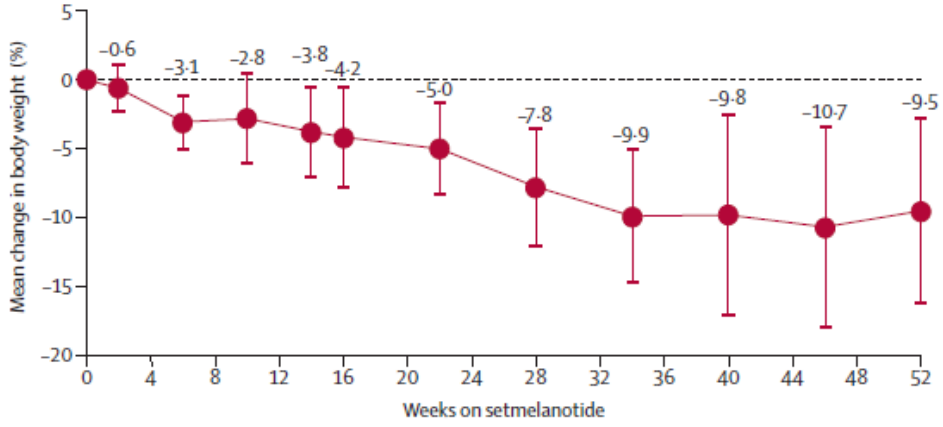
Table 24 Change in body weight from baseline after 52 weeks of setmelanotide treatment in patients aged ≥18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic[1]	Result
Body weight at ATB (kg)	N	15
	Mean (SD)	128.43 (16.591)
	Median (range)	129.83 (105.2, 167.3)
Change after 52 weeks (kg)	N	15
	Mean (SD)	-9.42 (9.393)
	Median (range)	-8.13 (-27.0, 7.5)
	95% CI	-14.63, -4.22
	p-value	0.0008

Percent change after 52 weeks	N	15
	Mean (SD)	-7.57 (7.139)
	Median (range)	-6.16 (-18.6, 4.5)
	95% CI	-11.52, -3.62
	p-value	0.0005

[1] 95% CI and p-value based on Rubin's rule. p-value is one-sided and compared with alpha = 0.025. Source: [40].

Figure 7. Mean change in body weight from active-treatment baseline in patients aged ≥18 years (Study RM-493-023, pivotal patient FAS)



6.1.4.3 Change in body weight after 14 weeks of setmelanotide treatment compared with placebo

In all patients (pivotal and supplemental) aged ≥18 years, treatment with setmelanotide over 14 weeks resulted in significantly greater reduction in body weight from the placebo-controlled period baseline compared with placebo-treated patients (Table 25). Patients receiving setmelanotide had a mean reduction in body weight of [redacted] kg, whilst mean weight for the placebo group remained virtually unchanged from baseline [redacted] over the 14-week treatment period. Change in body weight after 14 weeks of setmelanotide treatment is presented in **Figure 8**.

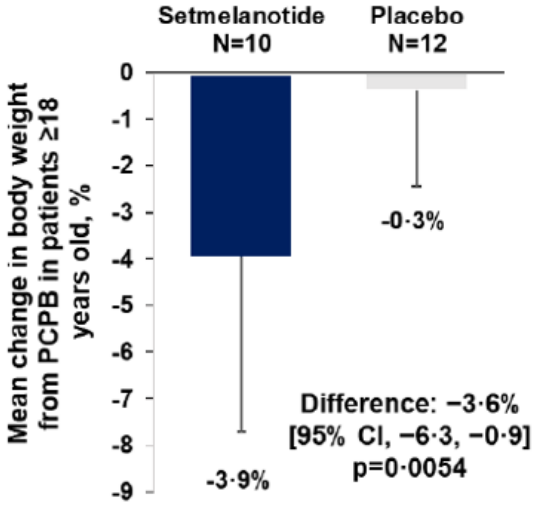
Table 25 Change in body weight from baseline after 14 weeks of setmelanotide treatment in patients aged ≥18 years (Study RM-493-023, all patient PCAS)

Parameter	Statistic	Setmelanotide (N = 10)	Placebo (N = 12)
Body weight at PCPB (kg)	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
Change after 14 weeks (kg)	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	

Percent change after 14 weeks (kg)	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	

Abbreviations: CI, Confidence interval; PCS placebo-controlled analysis set; PCPB, placebo-controlled period baseline; SD, Standard deviation. Source: [40].

Figure 8 Change in body weight after 14 weeks of setmelanotide treatment in patients aged ≥18 years (Study RM-493-023, all patient PCAS)



6.1.4.4 Change in BMI Z-score after 52 weeks of setmelanotide treatment in patients <18 years

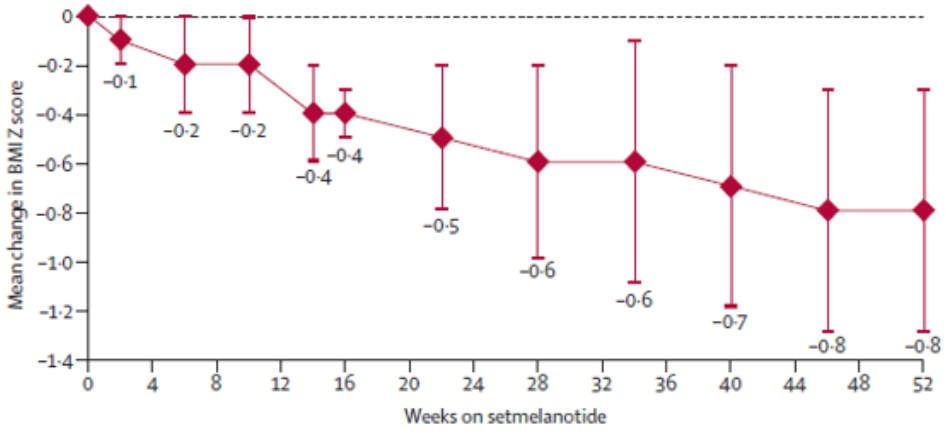
In pivotal patients aged <18 years, 52 weeks of setmelanotide treatment resulted in a significantly greater reduction in mean change in BMI Z-score from active-treatment baseline as compared with a reference value of 0% reduction (Table 26). Mean change over time is presented in Figure 9. The mean change in BMI Z-score at Week 52 was -0.75 points. Literature data suggest that a reduction in BMI Z-score of at least -0.15 to -0.20 is clinically meaningful in paediatric patients.

Table 26. Change in BMI Z-score from baseline after 52 weeks of setmelanotide treatment in patients aged <18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic	Result
BMI Z-score at ATB	N	16
	Mean (SD)	3.74 (1.339)
	Median (range)	3.54 (1.8, 7.1)
Change after 52 weeks	N	14
	Mean (SD)	-0.75 (0.458)
	Median (range)	-0.77 (-1.9, -0.2)
	95% CI	-1.02, -0.49

	p-value	<0.0001

Figure 9 Mean change in BMI Z-score from active treatment baseline in BBS patients <18 years (Study RM-493-023, pivotal patient FAS)



Overall, 85.7% of patients aged <18 years achieved at least a 0.2-point reduction from baseline in BMI Z-score with setmelanotide treatment and 71.4% achieved at least a 0.3-point reduction (Table 27).

Table 27. Proportion of patients aged <18 years achieving a BMI Z-score reduction from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic	Result
≥0.2 change from ATB (n=14)	n (%)	12 (85.7)
	(95% CI)	(57.2, 98.2)
≥0.3 change from ATB (n=14)	n (%)	10 (71.4)
	(95% CI)	(41.9, 91.6)

See further details on how the setmelanotide treatment effect was modelled for paediatric patients in Section 8.1.1.

6.1.4.5 Change in BMI 95th percentile after 52 weeks of setmelanotide treatment in patients <18 years

In pivotal patients aged <18 years, 52 weeks of setmelanotide treatment resulted in a statistically significant mean reduction in the BMI 95th percentile score of -17.30 from active-treatment baseline (Table 28); this shifted the mean from Class 3 (≥140% of the 95th percentile) to Class 2 (120% to <140% of the 95th percentile) obesity based on Kumar 2019.

Table 28 Change in BMI 95th percentile from baseline after 52 weeks of setmelanotide treatment in patients aged <18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic	Result

Percentage of the BMI 95th percentile score at ATB	N	16
	Mean (SD)	144.47 (35.806)
	Median (range)	139.24 (94.9, 239.8)
Percentage of the BMI 95th percentile score at Week 52	N	14
	Mean (SD)	126.82 (37.059)
	Median (range)	120.24 (74.2, 216.7)
Change after 52 weeks	N	14
	Mean (SD)	-17.30 (7.674)
	Median (range)	19.45 (-28.7, -6.4)
	95% CI	-21.73, -12.87
	p-value	<0.0001

6.1.4.6 Change in BMI after 52 weeks of setmelanotide treatment

In pivotal patients aged ≥18 years, 52 weeks of setmelanotide treatment resulted in a statistically significant mean BMI change from active-treatment baseline of -4.22 kg/m^2 and a mean percent change of -9.09%. In pivotal patients aged <18 years, 52 weeks of setmelanotide treatment resulted in a statistically significant mean reduction in BMI from active-treatment baseline of -3.36 kg/m^2 and -9.50% (Table 29).

Table 29 Change in BMI from baseline after 52 weeks of setmelanotide treatment in patients aged <18 years or aged ≥18 years (Study RM-493-023, pivotal patient FAS)

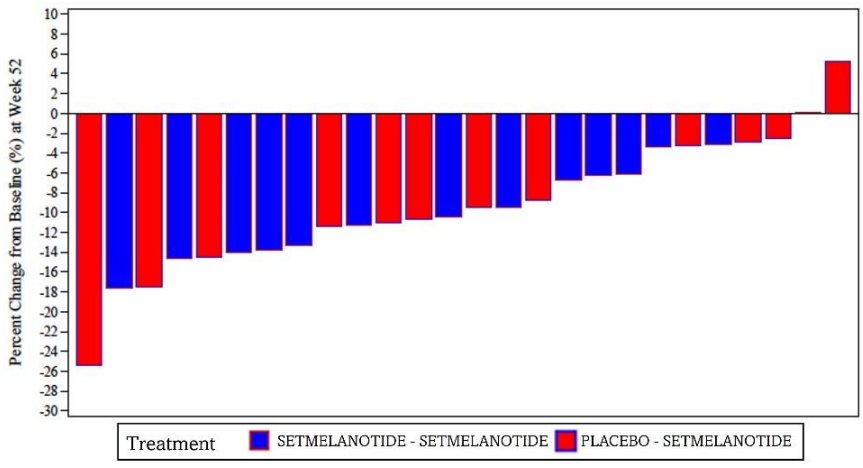
Parameter	Statistic [1]	<18 years	≥18 years
BMI at ATB (kg/m^2)	N	16	15
	Mean (SD)	37.44 (9.439)	46.35 (5.857)
	Median (range)	36.62 (24.4, 61.3)	46.22 (39.2, 57.8)
Change after 52 weeks (kg/m^2)	N	14	12
	Mean (SD)	-3.36 (2.070)	-4.22 (3.335)
	Median (range)	-3.56 (-6.9, 0.0)	-4.62 (-8.4, 3.0)

	95% CI	-4.55, -2.16	-6.34, -2.10
	p-value	<0.0001	0.0005
Percent change after 52 weeks	N	14	12
	Mean (SD)	-9.50 (6.440)	-9.09 (6.760)
	Median (range)	-9.99 (-25.4, 0.1)	-9.90 (-17.6, 5.3)
	95% CI	-13.22, -5.78	-13.39, -4.80
	p-value	<0.0001	0.0003

[1] 95% CI and p-value based on Rubin's rule.

Figure 10 shows individual patient data of percent change from baseline in BMI. All but 2 pivotal patients treated with setmelanotide for 52 weeks showed reductions from active-treatment baseline in percent change in BMI. All patients included in the figure (n=26) received setmelanotide over 52 weeks. Six patients in the pivotal cohort discontinued and therefore did not receive 52 weeks of setmelanotide, and are not represented in the Figure.

Figure 10 Waterfall plot of percent change in BMI from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal patient FAS)



7. Comparative analyses of efficacy

The head-to-head study RM-493-023 was included as evidence of efficacy, the following section describing the comparative analysis was considered not relevant to this application and chapter 7 have been omitted, as per the DMC guideline. However, as requested in the template, Table 32 below is filled in for comparative efficacy for setmelanotide and placebo in the placebo-controlled period of 14 eeks in RM-493-023. For the 52-week efficacy results see section 6.1.4.

7.1.1 Differences in definitions of outcomes between studies

No applicable.

7.1.2 Method of synthesis

Not applicable. Results from the comparative analysis

Table 30. Results from the comparative analysis of setmelanotide vs. placebo for genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above

Outcome measure	Setmelanotide	Placebo	Result
14 weeks placebo-controlled period			
Secondary endpoint: Weekly average percentage change in most/worst hunger over 24 hours from baseline after 14 weeks of setmelanotide treatment in patients aged ≥12 years without cognitive impairment (Study RM 493 023, all patient PCAS)	N=6 Mean (SD): -30.09 (20.264) Median (range): -29.69 (-52.4, -6.3) 95% CI: -51.35, -8.82	N=12 Mean (SD): -15.71 (14.513) Median (range): -12.93 (-36.7, -1.5) 95% CI: -24.93, -6.48	Difference (95% CI): -14.38 (-31.90, 3.14) p-value: 0.0505
Secondary endpoint: Percent change (kg) in body weight from baseline after 14 weeks of setmelanotide treatment in patients aged ≥18 years (Study RM-493-023, all patient PCAS)	N=10 Mean (SD): -3.93 (3.788) Median (range): -2.94 (-13.2, -0.9)	N=12 Mean (SD): -0.34 (2.106) Median (range): 0.01 (-4.9, -3.2)	Difference (95% CI): -3.59 (-6.26, -0.93) p-value: 0.0054
Exploratory endpoint: Percentage change in BMI after 14 weeks of setmelanotide treatment for	N= 26 Mean (SD): -3.95 (4.318)	N=24 Mean (SD): -0.03 (2.431)	Difference (95% CI): -3.92 (-5.94, -1.91)

Outcome measure	Setmelanotide	Placebo	Result
patients with BBS (Study RM-493-023, all patient PCAS)	Median (range): -2.94 (-13.2, 3.1) 95% CI: -5.69, -2.2	Median (range): -0.04 (-4.9, 4.5) 95% CI: -1.05, 1.00	p-value: 0.0001

7.1.3 Efficacy – results per [outcome measure]

Not applicable, see section 6.1.4

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Patient characteristics

Patient characteristics for the model population were informed by baseline data from Study RM-493-023 (as have been presented in section 6.1.2). This included the initial patient distribution for BMI/BMI Z-score categories and sex. A hyperphagia severity parameter, stratified to low, moderate and high severity, served as an intermediate outcome that influenced patient quality-of-life score.

8.1.2 Setmelanotide treatment effect

Setmelanotide treatment effect comprises improvements in BMI/BMI Z-score and hyperphagia score. The modelled treatment effect on BMI/BMI Z-score was quantified as the average number of BMI/BMI Z-score categories that treatment responders improved by, using 52-week clinical trial results [40], compared with baseline BMI/BMI Z-score categories.

The assumption that all paediatric patients who respond to treatment with setmelanotide would achieve a reduction in BMI-Z/BMI class of 2 levels is based on the following considerations:

- It is key to emphasize the limitations of the lower and upper BMI-Z score class ranges, which are less sensitive to changes in BMI-Z. The BMI-Z score classes defined in the study were <1, 1 to <2, 2 to <2.5, 2.5 to <3, 3 to <3.5, 3.5 to <4, and >4. At the extremities, the range in BMI-Z is greater than the 0.5 ranges in the middle classes.
- There were four patients with baseline BMI-Z >4 (some much greater than 4), and one patient with baseline BMI-Z 1-2. If classes at the extremities had a range of 0.5 (as the classes between 2 and 4), then for patients with BMI-Z >4, one would have experienced a 3-class reduction in BMI-Z, two patients would have

experienced a 2-class reduction in BMI-Z, and one patient would have experienced a 0-class reduction. The patient with baseline BMI-Z 1-2 lost 1.91 points in BMI-Z and was no longer obese, which would correspond to a 4-class reduction. Based on classes being defined by increments in 0.5 BMI-Z scores, the mean shift in classes is 1.92, which is in line with this approach (see Table 31 below).

- The mean difference in BMI-Z score from baseline is 0.87, which corresponds to a 1.75 class change (0.87/0.5), closer to a 2-class shift (see Table 31 below). Thus, a 2-class change reflects the impact on BMI-Z experienced by patients.
- The choice of the class ranges was based on the availability of published data to estimate the risk of comorbidities and the disutility of obesity.
- Furthermore, in clinical practice, which will involve multidisciplinary care including the management of obesity (incl. active management of diet and exercise), the effect of hyperphagia reduction on BMI-Z in patients treated with setmelanotide is anticipated to be greater than that observed in the clinical trial, in which changes to diet and exercise were not allowed. Additionally, the assumptions for hyperphagia transitions used in the base case analysis are conservative, as no transitions to a no hyperphagia state have been assumed.

Table 31. BMI Z-score shift data for individual BBS patients aged <18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients), considering BMI-Z class intervals of 0.5

Table 32 and Table 33 show the modelled treatment effect of setmelanotide on the BMI/BMI Z-score when paediatric (base case analysis) and adult treatment initiation are considered, respectively.

Table 32. Modelled treatment effect of setmelanotide on the BMI Z-score category (paediatric treatment initiation).

Response rate*	Decrease in BMI Z-score category for responders**	Source

85.7%	[redacted]	Based on Clinical trial NCT03746522 (Study RM-493-023) data at 52-week time point [40]

BMI: Body mass index *A paediatric treatment responder was defined as a patient aged <18 years at baseline who achieved a BMI Z-score decrease of ≥0.2 from baseline to the 52-week endpoint based on clinical trial results. The response rate using this definition was 85.7% ** In the model, the treatment effect on BMI is assumed to not occur until the end of the first year of treatment.

Table 33. Modelled treatment effect of setmelanotide on the BMI category (Adult treatment initiation).

Response rate*	Decrease in BMI category for responders**	Source
46.7%	[redacted]	Based on Clinical trial NCT03746522 (Study RM-493-023) data at 52-week time point [40]

BMI: Body mass index *An adult treatment responder was defined as a patient aged >18 years at baseline who achieved a ≥10% weight loss from baseline to the 52-week endpoint based on clinical trial results. The response rate using this definition was 46.7% ** In the model, the treatment effect on BMI is assumed to not occur until the end of the first year of treatment.

BMI/BMI Z-score was assumed to be stable after responding to treatment. Consequently, setmelanotide treatment responders who do not discontinue treatment remain in the same BMI/BMI Z-score category (i.e., the one the transitioned to after the first year of treatment) for the rest of their lifetime. This assumption was based on Pomeroy, J. et al. (2021) [4], who showed that BMI Z-score for BBS patients peaked at 2 to 5 years of age and subsequently decreased or stabilized. Patients with response to setmelanotide who discontinue treatment are assumed to revert to their baseline BMI/BMI Z-score category immediately and remain in that category for the rest of their lifetime, with no tapering of treatment effect. No long-term data are available to inform on the effect of treatment waning and it was assumed to be negligible.

With regards to the effect of setmelanotide on hyperphagia, it is important to consider that validated methods of measuring hyperphagia in BBS patients do not exist. Consequently, hyperphagia was not measured in the pivotal trial and it was not possible to collect direct evidence of the impact of setmelanotide treatment on hyperphagia. As a result, assumptions were made based on the link between hyperphagia and weight. Hyperphagia is considered the underlying cause of obesity in BBS patients. This means that it must be reduced significantly for patients to experience the level of weight loss seen in clinical trials.

Consequently, the effect of setmelanotide on hyperphagia reflects that seen for BMI/BMI Z-score. It could be expected that responding patients would have a significantly reduced hyperphagia level, as this would be necessary to drive a clinically meaningful improvement in their BMI/BMI Z-score. Therefore, it is assumed that setmelanotide treatment responders transition from the baseline state of severe hyperphagia to a state of mild

hyperphagia. A clinically meaningful improvement in BMI/BMI Z-score is unlikely to occur through a shift to moderate hyperphagia, especially as lifestyle modifications were not allowed in the study.

As with the BMI/BMI Z-score category, setmelanotide treatment responders who do not discontinue treatment remain with the same hyperphagia state for the rest of their lifetime (i.e., mild hyperphagia). Patients with response to setmelanotide who discontinue treatment are also assumed to revert to their baseline hyperphagia state (i.e., severe hyperphagia) immediately and remain in that state for the rest of their lifetime, with no tapering of treatment effect.

Finally, patients who do not respond to setmelanotide discontinue treatment and do not experience treatment effect. In the base case analysis, setmelanotide non-responders are assumed to discontinue treatment after 14 weeks. Hunger levels fall rapidly on initiation of setmelanotide treatment. It is therefore assumed that clinicians can accurately identify patient response at 14 weeks based on changes in hyperphagia and other clinical parameters. Treatment discontinuation after 1 year for setmelanotide non-responders is explored in a scenario analysis.

8.1.3 Discontinuation rate

Setmelanotide is well tolerated and discontinuation rates for patients responding to treatment are assumed to be very low. Consequently, a discontinuation rate of 1% per year is used. This rate is considered reasonable as discontinuation due to adverse events or lack of efficacy occurs soon after treatment initiation (i.e., after 14 weeks of treatment with setmelanotide in the base case analysis) and it therefore should not be considered as contributor to the yearly discontinuation. The RM-493-023 clearly showed that response in hunger was seen after 10-12 weeks, and all early discontinuations are assumed to be accounted for before model entry. Patients who discontinue treatment with setmelanotide receive BSC alone.

8.1.4 Extrapolation of efficacy data

Not applicable.

8.1.5 Calculation of transition probabilities

Not applicable.

8.2 Presentation of efficacy data from additional documentation

8.2.1 Best supportive care treatment effect

Patients receiving only BSC (lifestyle, dietary interventions, and behavioural therapy) are assumed to have no treatment effect in terms of BMI/BMI Z-score or hyperphagia state. This is because management with diet and exercise has no impact on hyperphagia and

consequently, it is unlikely to have a meaningful effect on obesity for this population. Additionally, Danish clinical experts confirmed that patients with BBS and obesity do not experience spontaneous significant reductions in BMI Z-score or BMI over time [37, 38]. Therefore, these patients remain in their baseline BMI/BMI Z-score category and their baseline hyperphagia state (i.e., severe hyperphagia) their whole lifetime.

This assumption is also supported by data from the CRIBBS database (Clinical Registry Investigating BBS Database), which is a large registry of BBS patients treated in expert centres in the US and in other countries. The weight and hunger of the CRIBBS population is closely monitored by parents and caregivers. While on BSC, some of these patients are losing weight while others are gaining it. Clinical experts also confirmed that while some patients may lose some weight, more patients are actually gaining weight with worsening of obesity over time. Consequently, as a conservative proxy, a constant BMI-Z or BMI level across the model time horizon was assumed for patients receiving BSC.

8.2.2 Mortality

No mortality data specific to the BBS population with obesity was identified in the SLR. As a consequence, mortality data was derived from an innovative process by which a comprehensive model was built and used to estimate the effect of early onset of obesity on comorbidities and mortality risk (see Appendix K).

The Early Onset Obesity Model described in Appendix K was used to derive mortality risks by age and BMI/BMI-Z score category. The resulting mortality risks increased with age and BMI/BMI-Z score category. The full description on how these mortality risks were obtained is presented in Appendix K of the application.

As it is described in section 8.1.2, paediatric patients responding to treatment with setmelanotide experience a reduction of 2 levels in their BMI-Z score category. However, patients receiving BSC alone remain in the same BMI/BMI-Z score category for their entire lifetime. Consequently, patients responding to setmelanotide have, on average, a lower BMI/BMI-Z score category than patients receiving BSC alone.

As described before, the mortality risk derived from the Early Onset Obesity Model increases with age and BMI/BMI-Z score category. Therefore, patients responding to setmelanotide have, on average, a lower mortality risk than patients receiving BSC alone.

8.3 Modelling effects of subsequent treatments

No subsequent lines of treatment are modelled. Patients who discontinue treatment with setmelanotide receive BSC alone for the rest of their lifetime. Patients receiving BSC alone from model start keep receiving BSC alone for the rest of their lifetime. The modelled efficacy for the intervention and comparator is described above in section 8.1.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Table 34 shows the modelled average treatment length and the average time spent in each BMI Z-score/BMI category by treatment arm.

Table 34 Overview of modelled average treatment length and average time spent in each BMI Z-score/BMI category, undiscounted and not adjusted for half cycle correction (paediatric treatment initiation)

Treatment	Modelled average treatment length (years)	Average time spent in each BMI Z-score/BMI category (years)						
		0.0-1.0/ 20-25	1.0-2.0/ 25-30	2.0-2.5/ 30-35	2.5-3.0/ 35-40	3.0-3.5/ 40-45	3.5-4.0/ 45-50	≥ 4.0/ ≥ 50
Setmelanotide + BSC*	39.061	5.732	5.285	12.907	11.122	3.453	0.188	0.375
BSC	53.033	0.000	4.403	10.444	9.318	13.745	6.502	8.622
Patients who discontinue treatment with setmelanotide and start to receive BSC alone	18.759	0.000	0.621	4.085	3.147	5.672	3.543	1.692

*Patients who discontinue treatment with setmelanotide and start to receive BSC alone were not considered for this calculation.

BMI: Body mass index; BSC: Best supportive care

9. Safety

9.1 Safety data from the clinical documentation

Safety results are presented for the safety analysis set (SAS) population, defined as all patients who received at least 1 study drug dose [40]. Furthermore, the intensity of all adverse events (AE) including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions were graded per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 [40].

Table 35 presents the summary of adverse events at 14 weeks (double-blind period) for the SAS population, whilst **Table 36** presents the summary of AEs at 52 weeks (end of the Study RM-493-023 study, designated as full study period). The majority of patients (96.2%)

experienced at least 1 treatment emergent adverse event (TEAE) during the double-blind period of the study and all patients experienced at least 1 TEAE during the full study. Overall, the majority of TEAEs were mild or moderate in severity. A total of 3 serious adverse events (SAE) were reported during the full study, one of which was considered by the Investigator to be treatment-related while patient was receiving placebo[40].

Table 35 Overview of safety events (14 weeks)

	Setmelanotide (N=27) [40]	Placebo (N=25) [40]	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	26 (96.3)	24 (96.0)	NA
Number of serious adverse events*, n	NA	NA	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	1 (3.7)	2 (8.0)	NA
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade 3 events§, n (%)	NA	NA	NA
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NA	NA	NA
Number and proportion of patients who had a dose reduction, n (%)	NA	NA	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NA	NA	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	2 (7.4)	3 (12.0)	NA

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

§ CTCAE v. 5.0 must be used if available.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NA, Not applicable.

Table 36 Overview of safety events (52 weeks)

	Setmelanotide (N=52) [40]
Number of adverse events, n	NA
Number and proportion of patients with ≥1 adverse events, n (%)	52 (100.0)
Number of serious adverse events*, n	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	3 (5.8)
Number of CTCAE grade ≥ 3 events, n	NA
Number and proportion of patients with ≥ 1 CTCAE grade 3 events§, n (%)	3 (5.8)
Number of adverse reactions, n	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NA
Number and proportion of patients who had a dose reduction, n (%)	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	6 (11.5)

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

§ CTCAE v. 5.0 must be used if available. Grade 3 events were classified as severe events in the trial.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NA, Not applicable.

Source: [40].

All SAEs occurring during the double-blind study period (14 weeks) are summarized by treatment group in **Table 38** by MedDRA system organ class and preferred term for the SAS population. Overall, 3 (5.8%) patients experienced SAEs during the double-blind study period, 2 of whom were receiving placebo. One SAE was considered by the Investigator to be related to study drug (anaphylactic reaction in a placebo patient). The 1 SAE (anaemia) reported in a patient receiving setmelanotide was reported as being due to gynaecological bleeding and was judged by the Investigator to be most likely due to initiation of oral contraceptives. No SAEs were reported in >1 patient [40].

Table 37 Serious adverse events (14 weeks)

Adverse events	Intervention (N=27)		Comparator (N=25)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events

Adverse events	Intervention (N=27)		Comparator (N=25)	
Blood and lymphatic system disorders, n (%)	1 (3.7)	NA	0	NA
Anaemia	1 (3.7)	NA	0	NA
Eye disorders, n (%)	0	NA	1 (4.0)	NA
Blindness	0	NA	1 (4.0)	NA
Immune system disorders, n (%)	0	NA	1 (4.0)	NA
Anaphylactic reaction	0	NA	1 (4.0)	NA

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

Note: this table summarises all SAEs that occurred as there was no data analysis for SAEs with a frequency of ≥ 5% recorded in the study.

Source: [40].

All SAEs occurring during the full study (52 weeks) are summarized by treatment group in **Table 38** by MedDRA system organ class and preferred term for the SA population. Overall, 3 (5.8%) patients experienced a total of 5 SAEs during the full study. After the double blind treatment period, 1 patient (who experienced complete vision loss [blindness] during the double-blind period), had 2 events of suicidal ideation (verbalized suicidal thought [non-action]). The patient had no previous history of depression, and the events were judged by the Investigator to be unlikely related to study medication and attributable to concomitant disease [40].

Table 38 Serious adverse events (52 weeks)

Adverse events	Total (N=52)	
	Number of patients with adverse events	Number of adverse events
Blood and lymphatic system disorders, n (%)	1 (1.9)	NA
Anaemia	1 (1.9)	NA

Eye disorders, n (%)	1 (1.9)	NA
Blindness	1 (1.9)	NA
Immune system disorders, n (%)	1 (1.9)	NA
Anaphylactic reaction	1 (1.9)	NA
Psychiatric disorders, n (%)	1 (1.9)	NA
Suicidal ideation	1 (1.9)	NA

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

Note: this table summarises all SAEs that occurred as there was no data analysis for SAEs with a frequency of ≥ 5% recorded in the study.

Source: [40].

AEs that are included in the health economic model are shown in Table 39. Included AE's only effect the utility of not the cost in the analysis. The main TEAEs experienced by patients receiving setmelanotide during study RM-493-023 were skin hyperpigmentation (59.1%), injection site erythema (45.5%), nausea (22.7%) and vomiting (27.3%) [40] However, the impact of skin hyperpigmentation is highly variable. According to Danish clinical experts, for some patients, skin hyperpigmentation could be welcomed while for others it may be less welcomed [37, 38]. Consequently, skin hyperpigmentation was excluded from the analysis. No treatment-related adverse events are included for the BSC arm, as BSC consists of lifestyle, dietary interventions, and behavioural therapy.

The event rate for nausea/vomiting in the model was calculated as the average of the observed rate of both events in the double-blind placebo-controlled period of study RM-493-023. The event rate for injection site reaction in the model was assumed to be equivalent to the observed rate of injection site erythema in the double-blind placebo-controlled period of study RM-493-023.

Table 39 Adverse events used in the health economic model

Adverse events	Setmelanotide + BSC	BSC		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Nausea/vomiting	Nausea: 5 (22.7%)	-		See above

	Vomiting: 6 (27.3%) Average: 25%		Double-blind placebo-controlled period of study RM-493-023 [40]
Injection site reaction	10 (45.5%)	-	

BSC: Best supportive care

Refer to Appendix E for further details on safety data.

9.2 Safety data from external literature applied in the health economic model

Not applicable. For the external literature used for disutilities for AE's see section 5.2

10. Documentation of health-related quality of life (HRQoL)

In this submission health effects were captured as utility values and were expressed in quality-adjusted life years (QALYs), as recommended by the DMC. HRQoL was measured in RM-493-023 using IWQOL Lite, PedsQL and Short Form (SF)-36 (or SF-10) Health Survey. HRQoL was also measured in RM-493-023 using EQ-5D after 52 weeks of treatment with setmelanotide.

In RM-493-023 participants with BBS treated with setmelanotide experienced and maintained substantial improvements. in measures of quality of life at 1 year. After 52 weeks of treatment, 85% of participants reported clinically meaningful improvements in or preserved their nonimpaired HRQoL; 75% of patients with impaired HRQoL at baseline experienced clinically meaningful improvement, and among patients with no impairment HRQoL at baseline all patients improved or preserved their non impaired HRQoL status:

- Among adult participants with BBS (≥18yo) who reported baseline and 52-week measurements, the majority (8/11) had impaired (note: Impairment was defined based on total score on IWQOL-Lite, with definitions for severe (<71.8), moderate (71.9–79.4), mild (79.5–87.0), or no (87.1–94.6). There were 63% (5/8) participants who experienced a clinically meaningful improvement after 52 weeks of setmelanotide therapy. The minimal clinically important difference is defined as > 7.7 improvement in total score on the IWQOL-Lite. Among adults without HRQoL impairment (3/11), all improved or preserved ((clinically meaningful improvement n=1, preserved n=2) their non impaired quality of life, Table 82. Improvements were observed across all domains including public-distress, self-esteem, sexual life and work.
- Among paediatric participants with BBS (<18yo), 4 of 9 had impaired HRQoL on the PedsQL at baseline and all experienced clinically meaningful improvements on their mean PedsQL score after 52 weeks of treatment with setmelanotide. Among participants with no impairment of HRQoL at baseline (n=5), all

preserved or improved their nonimpaired HRQoL status (clinically meaningful improvement: n=2; preserved HRQoL: n=3), Table 83. In line with published literature, the MCID was defined as >4.44 improvement in total score. (See further Appendix F).

As EQ-5D was not deemed suitable to capture the impact of hyperphagia (the biggest driver of quality of life in BBS patients) these data were, therefore, considered inappropriate for use in the cost-effectiveness analysis. In addition, no HRQoL data suitable for inclusion in the health economic analysis were identified by the SLR (see Appendix I).

Therefore, HSUV were derived from a vignette study and from targeted searches. The HRQoL results from the clinical trial are presented in Appendix F. In the cost effectiveness analysis, the TTO from a vignette study was used to estimate the impact on hyperphagia. This resulted in utility multipliers indicating a greater severity of hyperphagia with lower utility multiplier. Literature-based EQ-5D values were used to estimate HRQoL for BBS patients with obesity and the impact of obesity-related comorbidities. Standard gamble (SG) adjusted utility scores was used to estimate the impact of adverse events on QoL. The utility value in each model cycle is calculated by applying a hyperphagia-severity utility-multiplier to utility values by BMI/BMI Z-score category and age, applying a QALY multiplier for non-obesity-related BBS symptoms, and then applying comorbidity disutilities by BMI/BMI Z-score category and adverse events (only the first model cycle). Table 40 shows an overview of the included HRQoL instruments used for deriving HSUV.

Table 40 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
TTO	[68]	Vignette-based study to estimate the impact of hyperphagia on QoL.
EQ-5D-Y	[69, 84]	To estimate the utility values by BMI Z-score category for the paediatric patient population.
EQ-5D	RM-493-023 and [70]	To estimate the utility values by BMI category and age group for BBS patients aged ≥18 years.
EQ-5D-3L	[72] and [71]	To estimate the impact of obesity-related comorbidities on QoL.
Standard gamble (SG) adjusted* utility scores	[74, 75]	To estimate the impact of adverse events on QoL.

* SG adjusted scores on a scale ranging from 0 (death) to 1 (perfect health). Adjusted scores were derived through a linear transformation of raw scores using the following formula: SG adj = (SG raw x (1 – worst)) + worst

BBS: Bardet-Biedl syndrome; BMI: Body mass index; EQ-5D: EuroQol 5 Dimension; QoL: Quality of life; TTO: Time trade-off

10.1 Presentation of the health-related quality of life

HRQoL instruments included from RM-493-023 were not informing clinical effectiveness and health state utilities were obtained from other sources, and multiple instruments, and is therefore not described below, refer to section 10.3 below.

10.1.1 Study design and measuring instrument not applicable

Not applicable, see section 10.3

10.1.2 Data collection not applicable

Not applicable, see section 10.3

Table 41 Pattern of missing data and completion not applicable

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	N/A	N/A	N/A	N/A
Etc.	N/A	N/A	N/A	N/A

10.1.3 HRQoL results not applicable

Not applicable, see section 10.3

Table 42 HRQoL [instrument 1] summary statistics N/A

	Intervention		Comparator		Intervention vs. comparator
N/A	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	N/A		N		

10.2 Health state utility values (HSUVs) used in the health economic model

The HSUV forming the basis health economic analysis were derived from alternative sources, see further section 10.3.

10.2.1 HSUV calculation

In this application Danish preference weights have not been used. According to the DMC methods guide section 7.1.3 use of EQ-5D-5L can be omitted when it is not appropriate.

While EQ-5D is a valid instrument for calculating HRQoL in patients with obesity, it is unlikely to be sensitive to the severe hyperphagia that patients with BBS and obesity experience. Previous HRQoL studies reflect the general obese population and do not characterize the impact of hyperphagia, independent of obesity, on HRQoL. In the case of BBS patients, hyperphagia is a serious condition that has substantial effect on HRQoL. However, none of the EQ-5D dimensions captures hyperphagia. Hyperphagia may be considered a sensory deprivation condition, as it is characterized by impaired satiety whereby patients constantly feel hungry, even after eating. EQ-5D has been shown to not be sensitive to sensory deprivation conditions [85].

In addition, certain disease populations may adapt to their condition. BBS is a genetic disease and hyperphagia is experienced from birth. Given the early manifestation of hyperphagia in patients with BBS, affected adult patients may be unable to fully recognize the severity of their hunger as it is their 'normal' state to which they have adapted to from an early age. Further, individuals with hyperphagia due to BBS may have developed coping strategies due to the early onset of symptoms, which could influence the ability of quality-of-life measures to detect health changes. Accordingly, EQ-5D may not be sensitive enough to detect the magnitude of quality-of-life impact in patients with hyperphagia and obesity due to BBS. This is likely to mean that the quality-of-life benefits of interventions to address hyperphagia will be similarly underestimated.

The QoL values reported in study RM-493-023 indicate that patients with BBS have a QoL slightly below population norms. This seems unreasonable in a disease whose manifestations can include obesity, hyperphagia, vision loss, undeveloped genitals, and kidney failure. It is therefore apparent that these QoL scores do not accurately reflect the lived experience of BBS patients.

In summary, It has previously been suggested that EQ-5D does not fully capture the impact of sensory impairment on QoL [85], and this may also be true for hyperphagia. This may explain the differences between how patients describe the impact of their condition and the EQ-5D values reported in the study. Additionally, patients with hyperphagia and BBS have experienced hyperphagia since infancy. Consequently, they are probably unaware of what it feels like to not be burdened by constant feelings of hunger and food-seeking behaviours or the impact these feelings have on their daily lives. It is also logical to assume that patients who have never experienced good health are inclined to find their life more bearable than it might appear to a person without disability.

HSUVs have been age-adjusted according to section 7.3 of the methods guide.

10.2.1.1 Mapping

As the HRQoL data from clinical trials were not used in the cost-effectiveness model. The health-utility data for hyperphagia were estimated using the vignette study. HRQoL data for utility values by BMI Z-score in the paediatric population were mapped from PedsQL to EQ-5D using evidence from Riazi 2010 [69] and the mapping algorithm presented by Khan 2014 [84]. Data from the early to post-pubertal subgroup with BMI Z-score averages of 3.5 (obese) and 0.3 (healthy) were used to populate the model BMI Z-score 0.0 to <1.0 and 3.5 to <4.0 category utility values, respectively. These values were mapped from PedsQL to EQ-5D using the ordinary least squares regression mapping algorithm shown in Table 43, and linear extrapolation was used to calculate utility values for the remaining BMI Z-score categories [84].

Table 43 The ordinary least squares regression algorithm used to map BMI Z score category utility values

	Ordinary least squares 5 coefficient	Obese group (mean BMI Z-score of 3.5)	Healthy control group (mean BMI Z-score of 0.3)
Constant	-0.428496	1.0	1.0
Physical functioning	0.009127	70.9	82.9
Emotional functioning	0.006611	66.5	73.2
Social functioning	0.005705	77.3	88.9
School functioning	0.006011	65.5	73.9
Physical functioning squared	0.000020	5026.8	6872.4
Emotional functioning squared	-0.000048	4422.3	5358.2
Social functioning squared	0.000011	5975.3	7903.2
School functioning squared	-0.000017	4290.3	5461.2
Physical functioning × emotional functioning	-0.000004	4714.9	6068.3
Physical functioning × social functioning	-0.000055	5480.6	7369.8
Physical functioning × school functioning	-0.000066	4644.0	6126.3
Emotional functioning × social functioning	-0.000009	5140.5	6507.5
Emotional functioning × school functioning	0.000059	4355.8	5409.5

Social functioning × school functioning	-0.000027	5063.2	6569.7
	Mapped EQ-5D	**0.82**	**0.89**

10.2.2 Disutility calculation

Table 44 below is not filled in the tables in 10.3 below includes the same type of information.

10.2.3 HSUV results

The steps required in this section have been completed under section 10.3

Table 44 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs - not applicable				

10.3 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

In the cost effectiveness analysis HRQoL impact are captured through five pathways: 1) BMI/BMI Z-score category and age, 2) hyperphagia severity, 3) disutility due obesity-related comorbidities, 4) disutility of non-obesity-related BBS symptoms, 5) disutility associated with treatment-related adverse events. Based on DMC guidelines, caregiver disutility is not included. The study design, data collection and HRQoL results for the different instruments applied in the health economic analysis are described below, and section 10.3.1-10.3.2 has been repeated for all instruments as per the template.

10.3.1 Study design TTO vignette study

While utility values associated with obesity are available in published literature, no studies have estimated utilities associated with hyperphagia and impacts on patients' quality of life beyond obesity. The purpose of the vignette study was to estimate health state utilities associated with various levels of hyperphagia. The health state vignettes representing varying severity levels of hyperphagia were developed using published studies [36, 86], and iterative interviews with clinicians who had experience treating patients with hyperphagia. Clinicians were asked to define hyperphagia and its symptoms, impact, screening procedures, and concepts that may be included in screening tools. These interviews included open-ended questions designed to elicit description of the typical experience of a patient with hyperphagia and continued until all clinicians agreed on clearly described health states and accurate hyperphagia descriptions.

Four health states were developed: A (no hyperphagia), B (mild hyperphagia), C (moderate hyperphagia), and D (severe hyperphagia). The health states and utility assessment procedures were pilot tested with 21 individuals in April 2021 to ensure the health states and methods were clear to respondents before conducting the larger utility valuation study [87].

In time trade-off (TTO) interviews, participants from the United Kingdom general population valued the health state vignettes drafted from literature review and input from clinicians who treat patients with hyperphagia. A composite TTO (cTTO) approach was followed, with health states perceived to be better than dead valued via conventional trade-off methods and health states perceived to be worse than dead valued with a lead-time procedure.

10.3.2 Data collection TTO vignette study

In the Vignette study TTO interviews, with participants from the United Kingdom general population valued four health state vignettes drafted from literature review and input from clinicians who treat patients with hyperphagia. Health states described patients with no hyperphagia, as well as mild, moderate, and severe hyperphagia. A total of 215 participants completed interviews (39.5% male; mean [range] age 39.1 [18-76] years).

10.3.3 HRQoL Results TTO vignette study

N/A see below for HSUV and disutility results.

10.3.4 HSUV and disutility results TTO vignette study

No studies have estimated utilities associated with hyperphagia and impacts on patients' QoL beyond obesity. A Vignette study assessing the utilities associated with hyperphagia was done to estimate health state utilities associated with various levels of hyperphagia. Using a conservative alternative, accepted methodology, whereby any negative utility scores from responders for any of the health states were set to zero, a utility multiplier of 0.98 was derived for no hyperphagia, 0.91 for mild hyperphagia, 0.72 for moderate hyperphagia and [redacted] for severe hyperphagia. The health state utility values derived from the vignette study are shown in **Table 45**.

In addition, an assumption was made of a utility multiplier of 0.8 associated with symptoms such as blindness and cognitive impairment was applied.

Table 45 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Hyperphagia level				
Mild hyperphagia	0.91 [0.90-0.92]	Vignette based TTO	N/A	
Moderate hyperphagia	0.72 [0.68-0.76]	Vignette based TTO	N/A	

Severe hyperphagia	[redacted] [0.30-0.46]	Vignette based TTO	N/A
Utility multiplier			
Non-obesity-related BBS symptoms	0.8 [0.64-0.96]*	Assumption	N/A

*The 95% CI was derived assuming that the standard error is 10% of the mean value

CI: Confidence interval; TTO: Time trade-off

10.3.5 Study design EQ-5D and EQ-5D-Y

As no reliable HRQoL data for the BBS population were identified by literature search or in clinical trials, utility values were obtained from other literature on HRQoL impact within the general obese population using EQ-5D and EQ-5D-Y. The utility values decrease with increased BMI/BMI Z-score category and age, which is reasonable. Baseline utility values were calculated for each treatment arm based on the distribution of patients across BMI Z-score categories; these are impacted by whether the patient remains on or discontinues setmelanotide treatment.

Paediatric BBS patient population utility values for two BMI Z-score categories were taken from a clinical study of a UK obese paediatric population that completed PedsQL. Mapping of these data from PedsQL to EQ 5D is described, with the resulting utility values by BMI Z score category, in

HRQoL values by BMI score for BBS patients aged ≥18 years were based on Medical Expenditure Panel Survey data from published literature; these values varied with age, thereby addressing the tenet that quality of life generally decreases as patients age.

10.3.6 Data collection EQ-5D

Not applicable.

10.3.7 HRQoL Results EQ-5D

N/A, see below for HSUV and disutility results.

10.3.8 HSUV and disutility results EQ-5D

The utility values by BMI Z-score and BMI category for by age for the paediatric patient population (1-18 years) and adults (18 to +70) are shown in Table 46 below.

Table 46. Overview of HSUV (utility values by BMI Z-score and BMI category and age)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
BMI Z-score category paediatrics (0-18 years)				

0.0-1.0	0.89 [0.71-1]	EQ-5D-Y	UK	Calculated from the source
1.0-2.0	0.87 [0.70-1]	EQ-5D-Y	UK	Extrapolated
2.0-2.5	0.86 [0.69-1]	EQ-5D-Y	UK	Extrapolated
2.5-3.0	0.85 [0.68-1]	EQ-5D-Y	UK	Extrapolated
3.0-3.5	0.83 [0.67-1]	EQ-5D-Y	UK	Extrapolated
3.5-4.0	0.82 [0.66-0.98]	EQ-5D-Y	UK	Calculated from the source
≥4.0	0.81 [0.65-0.97]	EQ-5D-Y	UK	Extrapolated
BMI category 18 to 30				
20 to <25 kg/m2	0.91 [0.73-1]	EQ-5D	US	
25 to <30 kg/m2	0.91 [0.73-1]	EQ-5D	US	
30 to <35 kg/m2	0.89 [0.72-1]	EQ-5D	US	
35 to <40 kg/m2	0.88 [0.71-1]	EQ-5D	US	
40 to <45 kg/m2	0.84 [0.68-1]	EQ-5D	US	
45 to <50 kg/m2	0.84 [0.68-1]	EQ-5D	US	
≥50 kg/m2	0.80 [0.64-0.96]	EQ-5D	US	
BMI category 31 to 40				
20 to <25 kg/m2	0.89 [0.72-1]	EQ-5D	US	
25 to <30 kg/m2	0.89 [0.72-1]	EQ-5D	US	
30 to <35 kg/m2	0.86 [0.69-1]	EQ-5D	US	
35 to <40 kg/m2	0.83 [0.67-0.99]	EQ-5D	US	
40 to <45 kg/m2	0.82 [0.66-0.98]	EQ-5D	US	
45 to <50 kg/m2	0.82 [0.66-0.98]	EQ-5D	US	
≥50 kg/m2	0.77 [0.62-0.92]	EQ-5D	US	
BMI category 41 to 50				
20 to <25 kg/m2	0.86 [0.69-1]	EQ-5D	US	

25 to <30 kg/m2	0.86 [0.69-1]	EQ-5D	US
30 to <35 kg/m2	0.82 [0.66-0.98]	EQ-5D	US
35 to <40 kg/m2	0.79 [0.64-0.94]	EQ-5D	US
40 to <45 kg/m2	0.75 [0.60-0.90]	EQ-5D	US
45 to <50 kg/m2	0.75 [0.60-0.90]	EQ-5D	US
≥50 kg/m2	0.70 [0.56-0.84]	EQ-5D	US
BMI category 51 to 60			
20 to <25 kg/m2	0.83 [0.67-0.99]	EQ-5D	US
25 to <30 kg/m2	0.83 [0.67-0.99]	EQ-5D	US
30 to <35 kg/m2	0.80 [0.64-0.96]	EQ-5D	US
35 to <40 kg/m2	0.77 [0.62-0.92]	EQ-5D	US
40 to <45 kg/m2	0.73 [0.59-0.87]	EQ-5D	US
45 to <50 kg/m2	0.73 [0.59-0.87]	EQ-5D	US
≥50 kg/m2	0.69 [0.55-0.83]	EQ-5D	US
BMI category 61 to 70			
20 to <25 kg/m2	0.81 [0.65-0.97]	EQ-5D	US
25 to <30 kg/m2	0.81 [0.65-0.97]	EQ-5D	US
30 to <35 kg/m2	0.79 [0.64-0.94]	EQ-5D	US
35 to <40 kg/m2	0.76 [0.61-0.91]	EQ-5D	US
40 to <45 kg/m2	0.71 [0.57-0.85]	EQ-5D	US
45 to <50 kg/m2	0.71 [0.57-0.85]	EQ-5D	US
≥50 kg/m2	0.66 [0.53-0.79]	EQ-5D	US
BMI category >70			
20 to <25 kg/m2	0.79 [0.64-0.94]	EQ-5D	US
25 to <30 kg/m2	0.79 [0.64-0.94]	EQ-5D	US
30 to <35 kg/m2	0.76 [0.61-0.91]	EQ-5D	US

35 to <40 kg/m2	0.74 [0.59-0.89]	EQ-5D	US
40 to <45 kg/m2	0.69 [0.55-0.83]	EQ-5D	US
45 to <50 kg/m2	0.69 [0.55-0.83]	EQ-5D	US
≥50 kg/m2	0.66 [0.53-0.79]	EQ-5D	US

*The 95% CI was derived assuming that the standard error is 10% of the mean valueBMI: Body mass index; CI: Confidence interval; EQ-5D-Y: EuroQol 5 Dimension Youth, EQ-5D: EuroQol 5 Dimension

10.3.9 Study design EQ-5D-3L

The impact of comorbidities on QoL were applied as comorbidity-specific disutilities to utility values using an additive approach, which aligned with published methodologies, Ara 2010 [88]. Disutility values were identified using multiple approaches, including an SLR for HRQoL data in the general obese population and targeted searches to fill data gaps. Data for sleep apnoea, osteoarthritis, and T2DM were obtained from the results of a multiple linear regression model of HRQoL based on Health Survey for England data reported by Søltoft 2009 [72].

10.3.10 Data collection EQ-5D-3L

Not applicable.

10.3.11 HRQoL results EQ-5D-3L

N/A, see below for HSUV and disutility results.

10.3.12 HSUV and disutility results EQ-5D-3L

The cardiovascular event disutility (-0.066) was derived using individual event disutilities including myocardial infarction, angina, stroke, and transient ischaemic attack. A composite cardiovascular event disutility was calculated by weighting individual-event disutilities by the frequency of each when a cardiovascular event occurred. The disutilities associated with comorbidities are shown in Table 47.

The impact of comorbidities on QoL increases with obesity severity. To account for this, the average disutility for each comorbidity shown in Table 47 was disaggregated along a log-linear distribution. This resulted in disutilities by BMI/BMI-Z score categories that increased as obesity severity increased (Table 48). Here is a detailed explanation of this process:

Comorbidity disutilities were disaggregated along a log-linear distribution. This calculation was done by first determining the upper limits of each BMI-Z score category, while bounding our BMI-Z score categories with levels <0 and levels >4.5. The upper limit for level <0 was 0, and the upper limit for scores >4.5 was assumed to be 5. The cumulative distribution of each BMI-Z score category was then calculated using the NORM.DIST function where the arguments are the upper limit of each category, the mean BMI SDS score from the Lindberg, L et al. (2020) publication [31] (multiplied by 100 to allow the

distribution function to calculate), and the standard deviation of the mean SDS score. These cumulative distributions were utilized to calculate probabilities of being in each category by finding the difference between each cumulative distribution. The disutility value for each category was calculated by exponentiating the product of the probability (which was used as a weight) and a calibration parameter. This calibration parameter was back-calculated using the goal seek functionality in Excel, to estimate disutilities for each category that would enable the weighted average of the comorbidity disutilities to equal the average comorbidity disutility. [Sleep apnoea example from the health economic model ("Detailed Inputs" tab): Goal Seek for cell I319 to equal the sleep apnoea disutility of 3.36 by changing the calibration variable in cell C310]. The adjusted disutilities were calculated by dividing the calculated disutilities by 100 to convert them back to the utility scale.

Table 47. Comorbidity-specific disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Sleep apnoea	-0.034	EQ-5D-3L	UK	
Osteoarthritis	-0.187	EQ-5D-3L	UK	
T2DM	-0.043	EQ-5D-3L	UK	
NASH	0.000	EQ-5D-3L	UK	
Cardiovascular events	-0.066	EQ-5D-3L	UK	

EQ-5D-3L: EuroQol 5 Dimension 3 Level; NASH: nonalcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus

Table 48. Disutility values by BMI/BMI Z-score category for each comorbidity

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Sleep apnoea by BMI/BMI/Z category				
20 to <25 / 0.0 to <1.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK	
25 to <30 / 1.0 to <2.0	-0,022 [-0.02: -0.03]	EQ-5D-3L	UK	
30 to <35 / 2.0 to <2.5	-0,026 [-0.02: -0.03]	EQ-5D-3L	UK	
35 to <40 / 2.5 to <3.0	-0,032 [-0.03: -0.04]	EQ-5D-3L	UK	
40 to <45 / 3.0 to <3.5	-0,039 [-0.03: -0.05]	EQ-5D-3L	UK	

45 to <50 / 3.5 to <4.0	-0,047 [-0.04: -0.06]	EQ-5D-3L	UK
≥50 / ≥4.0 to 4.5	-0,057 [0.05-0.07]	EQ-5D-3L	UK
Osteoarthritis by BMI/BMI/Z category			
20 to <25 / 0.0 to <1.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
25 to <30 / 1.0 to <2.0	-0,062 [-0.05: -0.07]	EQ-5D-3L	UK
30 to <35 / 2.0 to <2.5	-0,098 [-0.08: -0.12]	EQ-5D-3L	UK
35 to <40 / 2.5 to <3.0	-0,154 [-0.12: -0.18]	EQ-5D-3L	UK
40 to <45 / 3.0 to <3.5	-0,244 [-0.20: -0.29]	EQ-5D-3L	UK
45 to <50 / 3.5 to <4.0	-0,385 [-0.31: -0.46]	EQ-5D-3L	UK
≥50 / ≥4.0 to 4.5	-0,607 [-0.49: -0.73]	EQ-5D-3L	UK
NASH **by BMI/BMI/Z category**			
20 to <25 / 0.0 to <1.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
25 to <30 / 1.0 to <2.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
30 to <35 / 2.0 to <2.5	0,000 [0.00: 0.00]	EQ-5D-3L	UK
35 to <40 / 2.5 to <3.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
40 to <45 / 3.0 to <3.5	0,000 [0.00: 0.00]	EQ-5D-3L	UK
45 to <50 / 3.5 to <4.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
≥50 / ≥4.0 to 4.5	0,000 [0.00: 0.00]	EQ-5D-3L	UK
T2DM **by BMI/BMI/Z category**			
20 to <25 / 0.0 to <1.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
25 to <30 / 1.0 to <2.0	-0,025 [-0.02: -0.03]	EQ-5D-3L	UK
30 to <35 / 2.0 to <2.5	-0,032 [-0.03: -0.04]	EQ-5D-3L	UK
35 to <40 / 2.5 to <3.0	-0,040 [-0.03: -0.05]	EQ-5D-3L	UK
40 to <45 / 3.0 to <3.5	-0,050 [-0.04: -0.06]	EQ-5D-3L	UK
45 to <50 / 3.5 to <4.0	-0,064 [-0.05: -0.08]	EQ-5D-3L	UK
≥50 / ≥4.0 to 4.5	-0,080 [-0.06: -0.10]	EQ-5D-3L	UK

Cardiovascular events **by BMI/BMI/Z category**			
20 to <25 / 0.0 to <1.0	0,000 [0.00: 0.00]	EQ-5D-3L	UK
25 to <30 / 1.0 to <2.0	-0,033 [-0.03: -0.04]	EQ-5D-3L	UK
30 to <35 / 2.0 to <2.5	-0,044 [-0.04: -0.05]	EQ-5D-3L	UK
35 to <40 / 2.5 to <3.0	-0,060 [-0.05: -0.07]	EQ-5D-3L	UK
40 to <45 / 3.0 to <3.5	-0,081 [-0.06: -0.10]	EQ-5D-3L	UK
45 to <50 / 3.5 to <4.0	-0,109 [-0.09: -0.13]	EQ-5D-3L	UK
≥50 / ≥4.0 to 4.5	-0,146 [-0.12: -0.17]	EQ-5D-3L	UK

*The 95% CI was derived assuming that the standard error is 10% of the mean value

BMI: Body mass index; CI: Confidence interval ; EQ-5D-3L: EuroQol 5 Dimension 3 Level; NASH: nonalcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus; BBS: Bardet-Biedl syndrome

10.3.13 Study design Standard gamble

The main AEs experienced by patients taking setmelanotide during study RM-493-023 were skin hyperpigmentation (59.1%), injection site erythema (45.5%), nausea (22.7%) and vomiting (27.3%) [40]. However, the impact of skin hyperpigmentation on utility is highly variable. According to Danish clinical experts for most patients, skin hyperpigmentation could be acceptable while for others it may be less tolerable [37, 38]. Consequently, the effect of skin hyperpigmentation on QoL was excluded from the analysis. It is expected for the included AEs (nausea and vomiting and Injection site erythema) to resolve during the treatment titration period. Consequently, the disutilities associated with these AEs are applied for 2 weeks during the first year of the analysis. No treatment-related adverse events are included for the BSC arm. As disutilities associated with AEs were not explicitly collected in the RM-493-023 study, these values were sourced from published literature [74, 75].

10.3.14 Data collection Standard gamble

Not applicable.

10.3.15 HRQoL results Standard gamble

Not applicable, see below for HSUV and disutility results.

10.3.16 HSUV and disutility results Standard gamble

Utility decrements associated with AEs were sourced from literature and are shown in

Table **49**.

Table 49. Disutility associated with adverse events.

Adverse event	Results [95% CI]*	Instrument /method	Tariff (value set) used	Comments
Nausea and vomiting	-0.04 [-0.03: -0.05]	Standard gamble (SG) adjusted**	-	Assumed duration: 2 weeks
Injection site erythema	-0.011 [-0.009: -0.013]			Assumed duration: 2 weeks

*The 95% CI was derived assuming that the standard error is 10% of the mean value

** SG adjusted scores on a scale ranging from 0 (death) to 1 (perfect health). Adjusted scores were derived through a linear transformation of raw scores using the following formula: SG adj = (SG raw x (1 – worst)) + worst

CI: Confidence interval

11. Resource use and associated costs

Costs considered in the analysis include drug acquisition costs, monitoring costs, BMI/BMI/Z score-related health care costs, comorbidity costs and non-medical costs. All costs are reported in DKK. Resource use was verified to be relevant to the Danish setting by two Danish clinical experts [37, 38].

11.1 Pharmaceutical costs (intervention and comparator)

Annual drug acquisition costs for setmelanotide are calculated using the average patient dose from the clinical trial for day 1 and during titration, combined with the expected post-titration dose for the real-world population. In the clinical trial, the average observed post-titration doses were 2.7 mg per day for paediatric patients and 2.9 mg per day for adult patients. However, clinical experts suggest a slightly lower dose in real life since:

- The trial protocol defined a target dose of 3mg per day for both adult and paediatric patients, whereas in real life physicians indicate that they will not continue to increase the dose if patients are responding well to therapy at 2mg per day, or even at 1mg per day in patients < 16.
- Reduction in dose can occur in patients achieving very high weight loss due to a change in therapeutic objective: from weight/BMI reduction to weight/BMI maintenance.
    - This change in therapeutic objective is unlikely to occur in the first 12 months of therapy so it was not observed during the duration of the trial.
    - However, it has been observed after a few years of therapy in several patients with POMC deficiency (the other label indication for setmelanotide).

As a result, the average post-titration doses used in the analysis were slightly lower than the observed at 12 months in the trial:

- 2,5 mg per day for paediatric patients (0.2 mg per day lower on average)
- 2,8 mg per day for adult patients (0.1 mg per day lower on average)

The starting dose, dose during titration, and post-titration dose are used to calculate the average year 1 dose and costs for both paediatric and adult patients with BBS:

- With an average starting dose for paediatric patients with BBS of [redacted] mg on day 1, a 2-week titration-period dose of [redacted] mg/day, and a predicted [redacted] mg/day post-titration dose, the average year 1 setmelanotide dose is [redacted] mg/day. The average daily setmelanotide dose for years 2 and onwards is assumed to be equivalent to the [redacted] mg/day post-titration dose.

- With an average starting dose for adult patients with BBS of [redacted] on day 1, a 2-week titration-period dose of [redacted] mg/day, and a predicted [redacted] mg/day post-titration dose, the average year 1 setmelanotide dose is [redacted] mg/day. The average daily setmelanotide dose for years 2 and onwards is assumed to be equivalent to the [redacted] mg/day dose post-titration dose.

In turn, drug acquisition for BSC is assumed to be 0. This is because diet and exercise instruction are expected to occur during regular physician visits and be encompassed in monitoring costs (see **Table 52**)

Table 50 shows the pharmaceutical costs used in the model. Table 51 shows the annual costs of treatment with setmelanotide for year one and year two and onwards for paediatric and adult patients in Denmark, respectively.

Table 50 Pharmaceutical costs used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]
Imcivree® (setmelanotide)	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, Best supportive care; DKK, Danish krona; NA, Not applicable.

Table 51 Annual treatment cost with setmelanotide for paediatric and adult patients in Denmark (DKK)

Paediatric treatment initiation		Adult treatment initiation	
Year 1	Year 2+	Year 1	Year 2+
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Krona.

The analysis assumes that treatment with setmelanotide does not lead to any waste as the remaining medication can be used for additional doses.

11.2 Pharmaceutical costs – co-administration – not applicable

Not applicable.

11.3 Administration costs

Setmelanotide administration costs are assumed to be negligible, as patients are expected to be able to self-administer their dose once daily with the help of their caregiver, if needed (for paediatric patients and/or those with visual or cognitive impairment), at the patient´s home. Therefore, no healthcare visits are required for the administration of setmelanotide and consequently, no administration costs are included in the analysis.

Furthermore, administration costs for BSC are assumed to be 0. This is because diet and exercise instruction are expected to occur during regular physician visits and be encompassed in monitoring costs, described in the following section.

11.4 Disease management costs

The disease management costs are divided in monitoring costs, BMI-related health care costs and comorbidity costs. Monitoring resource utilization frequencies and unit costs are presented in **Table 52**. The monitoring resource use and frequencies were based on Danish clinical expert input [37, 38]. It is expected for setmelanotide patients to experience approximately 3 additional physician visits compared to BSC patients in year 1. In the remaining years on treatment with setmelanotide, a reduction in physician visits to 1 per year is expected. This was also confirmed by a Danish clinical expert.

Table 52 Monitoring resource use unit costs used in the model

Resources	Frequency	Unit Costs [DKK]	Code	Reference
Complete blood count	Once yearly	13.00	Neutrofilocytter; antalk	Rigshospitalet's Labportal [89]
Liver function test	Once yearly	118.00	Alanine transaminase [ALT] + Aspartattransaminase [ASAT] + Alkalisk Phosphatase + GGT + Bilirubiner + Koagulationsfaktor II+VII+X + Albumin	Rigshospitalet's Labportal [89]

Comprehensive metabolic panel	Once yearly	260.69	P-kreatinin + P-glucose Rigshospitalet's Labportal: Karbamid;P + Alanine transaminase [ALT] + Aspartattransaminase [ASAT] + Alkalisk Phosphatase + GGT + Bilirubiner + Koagulationsfaktor II+VII+X + Albumin"	Takstkort 29A [90]
Physician visit	Setmelanotide + BSC: Year 1: Once every two months; Year 2+: once yearly BSC: Once every four months	659.52	Gennemsnit pædiatri konsultation og ledende sygeplejersker (1 time)	Takstkort 19A Pædiatri og Værdisætning af enhedsomkostninger [91]

Abbreviations: BSC, Best supportive care; DKK, Danish krona

The annual monitoring costs for setmelanotide plus BSC and BSC alone for year 1 and year 2 onwards are presented in **Table 53**.

Table 53 Annual monitoring costs per patient (paediatric treatment initiation) in DKK for setmelanotide plus BSC and BSC alone for year 1 and year 2+

Setmelanotide + BSC		BSC	
Year 1	**Year 2+**	**Year 1**	**Year 2+**
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: BSC: Best supportive care

BMI-related health care costs are also part of the disease management costs. The average annual healthcare costs per person for each BMI/BMI Z-score category were informed by a Danish register-based study [76]. This study included adults (≥18 years) who had been registered in the Danish National Patient Register (NPR) from 2002 through 2018 with a primary or secondary BMI-specific diagnosis of obesity at a hospital. The study population was categorized according to the World Health Organization's (WHO) classification of obesity as obesity class I (BMI 30–34.9 kg/m^2), obesity class II (BMI 35–39.9 kg/m^2), or obesity class III (BMI≥40 kg/m^2). The average annual healthcare costs per person reported in the study (Table 54) included: costs of primary care visits, inpatient hospitalization(s), outpatient visit(s), home care and prescription medicines [76]. These costs reflect healthcare utilisation by obese patients and do not inform on use for non-obesity related BBS comorbidities that are likely to be present in the modelled population.

Table 54 Average annual healthcare costs per person for adult treatment initiation by BMI category in Denmark

BMI category	Average annual healthcare costs per person [DKK]*	Source
30 to <35 kg/m^2	41,325.24	[76]
35 to <40 kg/m^2	45,567.36	
≥40 kg/m^2	45,619.55	

*The costs were converted from EUR to DKK using the last six months (December 2022- May 2023) average exchange rate (7,455393). Abbreviations: DKK, Danish krona.

The Danish register-based study did not report the average annual healthcare costs per person for individuals with a BMI of 25 to <30 kg/m^2. The average annual healthcare costs per person for this group were estimated to be [redacted] DKK. This value was obtained by linear extrapolation of the costs associated to the BMI categories of 30 to <35 kg/m^2 and 35 to <40 kg/m^2. The average annual healthcare costs per person for individuals with a BMI of 20 to <25 kg/m^2 were assumed to be 0. The average annual healthcare costs per person for paediatric patients by BMI Z-score category (Table 54) are assumed to be equivalent to the costs for adult patients by BMI score category (Table 55). These numbers were considered reasonable by a Danish experts [37].

Table 55 Average annual healthcare costs per person for paediatric treatment initiation by BMI Z-score category

BMI Z-score category	Average annual healthcare costs per person [DKK]*	Source
0.0 to <1.0	0	Assumption
1.0 to <2.0	[redacted]	
2.0 to <2.5	[redacted]	
2.5 to <3.0	[redacted]	
3.0 to <3.5	[redacted]	
3.5 to <4.0	[redacted]	
≥4.0	[redacted]	

* The costs were converted from EUR to DKK using the last six months (December 2022- May 2023) average exchange rate (7,455393). Abbreviations: BMI, Body Mass Index; DKK, Danish krona

Table 56 Average annual healthcare costs per adult treatment initiation by BMI category

BMI category	Average annual healthcare costs per person [DKK]*	Source
20 to <25 kg/m^2	0	Assumption
25 to <30 kg/m^2	[redacted]	Linear extrapolation
30 to <35 kg/m^2	[redacted]	[76]
35 to <40 kg/m^2	[redacted]	
40 to <45 kg/m^2	[redacted]	
45 to <50 kg/m^2	[redacted]	
≥50 kg/m^2	[redacted]	

* The costs were converted from EUR to DKK using the last six months (December 2022- May 2023) average exchange rate (7,455393). Abbreviations: BMI, Body Mass Index; DKK, Danish krona

The final costs included in the disease management costs were the comorbidity costs. The prevalence of comorbidities is relative to the different BMI/BMI Z-score categories and age. Given the lack of published data for BBS patients, the comorbidity prevalences for T2DM, CV, NAFLD and Sleep Apnoea were derived from an innovative process used to estimate the effect of early onset of obesity on comorbidities and mortality risk (see Appendix K). The prevalence inputs for osteoarthritis were taken from a cross-sectional survey of adults eligible for bariatric surgery in England [92], and were included in the health economic analysis based on the assumptions noted in Table 57.

Table 57. BMI-based prevalence values for osteoarthritis

BMI	Prevalence	Subgroup in source document
Osteoarthritis		
20 to <25 kg/m^2	6.10%	Lower CI of BMI <35 kg/m^2 group
25 to <30 kg/m^2	6.60%	Mean of BMI <35 kg/m^2 group
30 to <35 kg/m^2	10.40%	Average of upper CI of BMI <35 kg/m^2 group and lower CI of BMI 35 to 40 kg/m^2 group
35 to <40 kg/m^2	16.20%	Mean of BMI 35 to 40 kg/m^2 group

40 to <45 kg/m^2	17.00%	Average of upper CI of BMI 35 to 40 kg/m^2 group and lower CI of BMI >40 kg/m^2 group
45 to <50 kg/m^2	21.10%	Mean of BMI >40 kg/m^2 group
≥50 kg/m^2	26.90%	Upper CI of BMI >40 kg/m^2 group

Osteoarthritis prevalence for paediatric patients aged <18 years was calculated using the values for bounding BMI categories (20 to <25 kg/m^2 and ≥50 kg/m^2) from the adult population for the lowest and highest BMI Z-score categories (0.0 to <1.0 and ≥4.0). A linear increase in prevalence with each BMI Z-score category was assumed. The resulting paediatric osteoarthritis prevalence values are shown in Table 58.

Table 58. Osteoarthritis prevalence for pediatric patients

BMI Z-score	Osteoarthritis
0.0 to <1.0	6.10%
1.0 to <2.0	9.57%
2.0 to <2.5	13.03%
2.5 to <3.0	16.50%
3.0 to <3.5	19.97%
3.5 to <4.0	23.43%
≥4.0	26.90%

Five comorbidities are included in the cost effectiveness analysis: sleep apnoea, osteoarthritis, non-alcoholic steatohepatitis (NASH), type 2 diabetes (T2DM) and cardiovascular (CV) events.

Table 59 shows the average annual comorbidity costs per person, which were used to derive the comorbidity costs by age and BMI/BMI-Z category, based on comorbidity prevalence.

Table 59. Average annual comorbidity costs per person

Comorbidity	Cost (DKK)	Comment	Source
Sleep apnoea	25,680.61*	Average annual direct health costs per person (general practitioner services, hospital services and medication) after diagnosis.	Table 4 in Jennum, P et al. [77] The study included patients who received a first diagnosis of sleep apnoea from 1998 to 2009 registered in the Danish National Patient Register (NPR). The average annual direct health costs in Denmark were used
Osteoarthritis	7,435.25**	Weighted average annual direct costs per patient living with knee and hip osteoarthritis in Europe (Italy, Spain, Netherlands, Sweden, and France).	Table 3 in Salmon, J.H., et al [78] The study was based on a systematic review of cost-of-illness studies. 32 articles were selected for the review and ten of them were conducted in Europe. 13 articles reported annual direct costs per patient with knee and hip osteoarthritis (seven in Europe). The reported direct cost categories varied depending on the study. The weighted average annual direct costs per patient in the European countries were used as a proxy to estimate the Danish costs.
NASH	7,621.28***	Mean total annual health care costs per patient (hospitalizations, outpatient visits and prescribed drugs).	Supplementary Table 8 in Hagström, H., et al. [79] The study included patients diagnosed with biopsy-confirmed NAFLD at the Karolinska University Hospital, Huddinge, and Linköping University Hospital from 1971 to 2009. The mean total annual health care costs per patient

			in Sweden were used as a proxy to estimate the Danish costs.
T2DM	49,901.49****	Approximate total annual healthcare costs associated with T2DM excluding transportation costs divided by the approximate number of people diagnosed with T2DM in Denmark: DKK 8,820,000,000/250,000.	Pulleyblank et. al 2021 [80] Average annual total healthcare treatment costs of risk-group 2 patients (moderate disease). Weighted average hospital monitored and GP-monitored patients.
Cardiovascular events	35,988.29*****	Average annual cost per patient of health resource utilization associated with a new CV event in the "history of major CVD cohort" (patients with prior diagnosis of myocardial infarction, unstable angina pectoris, ischemic stroke, or revascularization).	Table 3 in Hallberg, S., et al. [81]. The study is a retrospective population-based cohort study conducted using Swedish national registers and electronic medical records. It included patients with hyperlipidaemia or prior CV events. The average annual costs per patient of health resource utilization in Sweden were used as a proxy to estimate the Danish costs.

* Inflated from 2009 Euros and converted to DKK using the last six months average exchange rate (December 31, 2022 - May 14, 2023; Exchange rate: 7.455393).** Inflated from 2013 Euros and converted to DKK using the last six months average exchange rate (December 31, 2022 - May 14, 2023; Exchange rate: 7.455393). ***Inflated from 2016 SEK and converted to DKK using the last six months average exchange rate (December 31, 2022 - May 15, 2023; Exchange rate: 0.66411). ****Inflated from 2016 DKK (inflation rate: 1.06723532363271) *****Inflated from 2012 Euros and converted to DKK using the last six months average exchange rate (December 31, 2022 - May 14, 2023; Exchange rate: 7.455393).

11.5 Costs associated with management of adverse events- not applicable

Not applicable, as AEs were assumed to not affect cost only utilities

Table 60 Cost associated with management of adverse events - not applicable

	DRG code	Unit cost/DRG tariff
[Adverse event]	Not applicable	

11.6 Subsequent treatment costs – not applicable

Not applicable.

Table 61 Pharmaceutical costs of subsequent treatments – not applicable

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
[Name of subsequent treatment]	Not applicable	[X]	[X]		
	[X]	[X]	[X]		

11.7 Patient costs

The analysis adopts an extended payer perspective. As a result, the following costs are included in the analysis:

- Costs associated with the patient's and carer's use of time in connection with treatment.
- Transportation costs linked to travelling to and from treatment.

The patient's and carer's hourly rate and the transportation costs are presented in **Table 62**.

Table 62 Patient costs used in the model

Activity	Unit cost [DKK]	Time spent (hours)
Patients (hourly rate)	203	1
Carers (hourly rate)	203	1
Transportation costs (round trip)	140	NA

Source: DMC, Værdisætning af Enhedsomkostninger 2023: Patient- og pårørenderelaterede omkostninger [93] . Abbreviations: NA, Not applicable

The indirect costs are applied according to the use of time for the disease management (number of physician visits) and the proportion of patients and carers incurring in indirect costs. A physician visit was assumed to take one hour. It was assumed that 100% of the patients and 50% of the carers incur in indirect costs (**Table 63**).

Time spent by caregivers on administrating setmelanotide was also considered. Conservatively, it was assumed that caregivers spend 30 minutes each time setmelanotide is administered to paediatric patients. However, it is important to note that the time required to perform a subcutaneous injection is limited, and this time

investment is likely offset by the time gained from not constantly dealing with food-related issues, such as monitoring patients for sneaking food into the house or implementing food-related restrictions.

Table 63. Use of time per year, number of trips per year and total indirect costs per year per treatment arm

	Setmelanotide + BSC (Year 1)		Setmelanotide + BSC (Year 2+)		BSC	
	Patients	Carers	Patients	Carers (%)	Patients	Carers (%)
Use of time (h) per year	6 (100%)	6 (50%)	1 (100%)	1 (50%)	3 (100%)	3 (50%)
Number of trips per year	6 (100%)		1 (100%)		3 (100%)	
Total costs per year (DKK)	2,667		444.5		1333.5	
Total costs per year for paediatric patients (DKK) - including time spent by caregivers on administrating setmelanotide	39,740		37,517		-	

Abbreviations: BSC: best supportive care.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost) – not applicable

Not applicable.

12. Results

12.1 Base case overview

Table 64 includes an overview of the base case.

Table 64 Base case overview

Feature	Description
Perspective	Limited societal
Type of model	Life table model
Time horizon	Lifetime (with a maximum patient age of 100 years)
Treatment line	1st line
Comparator	BSC alone
Population	Paediatric treatment initiation
Proportion of females	50%
Starting age (years)	6
Baseline Hyperphagia Distribution	100% severe
Response Evaluation Timeframe	14 weeks
Decrease in BMI Z-score class for responders	[redacted] levels
BMI Utility Measure	Estimates from Literature
Caregiver Burden Included	No
Setmelanotide Treatment Discontinuation	1% per year
Costs included	Treatment, Health care costs, Comorbidity costs, monitoring costs, non-medical costs.

12.1.1 Base case results

The results of the base case show that the cost of an additional QALY gained from using setmelanotide + BSC compared to BSC alone is predicted to be DKK 4,453,966. Treatment with setmelanotide + BSC is predicted to lead to [redacted] additional QALYs and [redacted] additional life years compared to treatment with BSC alone. Treatment with setmelanotide + BSC is predicted to lead to additional costs of DKK [redacted] compared to treatment with BSC alone (see Table 65).

Table 65 Base case results, discounted estimates (DKK)

	Setmelanotide + BSC	BSC alone	Difference
Costs outcomes			

Treatment costs	[redacted]	[redacted]	[redacted]
BMI-related health care costs	[redacted]	[redacted]	[redacted]
Comorbidity costs	DKK 704,854	DKK 956,752	-DKK 251,898
Indirect costs	DKK 301,934	DKK 30,631	DKK 271,303
Total costs	[redacted]	[redacted]	[redacted]
Clinical outcomes			
Life years	[redacted]	[redacted]	[redacted]
Quality-adjusted life years (QALYs)	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		**DKK 4,453,966**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

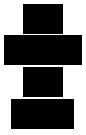
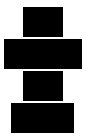
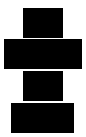
The impact of individual parameters on the ICER was tested in one-way deterministic sensitivity analyses. Driving model variables were varied over a plausible range. Model inputs were varied by 20% in either direction when logical. When this variation did not align with variable constraints, an absolute change was considered for the input. Some variables (such as hyperphagia, utility multipliers or comorbidity costs) were varied in groups, when varying all inputs of that type was more logical than varying one alone. Parameter variation is detailed in Table 66. The ICER was recorded at the upper and lower values to produce a tornado diagram.

The results of the deterministic sensitivity analyses are presented in Table 66 and Figure 11. The parameters that had the greatest impacts on the ICER were the baseline hyperphagia category distribution, the setmelanotide QALY multiplier and the baseline BMI Z-score category distribution.

Table 66 One-way sensitivity analyses results

	Change (lower value/higher value)	Reason / Rational / Source	Incremental cost (DKK) (lower value/higher value)	Incremental benefit (QALYs) (lower value/hig	ICER (DKK/QALY) (lower value/hig

				her value)	her value)
Base case	N/A	See above	[redacted]	[redacted]	DKK 4,453,966
Baseline hyperphagia category	Absolute change: (100% mild/ 100% severe)	See above	[redacted]	[redacted]	DKK 16,863,407.18/ DKK 4,453,965.69
Setmelanotide QALY multiplier	Percentage Change: (-20%/20%)	See above	[redacted]	[redacted]	DKK 6,166,141.12/ DKK 3,485,996.12
Baseline BMI z-score category	Absolute change: (100% 0-1/100% 4+)	See above	[redacted]	[redacted]	DKK 5,724,061.18/ DKK 4,058,518.10
Hyperphagia Utility Multiplier	Percentage Change: (-20%/20%)	See above	[redacted]	[redacted]	DKK 5,378,872.93/ DKK 3,800,468.10
BBS QALY multiplier	Percentage Change: (-20%/20%)	See above	[redacted]	[redacted]	DKK 5,378,872.93/ DKK 3,800,468.10
Setmelanotide unit cost	Percentage Change: (-20%/20%)	See above	[redacted]	[redacted]	DKK 3,561,187.92/ DKK 5,346,743.45
Hyperphagia treatment effect	Absolute change: (50% moderate / 100% mild)	See above	[redacted]	[redacted]	DKK 5,205,270.22/ DKK 4,453,965.69

Decrease in BMI-Z: Setmelanotide	Absolute change: (1 level /3 levels)	See above			DKK 4,877,572 .93/ DKK 4,184,784 .13
Comorbidity disutilities by BMI	Percentag e Change: (- 20%/20%)	See above			DKK 4,582,739. 58/ DKK 4,332,231. 03
Treatment Discontinuation	Absolute change: (0%/5%)	See above			DKK 4,466,529 .56/ DKK 4,429,928 .62
SMR for Setmelanotide	Absolute change: (1/5)	See above			DKK 4,421,122 .39/ DKK 4,453,965 .69
Baseline age paediatrics	Absolute change: (6/17)	See above			DKK 4,453,965. 69/ DKK 4,473,192. 40
Response rate: Setmelanotide	Percentag e Change (- 20%/20%)	See above			DKK 4,462,342. 66/ DKK 4,448,381. 64
Comorbidity costs by BMI	Percentag e Change: (- 20%/20%)	See above			DKK 4,460,404 .19/ DKK 4,447,527 .19
BMI-Related Health Care Costs	Percentage Change: (-20%/20%)	See above			DKK 4,455,957 .92/ DKK 4,451,973 .46
Setmelan otide Monitori ng Cost Years 2+	Percentage Change: (-20%/20%)	See above			DKK 4,453,507 .87/ DKK 4,454,423 .50

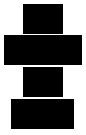
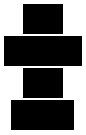
Nausea and vomiting probability	Percentage Change: (-20%/20%)	See above			DKK 4,453,812.44/ DKK 4,454,118.94
Nausea and vomiting disutility	Percentage Change: (-20%/20%)	See above			DKK 4,453,812.44/ DKK 4,454,118.94
Injection site erythema probability	Percentage Change: (-20%/20%)	See above			DKK 4,453,888.99/ DKK 4,454,042.39
Injection site erythema disutility	Percentage Change: (-20%/20%)	See above			DKK 4,453,888.99/ DKK 4,454,042.39
Setmelanotide Monitoring Cost Year 1	Percentage Change: (-20%/20%)	See above			DKK 4,453,915.92/ DKK 4,454,015.46
BSC Monitoring Cost	Percentage Change: (-20%/20%)	See above			DKK 4,453,992.81/ DKK 4,453,938.56
Percent female	Percentage Change: (-20%/20%)	See above			DKK 4,453,965.69/ DKK 4,453,965.69

Figure 11. Tornado diagram one-way sensitivity analysis results

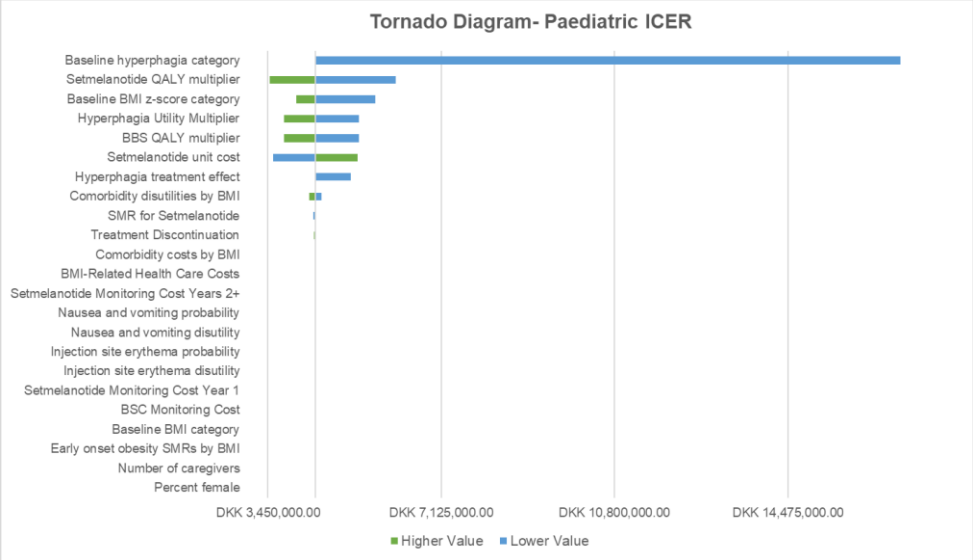


Table 67 shows different scenario analyses results. The analyses indicate that the base case results are stable to changes in key parameters. The results are most sensitive to the discount rates, the exclusion of comorbidities and the inclusion of caregiver burden.

Table 67 Scenario analyses results

	Change lower value/ higher value	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case		[redacted]	[redacted]	4,453,966
Timehorizon: Lifetime	10 years	[redacted]	[redacted]	4,276,023
	20 years	[redacted]	[redacted]	4,349,180
	50 years	[redacted]	[redacted]	4,425,531
Discount rates Costs: years 0-35: 3.5%; years 36-70: 2.5%; years 70+: 1.5% Outcomes: years 0-35: 3.5%; years 36-70: 2.5%; years 70+: 1.5%"	Costs: years 0-35: 4.5%; years 36-70: 3.5%; years 70+: 2.5% Outcomes: years 0-35: 4.5%; years 36-70: 3.5%; years 70+: 2.5%	[redacted]	[redacted]	4,430,093
	Costs: years 0-35: 4.5%; years 36-70: 3.5%;	[redacted]	[redacted]	1,704,695

	years 70+: 2.5% Outcomes: years 0-35: 0%; years 36-70: 0%; years 70+: 0%			
Response Evaluation Timeframe: 14 weeks	1 year	[redacted]	[redacted]	4,466,557
Setmelanotide Treatment Discontinuation: 1% per year	None	[redacted]	[redacted]	4,466,530
Comorbidities Included: Yes	No	[redacted]	[redacted]	5,219,490
Costs by BMI Included: Yes	No	[redacted]	[redacted]	4,463,927
Perspective: Limited societal	Payer	[redacted]	[redacted]	4,419,293
Caregiver Burden Included: No	Yes	[redacted]	[redacted]	3,572,411
SMR for Setmelanotide: 1	0.85	[redacted]	[redacted]	4,443,835
BBS population at treatment initiation: Paediatric 100% Adult 0%	Paediatric 60%, Adult 40%	[redacted]	[redacted]	4,570,009

The impact of the price of Imcivree® on the ICER is illustrated in

Figure 12.

Figure 12. Impact of setmelanotide price on ICER

12.2.2 Probabilistic sensitivity analyses

To evaluate uncertainty associated with parameter precision, probabilistic sensitivity analyses (PSA) were conducted. The PSA included all relevant model parameters; estimates of uncertainty were based on the uncertainty in the source data where data availability permitted. The appropriate distribution for each parameter included in the probabilistic sensitivity analysis (PSA) was chosen based on expected and plausible values for each (Table 86 in Appendix G summarizes all the parameters used in the PSA).

A second-order Monte Carlo simulation was run for 1,000 iterations including the simultaneous variation of all parameters. Multiple sets of parameter values were sampled from predefined probability distributions to characterize the uncertainty associated with the precision of mean parameter values. The results of the PSA are presented graphically in Figure 13. The incremental cost-effectiveness scatterplot presents the variation in incremental costs and incremental QALYs over 1,000 replications of setmelanotide + BSC vs. BSC alone. Based on the results of 1,000 simulations, the mean ICER is DKK 4,460,829. The cloud of points falls within the northeast quadrant, indicating higher costs and better outcomes.

Figure **14** shows the cost-effectiveness acceptability curve (CEAC) comparing setmelanotide + BSC to BSC alone. The curves indicate that setmelanotide + BSC has a 50% probability of being cost-effective at a willingness to pay of approximately 4,500,000 DKK.

Figure 13. Cost-effectiveness plane

Figure 14. Cost-effectiveness acceptability curve

13. Budget impact analysis

Based on the prevalence and incidence numbers for BBS in Denmark, Rhythm Pharma is assuming that approximately [redacted] paediatric patients in Denmark have BBS with obesity and severe hyperphagia and are eligible for treatment in Year 1 (see section 3.2 Table 6). A constant prevalence rate of [redacted] was assumed over the five-year period used for the budget impact calculations. The numbers presented in Table 68 represent the number of patients expected to be on setmelanotide + BSC or BSC treatment each year when setmelanotide is introduced and when it is not introduced. In the scenario where setmelanotide is introduced, a [redacted] market share was assumed in year 1, increasing to [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5. In the scenario where setmelanotide is not introduced, every year, 100% of patients receive BSC alone.

Table 68. Number of patients expected to be treated over the next five-year period if the pharmaceutical is introduced and not introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		

	Year 1	Year 2	Year 3	Year 4	Year 5
Setmelanotide + BSC	0	0	0	0	0
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

For the budget impact calculations (Table 69), drug acquisition, monitoring, BMI-related health care and comorbidity related costs were considered. For the calculations it was assumed that 100% of the population has a paediatric treatment initiation (i.e., at 6 years old). All included drug acquisition costs are in pharmacy selling price (PSP) including value added tax (VAT).

Table 69. Expected budget impact of recommending setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS, in adults and children 6 years of age and above with obesity and severe hyperphagia.

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

1. Jens Christian Holm, consultant in Paediatrics, PhD, head of research, and clinical- and research associate professor at the University of Copenhagen.
2. Signe Beck-Nielsen, Consultant, PhD, Center for Rare Diseases, Skejby, Aarhus University Hospital

15. References

1. EMA, *Summary of product characteristics - Imcivree*. 2022.
2. EMA. *EU/3/19/2192: Orphan designation for the treatment of Bardet-Biedl syndrome. Availble at: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-19-2192*. 2019.
3. Forsythe, E., et al., *Managing Bardet–Biedl syndrome—now and in the future.* Frontiers in pediatrics, 2018. **6**: p. 23.
4. Pomeroy, J., et al., *Bardet-Biedl syndrome: weight patterns and genetics in a rare obesity syndrome.* Pediatric Obesity, 2021. **16**(2): p. e12703.
5. CARE-BBS, *CARE-BBS study report. Caregiver burden in Bardet-Biedl syndrome (CARE-BBS): A survey of BBS-related obesity and hyperphagia impacts in the United States, United Kingdom, Canada, and Germany.* 2022.
6. Farooqi, I.S., *Monogenic Obesity Syndromes Provide Insights Into the Hypothalamic Regulation of Appetite and Associated Behaviors.* Biol Psychiatry, 2022. **91**(10): p. 856-859.
7. Yazdi, F.T., S.M. Clee, and D. Meyre, *Obesity genetics in mouse and human: back and forth, and back again.* PeerJ, 2015. **3**: p. e856.
8. Vaisse, C., J.F. Reiter, and N.F. Berbari, *Cilia and Obesity.* Cold Spring Harb Perspect Biol, 2017. **9**(7).
9. Guo, D.F. and K. Rahmouni, *Molecular basis of the obesity associated with Bardet-Biedl syndrome.* Trends Endocrinol Metab, 2011. **22**(7): p. 286-93.
10. Seo, S., et al., *Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling.* Hum Mol Genet, 2009. **18**(7): p. 1323-31.
11. Geets, E., M.E.C. Meuwissen, and W. Van Hul, *Clinical, molecular genetics and therapeutic aspects of syndromic obesity.* Clin Genet, 2019. **95**(1): p. 23-40.
12. da Fonseca, A.C.P., et al., *Genetics of non-syndromic childhood obesity and the use of high-throughput DNA sequencing technologies.* J Diabetes Complications, 2017. **31**(10): p. 1549-1561.
13. Wang, L., et al., *Bardet-Biedl syndrome proteins regulate intracellular signaling and neuronal function in patient-specific iPSC-derived neurons.* The Journal of Clinical Investigation, 2021. **131**(8).
14. Guo, D.F., et al., *The BBSome Controls Energy Homeostasis by Mediating the Transport of the Leptin Receptor to the Plasma Membrane.* PLoS Genet, 2016. **12**(2): p. e1005890.
15. Feuillan, P.P., et al., *Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance.* J Clin Endocrinol Metab, 2011. **96**(3): p. E528-35.
16. Loos, R.J.F. and G.S.H. Yeo, *The genetics of obesity: from discovery to biology.* Nat Rev Genet, 2022. **23**(2): p. 120-133.
17. Forsythe, E., et al., *Genetic predictors of cardiovascular morbidity in Bardet–Biedl syndrome.* Clinical genetics, 2015. **87**(4): p. 343-349.
18. Forsythe, E. and P.L. Beales, *Bardet–Biedl syndrome.* European Journal of Human Genetics, 2013. **21**(1): p. 8-13.
19. Castro-Sánchez, S., et al., *Exploring genotype-phenotype relationships in Bardet-Biedl syndrome families.* Journal of Medical Genetics, 2015. **52**(8): p. 503-513.
20. Katsanis, N., J.R. Lupski, and P.L. Beales, *Exploring the molecular basis of Bardet–Biedl syndrome.* Human molecular genetics, 2001. **10**(20): p. 2293-2299.
21. Forsythe, E. and P. Beales, *Bardet-Biedl Syndrome. 2003 Jul 14 [updated 2015 Apr 23].* GeneReviews University of Washington, Seattle, 2003.
22. Agrawal, H., G. Dokania, and H.D. Allen, *Visual Diagnosis: Visual Impairment, Polydactyly, and Obesity: Red Flags in a Child.* Pediatrics in Review, 2018. **39**(5): p. e21-e23.

23. Khan, O.A., et al., *Rarity of Laurence Moon Bardet Biedl Syndrome and its poor management in the Pakistani population.* Cureus, 2019. **11**(2).
24. Putoux, A., et al., *Phenotypic variability of Bardet-Biedl syndrome: focusing on the kidney.* Pediatric Nephrology, 2012. **27**: p. 7-15.
25. Sherafat-Kazemzadeh, R., S.Z. Yanovski, and J.A. Yanovski, *Pharmacotherapy for childhood obesity: present and future prospects.* International journal of obesity, 2013. **37**(1): p. 1-15.
26. Beales, P., et al., *New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey.* Journal of medical genetics, 1999. **36**(6): p. 437-446.
27. Weihbrecht, K., et al., *Keeping an eye on Bardet-Biedl syndrome: a comprehensive review of the role of Bardet-Biedl syndrome genes in the eye.* Medical research archives, 2017. **5**(9).
28. Mujahid, S., et al., *The endocrine and metabolic characteristics of a large Bardet-Biedl syndrome clinic population.* The Journal of Clinical Endocrinology & Metabolism, 2018. **103**(5): p. 1834-1841.
29. NHS Commissioning Board., *UK for Bardet-Biedl syndrome service*. 2013.
30. Bhaskaran, K., et al., *Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK.* Lancet Diabetes Endocrinol, 2018. **6**(12): p. 944-953.
31. Lindberg, L., et al., *Association of childhood obesity with risk of early all-cause and cause-specific mortality: A Swedish prospective cohort study.* PLoS Med, 2020. **17**(3): p. e1003078.
32. Santé, H., *Overweight and obesity in adults: first-line medical management. Availble at: https://www.has-sante.fr/upload/docs/application/pdf/2012-10/overweight_and_obesity_in_adults_first_line_medical_management_version_anglaise.pdf*. 2011.
33. Estrada, E., et al., *PDB109 BURDEN OF ILLNESS ASSOCIATED WITH HYPERPHAGIA AND SEVERE OBESITY.* Value in Health, 2019. **22**: p. S592.
34. Nigatu, Y.T., U. Bültmann, and S.A. Reijneveld, *The prospective association between obesity and major depression in the general population: does single or recurrent episode matter?* BMC Public Health, 2015. **15**(1): p. 1-8.
35. Djalalinia, S., et al., *Health impacts of obesity.* Pakistan journal of medical sciences, 2015. **31**(1): p. 239.
36. Heymsfield, S.B., et al., *Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia.* Obesity (Silver Spring), 2014. **22 Suppl 1**(0 1): p. S1-s17.
37. Holm, J.-C., *Interview*. 2023.
38. Signe Beck-Nielsen, *Interview*. 2023.
39. Haqq, A.M., et al., *Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alstrom syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period.* Lancet Diabetes Endocrinol, 2022a. **10**(12): p. 859-868.
40. Rhythm Pharmaceuticals Inc, *Clinical Study Report: RM-493-023 A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alstrom Syndrome (AS) Patients with Moderate to Severe Obesity. [Data on file].* 2021. .
41. Bertelsen, M., et al., *Prevalence and diagnostic spectrum of generalized retinal dystrophy in Danish children.* Ophthalmic epidemiology, 2013. **20**(3): p. 164-169.
42. Hjortshøj, T.D., et al., *Bardet-Biedl syndrome in Denmark—report of 13 novel sequence variations in six genes.* Human mutation, 2010. **31**(4): p. 429-436.

43. Hjortshøj, T.D., et al., *Risk for cancer in patients with Bardet-Biedl syndrome and their relatives.* American Journal of Medical Genetics Part A, 2007. **143**(15): p. 1699-1702.
44. Orphanet. *Bardet-Biedl syndrome*. 2021 2023-03-13]; Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=3244&Disease_Disease_Search_diseaseGroup=bardet-biedl&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Bardet-Biedl-syndrome&title=Bardet-Biedl%20syndrome&searc.
45. Forsythe, E. and B. PL, *Bardet-Biedl Syndrome. 2003 Jul 14 [updated 2015 Apr 23].* GeneReviews®[Internet]. Seattle (WA): University of Washington, Seattle, 1993. **2019**.
46. Bank, T.W. *Population total - Denmark*. 2022; Available from: https://data.worldbank.org/indicator/SP.POP.TOTL?locations=DK.
47. Lægehåndbogen., *Lægehåndbogen. Bardet-Biedls syndrom. Fagligt opdateret: 27.10.2021 Availble at: sundhet.dk*. 2021.
48. Buscher, A.K., et al., *Obesity in patients with Bardet-Biedl syndrome: influence of appetite-regulating hormones.* Pediatr Nephrol, 2012. **27**(11): p. 2065-2071.
49. Trier, C., et al., *Obesity treatment effect in Danish children and adolescents carrying Melanocortin-4 Receptor mutations.* Int J Obes (Lond), 2021. **45**(1): p. 66-76.
50. Haqq, A.M., et al. , *Impact of Setmelanotide on Metabolic Syndrome Risk in Patients With Bardet-Biedl Syndrome. Accepted for "oral presentation"*, in *Obesity Society's Obesity Week*. 2023: Dallas, USA.
51. Haqq, A.e.a. *Impact of Setmelanotide on Future Metabolic Syndrome Risk in Pediatric Patients With Bardet-Biedl Syndrome. Accepted for "oral presentation"*. in *Annual Meeting of the European Society for Paediatric Endocrinology*. 2023. The Hague, The Netherlands.
52. Poitou, C., et al., *Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the POMC, LEPR, and MC4R genes.* Surgery for obesity and related diseases, 2021. **17**(8): p. 1449-1456.
53. Cole, T.J., J.V. Freeman, and M.A. Preece, *Body mass index reference curves for the UK, 1990.* Arch Dis Child, 1995. **73**(1): p. 25-9.
54. Ford, A.L., et al., *What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health?* Arch Dis Child, 2010. **95**(4): p. 256-61.
55. Kolsgaard, M.L., et al., *Reduction in BMI z-score and improvement in cardiometabolic risk factors in obese children and adolescents. The Oslo Adiposity Intervention Study - a hospital/public health nurse combined treatment.* BMC Pediatr, 2011. **11**: p. 47.
56. Kirk, S., et al., *The relationship of health outcomes to improvement in BMI in children and adolescents.* Obes Res, 2005. **13**(5): p. 876-82.
57. Grossman, D.C., et al., *Screening for Obesity in Children and Adolescents: US Preventive Services Task Force Recommendation Statement.* Jama, 2017. **317**(23): p. 2417-2426.
58. Wiegand, S., et al., *Predicting weight loss and maintenance in overweight/obese pediatric patients.* Horm Res Paediatr, 2014. **82**(6): p. 380-7.
59. Fiechtner, L., et al., *Characteristics of achieving clinically important weight loss in two paediatric weight management interventions.* Pediatr Obes, 2021. **16**(9): p. e12784.
60. WHO, *World Health Organization. Computation of Centiles and Z-Scores for Height-for-Age, Weight-for-Age amd BMI-for-Age.*

61. Finansministeriet, *Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente*. 2021.
62. Haws, R., et al., *Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome.* Diabetes, Obesity and Metabolism, 2020. **22**(11): p. 2133-2140.
63. Haws, R., et al., *A Phase 3 Trial in Participants With Obesity Due to Bardet-Biedl Syndrome or Alström Syndrome: Efficacy and Safety of the Melanocortin 4 Receptor Agonist Setmelanotide.* 2021d(2472-1972 (Electronic)).
64. Argente, J., et al., *ODP606 Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome.* J Endrocr Soc., 2022. **6**(A14).
65. Argente, J., Clement, K., Dollfus, H., Han, J., Haqq, A., Martos-Moreno, G., ... & Haws, R., *Phase 3 Trial of Setmelanotide in Participants With Bardet-Biedl Syndrome: Placebo-Controlled Results.* Hormone Research in Paediatrics 2021. **94**: p. 30-31.
66. Haws, R., Clement, K., Dollfus, H., Haqq, A., Martos-Moreno, G., Chung, W., Mittleman, R., Stewart, M., Webster, M., Yuan, G., Argente, J.. E, *Efficacy and safety of open-label setmelanotide in bardet-biedl syndrome: a phase 3 trial.* Obesity (Silver Spring, Md.), 2021c. **29**: p. 12.
67. Forsythe, E., Haws, R, Argente, J, et al. , *Quality of life in patients with bardet-biedl syndrome in a setmelanotide phase 3 trial.* Obesity (Silver Spring), 2021. **29150, Poster 257**.
68. Evidera, *Data on file. Assessment of Utilities Associated with Hyperphagia*. 2021.
69. Riazi, A., et al., *Health-related quality of life in a clinical sample of obese children and adolescents.* Health and Quality of Life Outcomes, 2010. **8**(1): p. 134.
70. Alsumali, A., et al., *Cost-Effectiveness Analysis of Bariatric Surgery for Morbid Obesity.* Obes Surg, 2018. **28**(8): p. 2203-2214.
71. Sullivan, P.W., et al., *Catalogue of EQ-5D scores for the United Kingdom.* Med Decis Making, 2011. **31**(6): p. 800-4.
72. Søltoft, F., M. Hammer, and N. Kragh, *The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England.* Qual Life Res, 2009. **18**(10): p. 1293-9.
73. NICE, *Non-alcoholic fatty liver disease (NAFLD): assessment and management Appendix N, Cost-effectiveness analysis: diagnostic tests for NAFLD and advanced fibrosis*. 2016.
74. Matza, L.S., et al., *Utilities and disutilities for type 2 diabetes treatment-related attributes.* Qual Life Res, 2007. **16**(7): p. 1251-65.
75. Boye, K.S., et al., *Utilities and disutilities for attributes of injectable treatments for type 2 diabetes.* Eur J Health Econ, 2011. **12**(3): p. 219-30.
76. Spanggaard, M., et al., *The substantial costs to society associated with obesity - a Danish register-based study based on 2002-2018 data.* Expert Rev Pharmacoecon Outcomes Res, 2022. **22**(5): p. 823-833.
77. Jennum, P., R. Ibsen, and J. Kjellberg, *Social consequences of sleep disordered breathing on patients and their partners: a controlled national study.* Eur Respir J, 2014. **43**(1): p. 134-44.
78. Salmon, J.H., et al., *Economic impact of lower-limb osteoarthritis worldwide: a systematic review of cost-of-illness studies.* Osteoarthritis and Cartilage, 2016. **24**(9): p. 1500-1508.
79. Hagström, H., et al., *Health Care Costs of Patients With Biopsy-Confirmed Nonalcoholic Fatty Liver Disease Are Nearly Twice Those of Matched Controls.* Clin Gastroenterol Hepatol, 2020. **18**(7): p. 1592-1599.e8.
80. Pulleyblank, R., M. Laudicella, and K.R. Olsen, *Cost and quality impacts of treatment setting for type 2 diabetes patients with moderate disease severity: Hospital- vs. GP-based monitoring.* Health Policy, 2021. **125**(6): p. 760-767.

81. Hallberg, S., et al., *Healthcare costs associated with cardiovascular events in patients with hyperlipidemia or prior cardiovascular events: estimates from Swedish population-based register data.* Eur J Health Econ, 2016. **17**(5): p. 591-601.
82. EMA, *Guideline on clinical evaluation of medicinal products used in weight management* 2016.
83. FDA, *Guidance for Industry: Developing Products for Weight Management* 2007.
84. Khan, K.A., et al., *Mapping EQ-5D utility scores from the PedsQL™ generic core scales.* Pharmacoeconomics, 2014. **32**(7): p. 693-706.
85. Perneger, T.V. and D.S. Courvoisier, *Exploration of health dimensions to be included in multi-attribute health-utility assessment.* Int J Qual Health Care, 2011. **23**(1): p. 52-9.
86. Fehnel, S.E., et al., *Development Of The Hyperphagia Questionnaire For Use In Prader-Willi Syndrome Clinical Trials.* Value in Health, 2015. **18**(3): p. A25.
87. Howell, T.A., et al., *Health state utilities associated with hyperphagia: Data for use in cost-utility models.* Obes Sci Pract, 2023. **9**(4): p. 376-382.
88. Ara, R. and J.E. Brazier, *Populating an economic model with health state utility values: moving toward better practice.* Value Health, 2010. **13**(5): p. 509-18.
89. Rigshospitalet. *Rigshospitalets Labportal*. Available from: https://labportal.rh.dk/Labportal.asp?ShowStart=Y.
90. Læger.dk, *Takstkort 29A Laboratorieundersøgelser*. 2023.
91. Læger.dk, *Takstkort 19A Pædiatri* 2023.
92. Ahmad, A., et al., *Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey.* JRSM Open, 2014. **5**(1): p. 2042533313512479.
93. Medicinrådet, *Værdisætning af enhedsomkostninger*. 2023.
94. Rhythm Pharmaceuticals Inc, *Clinical Study Report: RM-493-022 [Data on file].*
95. M'Hamdi, O., et al., *Prevalence of Bardet-Biedl syndrome in Tunisia.* Journal of Community Genetics, 2011. **2**(2): p. 97-99.
96. Reinehr, T., et al., *Definable Somatic Disorders in Overweight Children and Adolescents.* Journal of Pediatrics, 2007. **150**(6): p. 618-622.e5.
97. Webb, M.P., et al., *Autosomal recessive Bardet-Biedl syndrome: First-degree relatives have no predisposition to metabolic and renal disorders.* Kidney International, 2009. **76**(2): p. 215-223.
98. Moore, S.J., et al., *Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study.* American Journal of Medical Genetics. Part A, 2005. **132A**(4): p. 352-60.
99. Hamlington, B., et al., *Characterization of courtesy stigma perceived by parents of overweight children with bardet-biedl syndrome.* PLoS ONE, 2015. **10**(10).
100. Saeed, S., et al., *Genetic causes of severe childhood obesity: A remarkably high prevalence in an inbred population of Pakistan.* Diabetes, 2020. **69**(7): p. 1424-1438.
101. Martos-Moreno GA, et al., *OR22-05 Rare Biallelic Variants in Obesity-Related Genes in the Madrid Pediatric Obesity Cohort.* Journal of the Endocrine Society, 2020. **4**(Supplement_1).
102. Haws, R., Clement, K., Dollfus, H., Freemark, M., Han, J., Haqq, A., Martos-Moreno, G., Webster, M., Stewart, M., Mittleman, R., Yanovski, J., Yuan, G., Argente, J.,, *Efficacy and safety of the melanocortin 4 receptor agonist setmelanotide in obesity due to bardet-biedl syndrome or alstrom syndrome: A phase 3 trial.* Hormone Research in Paediatrics, 2021b. **94**: p. 91.
103. Haws, R.M., et al., *The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alstrom syndrome: Phase 3 trial design.* Contemporary Clinical Trials Communications, 2021a. **22 (no pagination)**.

104. Han, J.C., et al., *Comprehensive Endocrine-Metabolic Evaluation of Patients with Alstrom Syndrome Compared with BMI-Matched Controls.* Journal of Clinical Endocrinology and Metabolism, 2018. **103**(7): p. 2707-2719.
105. Forsythe, E., et al., *The Multifaceted Burden Experienced by Caregivers of Individuals With Bardet-Biedl Syndrome: Findings from the CARE-BBS Study.* Hormone Research in Paediatrics, 2022a. **95**(SUPPL 2): p. 50-50.
106. Haws, R.M., et al., *Setmelanotide Treatment in Pediatric and Adolescent Patients With Bardet-Biedl Syndrome and Severe Obesity.* Hormone Research in Paediatrics, 2022. **95**: p. 118-119.
107. Forsythe, E., et al., *Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet-Biedl syndrome: phase 3 trial results.* Orphanet J Rare Dis, 2023. **18**(1): p. 12.
108. Argente, J., et al., *Effects of Setmelanotide Treatment in Children and Adolescents With Proopiomelanocortin (POMC) Deficiency, Leptin Receptor (LEPR) Deficiency, and Bardet-Biedl Syndrome (BBS).* Hormone Research in Paediatrics, 2022b. **95**(SUPPL 2): p. 74-75.
109. Haqq, A.M., et al., *Exploration of Clinical Improvements Following Setmelanotide in Patients With Bardet-Biedl Syndrome.* Obesity, 2022b. **30**: p. 142.
110. Dykens, E.M., et al., *Assessment of hyperphagia in Prader-Willi syndrome.* Obesity (Silver Spring), 2007. **15**(7): p. 1816-26.
111. Forsythe, E., et al., *Caregiver Burden in Bardet-Biedl Syndrome: a Survey of Obesity and Hyperphagia Impacts.* Hormone Research in Paediatrics, 2022b. **95**: p. 104-105.
112. NICE, *Setmelanotide for treating obesity caused by LEPR or POMC deficiency*. 2022.

Appendix A. Main characteristics of studies included

Table 70 - Table 72 present a summary of the main characteristics of the included studies.

Table 70 Main characteristic of study RM-493-023

Trial name: RM-493-023	NCT number: NCT03746522
Objective	To Evaluate the superiority of setmelanotide versus placebo over a period of 14 weeks, followed by an open-label treatment period of 52 weeks for patients who initially received placebo and of 38 weeks for those who initially received setmelanotide.
Publications – title, author, journal, year	• Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period, Haqq, R., et al., Lancet Diabetes Endocrinol, 2022. • ODP606 Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome Argente, J., et al.,. J Endrocr Soc., 2022. • Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome,Haws, R., et al.,. Diabetes, Obesity and Metabolism, 2020. • A phase 3 trial in participants with obesity due to Bardet-Biedl syndrome or Alström syndrome: efficacy and safety of the melanocortin 4 receptor agonist setmelanotide. Haws, R., et al., Journal of the Endocrine Society, 2021.
Study type and design	A randomised, double-blind, placebo-controlled, phase 3 study, with an open-label period. Additionally, the study had a paralell-group design with three treatment periods. In period one (14 weeks), patients were randomised in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive setmelanotide or placebo once daily via subcutaneous injection. In periods two (38-week open-label treatment period) and three (14-week open-label treatment period), all patients received setmelanotide. Hence, no randomization occurred in periods two and three. The study was completed.
Sample size (n)	38 patients were enrolled 36 patients entered the 52-week open-label period 28 patients completed the study.

Trial name: RM-493-023	NCT number: NCT03746522
Main inclusion criteria	• BBS clinical diagnosis as per Beales, 1999 (with either 4 primary features or 3 primary and 2 secondary features) Or AS diagnosis as per Marshall, 2007 (using major and minor age adjusted criteria). • Greater than or equal to ≥6 years of age. • Obese, defined as BMI ≥30 kg/m2 for patients ≥16 years of age or weight >97th percentile for age and sex on growth chart assessment for patients 6 to 15 years of age. • Study participant and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the study, and is able to understand and sign the written informed consent/assent. • Female participants of child-bearing potential must be confirmed non-pregnant and agree to use contraception as outlined in the protocol. Female participants of non-childbearing potential, defined as: surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening follicle stimulating hormone (FSH) level in the post-menopausal lab range), or failure to have progressed to Tanner Stage V and/or failure to have achieved menarche, do not require contraception during the study. • Male participants with female partners of childbearing potential must agree to use a double barrier method contraception if they become sexually active during the study or within 90 days following their participation in the study. Male patients must also not donate sperm during and for 90 days following their participation in the study.
Main exclusion criteria	• Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents (including herbal medications) that has resulted in >2% weight loss. These patients may be reconsidered approximately 1 month after cessation of such intensive regimens. • Current or prior (within prior 2 months) use of any medication, including those approved to treat obesity, that could impact the efficacy results of this study (eg, orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, liraglutide). Patients on a stable dose and regimen (for at least 2 months) of medication to treat attention deficit hyperactivity disorder (ADHD) may be enrolled in the study as long as they agree to remain on the same dose and regimen during the study. • Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain. Specifically, patients may be considered if surgery was not successful, resulted in <10% weight loss compared to pre-operative baseline weight, or

there is clear evidence of weight regain after an initial response to bariatric surgery. All patients with a history of bariatric surgery must be discussed with, and receive approval from, the Sponsor prior to enrollment.

- Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) disorders that the Investigator believes will interfere significantly with study compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
- In patients with no significant neurocognitive deficits:
- A PHQ-9 score of ≥15 and/or
- Any suicidal ideation of type 4 or 5 on the C-SSRS, any lifetime history of a suicide attempt, or any suicidal behaviour in the last month.
- Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
- History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests (as indicated by abnormal liver function tests, alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin >1.5x the upper limit of normal [ULN] for any of these tests) for an aetiology other than non-alcoholic fatty liver disease (NAFLD). Thus, any underlying aetiology besides NAFLD, including diagnosed non-alcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not be exclusionary.
- Moderate to severe renal dysfunction defined as <30 mL/min (Appendix 11.6).
- History or close family history (parents or siblings) of skin cancer or melanoma (excluding non-invasive basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
- Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by a qualified dermatologist during screening. Any concerning lesions identified during the screening period will be biopsied and results must be known to be benign prior to enrollment. If the pre-treatment biopsy

Trial name: RM-493-023	NCT number: NCT03746522
	results are of concern, the patient should be excluded from the study. • Patient is, in the opinion of the Study Investigator, not suitable to participate in the study. • Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing. • Significant hypersensitivity to study drug. • Inability to comply with QD injection regimen.
Intervention	Setmelanotide 1.0 mg, 2.0 mg or 3.0 mg administered subcutaneously once daily
Comparator(s)	Matching placebo administered subcutaneously once daily over the first 14 weeks. No comparator for the remaining study periods.
Follow-up time	52-weeks.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary Endpoint:** • The proportion of pivotal patients (BBS and AS) aged ≥12 years in the FAS population who achieved a clinically-meaningful reduction in body weight (≥10%) from active-treatment baseline. **Secondary Endpoints:** • Mean percent change in body weight from baseline in patients aged ≥12 years after ~52 weeks of treatment. • Percent change in daily hunger score from baseline in patients aged ≥12 years after ~52 weeks of treatment. Hunger was assessed in patients aged ≥12 years who were not considered cognitively impaired, using the Daily Hunger Questionnaire. In patients assessed as cognitively impaired, hunger was assessed using the Prader-Willi syndrome Food Problem Diary (PWS FPD), a caregiver-completed questionnaire designed to assess behaviours associated with hunger; the PWS FPD was used as there is no validated hunger assessment specifically for patients with BBS and cognitive impairment. Two global hunger questions were used to assess the current static hunger state comprising: the patient global impression of severity (PGIS) and the patient global impression of change (PGIC); the PGIS was administered at baseline and both PGIS and PGIC were administered at each subsequent visit. Three aspects of

hunger (average hunger in the last 24 hours, most/worst hunger in the last 24 hours, and morning hunger) were assessed daily using a numeric rating score for each from 0 to 10, with 0 = not hungry at all and 10 = hungriest possible.

- The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% after ~52 weeks of treatment.

Secondary efficacy analyses for the 14-week, placebo-controlled period comprised:

- Mean percent change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment.
- Mean percent change in weekly average of daily hunger score from baseline in patients aged ≥12 years after ~14 weeks of treatment.

Exploratory Endpoints:

- The proportion of patients of any age who achieved a ≥10% reduction from baseline in body weight after ~52 weeks of treatment.
- The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% at 14 weeks.
- Composite response rate, defined as patients who achieved either a ≥10% reduction in body weight or a ≥25% improvement in the weekly average of daily hunger score at ~52 weeks of treatment.
- The proportion of patients aged ≥12 years who met categorical thresholds of 5%, 15%, 20%, 25%, 30%, 35%, and 40% weight loss from baseline after ~52 weeks of treatment.
- The proportion of patients aged ≥12 years who achieved a ≥10% reduction from baseline in body weight or a ≥15% reduction in BMI after ~52 weeks of treatment.
- Change and percent change in BMI Z-score from baseline after ~52 weeks of treatment in paediatric patients by age group (6-11 years and/or 6-16 years).
- Descriptive statistics for change and percent change from baseline in waist circumference after ~52 weeks of treatment
- Descriptive statistics for change and percent change from baseline in total body mass (including body fat, non-bone lean mass, and bone density) after ~52 weeks of treatment.
- Summary statistics for global hunger response by active-treatment visit based on the questions: “Overall, how would you rate the hunger you experience now?” for patients aged ≥12 years; and “How hungry is your child acting now?” for patients aged <12 years.

Trial name: RM-493-023		NCT number: NCT03746522
	• Descriptive statistics for change and percent change from baseline in PWS-FPD and the Prader-Willi syndrome Sensory Experiences Questionnaire (PWS-SEQ) after ~14 weeks of treatment for cognitively impaired patients aged ≥12 years after ~52 weeks of treatment. • Descriptive statistics for change and percent change from baseline in measures of insulin sensitivity/resistance (fasting glucose, HbA1c, oral glucose tolerance test, and insulin) after ~52 weeks of treatment. • Descriptive statistics for change and percent change from baseline in fasting lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) after ~52 weeks of treatment. • SF-36 health survey version 2 (SF-36V2) and SF-10 health survey for children domain and composite summary score and change from baseline after ~52 weeks of treatment. • Quality of life after 14 and ~52 weeks of treatment, as measured by the Paediatric Quality of Life Inventory (PedsQL) or Impact of Weight on Quality of Life-Lite (IWQOL-Lite), age-dependent, and EQ-5D actual scores and change from baseline.	
Method of analysis	Intention-to-treat. The primary endpoint was assessed using the FAS. The FAS comprised patients who received at least 1 setmelanotide dose and had baseline data.	
Subgroup analyses	**Patients with cognitive impairment** • Ad-hoc analysis • 95% CI and one-sided p-values estimated using Rubin's rule.	
Other relevant information	Not applicable.	

Table 71 Main characteristic of study RM-493-022

Trial name:RM-493-022	NCT number: NCT03651765
Objective	To provide up to two years additional setmelanotide treatment for patients who completed a prior index study for genetic obesity disorders with a mutation upstream of the MC4 receptor in the melanocortin-leptin pathway.
Publications – title, author, journal, year	• ODP606 Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome Argente, J., et al.,. J Endrocr Soc., 2022.
Study type and design	An open-label extension study of up to an additional 2 years of treatment with setmelanotide for patients who had completed a prior setmelanotide study.
Sample size (n)	54
Main inclusion and exclusion criteria	**Inclusion criteria.** • Patients aged 2 or older (or aged >2 years as per local regulations) who have completed participation in a previous setmelanotide trial and demonstrated adequate safety and meaningful clinical benefit (efficacy). • Patient and/or parent or guardian is able to communicate with the investigator, understand and sign the written informed consent/assent, and comply with the trial requirements. • Agree to use a highly effective form of contraception throughout the trial. **Exclusion criteria:** • Pregnant and/or breastfeeding women. • Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion). • Current, clinically significant disease. • Documented diagnosis of schizophrenia, bipolar disorder, personality disorder, major depressive disorder, or other psychiatric disorder(s). • Suicidal ideation, attempt or behaviour. • History of significant liver disease. • Moderate to severe renal dysfunction as defined by a glomerular filtration rate (GFR) <30 mL/min. • History or close family history of melanoma or patient history of oculocutaneous albinism.

Intervention	Setmelanotide 1.0 mg, 2.0 mg or 3.0 mg administered subcutaneously once daily.
Comparator(s)	None.
Follow-up time	36 months.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Primary endpoint:** • The safety and tolerability of setmelanotide. **Secondary endpoints:** • No secondary endpoints were specified for this study **Exploratory endpoints:** • The proportion of patients with ≥10% weight loss; hunger score; body composition; waist circumference; lipid levels; quality of life; biomarkers predictive of a setmelanotide response; C-SSRS and PHQ-9 scores.
Method of analysis	Intention-to-treat.
Subgroup analyses	**Patients with cognitive impairment**
Other relevant information	N/A

Table 72 Main characteristic of study RM-493-014

Trial name: RM-493-014	NCT number: NCT03013543
Objective	The purpose of the study is to determine the effect of setmelanotide (RM-493) on weight, hunger assessments and other factors in patients with rare genetic disorders of obesity.
Publications – title, author, journal, year	Haws R, Brady S, Davis E, Fletty K, Yuan G, Gordon G, Stewart M, Yanovski J. Diabetes Obes Metab. 2020
Study type and design	An open-label, single-arm, basket-design, Phase 2 pilot study assessing the effect of setmelanotide on obesity in patients with various rare genetic disorders of obesity over an initial dose titration/proof-of-concept phase of up to 12-weeks. Patients who demonstrated at least 5 kg weight loss at the end of 12 weeks continued into the 52-week extension phase.
Sample size (n)	10

Main inclusion and exclusion criteria	**Inclusion criteria:**
	• Patients with the following genotypes and/or clinical assessment:
	  ○ POMC/PCSK1/LEPR heterozygous - not currently enrolling new patients.
	  ○ POMC/PCSK1/LEPR compound heterozygous (two different mutations in gene) or homozygous deficiency obesity.
	  ○ POMC/PCSK1/LEPR composite heterozygous (two or more mutations in two or more genes) deficiency obesity.
	  ○ Smith-Magenis Syndrome (SMS).
	  ○ SH2B1 deficiency obesity.
	  ○ Chromosomal rearrangement of the 16p11.2 locus causing obesity.
	  ○ CPE compound heterozygous or homozygous deficiency obesity.
	  ○ Leptin deficiency obesity with loss of response to metreleptin.
	  ○ SRC1 deficiency obesity.
	• MC4R deficiency obesity.
	• Age 6 years and above.

- Obese, defined as Body Mass Index (BMI) ≥ 30 kg/m2 for patients ≥16 years of age or BMI≥ 95th percentile for age and gender for patients 6 up to 16 years of age.
- Patient and/or parent or guardian is able to understand and comply with the requirements of the study and is able to understand and sign the written informed consent/assent.
- Female participants of child-bearing potential must be confirmed non-pregnant, and agree to use contraception as outlined in the protocol.
- Male participants with female partners of childbearing potential must agree to a double barrier method if they become sexually active during the study. Male patients must not donate sperm during and for 90 days following their participation in the study.

Exclusion criteria:

- Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents that has resulted in > 2% weight loss.
- Use of any medication that is approved to treat obesity within three months of first dose of study drug (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion).
- Gastric bypass surgery within the previous six months or any prior gastric bypass surgery resulting in >10% weight loss durably maintained
- Diagnosis of schizophrenia, bipolar disorder, personality disorder, major depressive disorder, or other psychiatric disorder(s)
- Suicidal ideation, attempt or behavior
- Clinically significant pulmonary, cardiac, or oncologic disease
- HbA1c >9.0% at Screening
- History of significant liver disease
- Glomerular filtration rate (GFR) <30 mL/min at Screening.
- History or close family history of melanoma or patient history of oculocutaneous albinism
- Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions.
- Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
- Patients previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
- Inability to comply with QD injection regimen.
- Females who are breastfeeding or nursing.

Intervention	Setmelanotide 0.5 mg, 1.0 mg with dose titration in 0.5 mg increments every 2 weeks to a maximum of 3.0 mg, administered subcutaneously once daily.
Comparator(s)	None.
Follow-up time	52 weeks.
Is the study used in the health economic model?	No. The trial was not designed as an efficacy study.
Primary, secondary and exploratory endpoints	**Primary Endpoint: [Time Frame: Baseline to 3 months].** • Effect of Setmelanotide on Body Weight Reduction The proportion of patients in each subgroup of RGDO who achieve at least 5% body weight reduction from baseline at ~3 months treatment with setmelanotide. **Secondary Endpoint (timeframe: baseline to 3 months):** • Change and percentage change in body weight. • Change and percentage change from baseline in body weight. • Change in daily most hunger scores. • Change in the weekly average of the daily hunger score from Baseline at 3 months. • Change in waist circumference. • Change from baseline in waist circumference. • Mean percent change in BMI. • Mean percent change in body mass index from baseline at 3 months. • Mean change in BMI-Z score in patients <12 years old. • Mean change in BMI-Z score from Baseline at 3 months. • Mean change in BMI-Z score in patients ≥12 to <18 years old. • Mean change in BMI-Z score in patients ≥12 to <18 years old from Baseline at 3 months.
Method of analysis	**Intention-to-treat**
Subgroup analyses	N/A
Other relevant information	N/A

Appendix B. Efficacy results per study

B.1 Results per study RM-493-023

Table 73 show the results of the outcomes in study RM-493-023.

Table 73 Results per study

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Primary endpoint: Proportion of pivotal FAS patients ≥12 years of age who achieved a ≥10% reduction in body weight from	Pivotal ≥12-year-old FAS, after last enrolled patient in the Pivotal cohort has completed Period 2 (W52)	31	N/A	Estimated % 32.3	(16.7,51.4)	0.006	N/A	N/A	N/A	The clinically meaningful reduction in body weight was defined as ≥10% from active-treatment baseline after ~52 weeks of setmelanotide treatment. The estimated proportion was statistically significant (p=0.0006) compared with a historical control rate of 10%. Estimated %, 95% CI and p-value are based on Rubin's Rule. P-value is one-sided and compared with alpha = 0.025	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
baseline after ~52 weeks of treatment compared to a historical untreated proportion of 10%											
Primary endpoint (post-hoc analysis): Proportion of BBS patients ≥12 years of age who achieved a ≥10% reduction	BBS patients ≥12 years	28	N/A	Estimated % 35.7	(18.6, 55.9)	0.0002	N/A	N/A	N/A	See above.	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
in body weight											
Primary endpoint (post-hoc analysis): Proportion of BBS patients ≥18 years of age who achieved a ≥10% reduction in body weight	BBS patients ≥18 years	15	N/A	Estimated % 46.7	(21.3, 73.4)	0.0003	N/A	N/A	N/A	See above.	[40]
First key secondary endpoint: Mean percent change	Pivotal ≥12-year-old FAS	31	N/A	Mean (SD), -5.21 (7.892)	(-8.10, -2.31)	0.0005	N/A	N/A	N/A	95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
from active treatment baseline in body weight after ~52 weeks of treatment for patients in the ≥18yo pivotal FAS populatio n											
First key secondary endpoint (post-hoc analysis): Mean percent change	Pivotal ≥18-year-old FAS, after last enrolled patient in the Pivotal cohort has completed	15	N/A	Mean (SD), -7.57 (7.139)	(-11.52, -3.62)	0.0005	N/A	N/A	N/A	95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
from active treatment baseline in body weight after ~52 weeks of treatment for patients in the ≥18yo pivotal FAS populatio n	Period 2 (W52)										
Second key secondary endpoint: Mean percent change from	≥12yo FAS, pivotal, not cognitively impaired	16	NA	Mean (SD): -30.91 (24.733)	-44.09, -17.73	<0.0001	N/A	N/A	N/A	The mean value is given in Mos/worst hunger over 24 hours. Peak (most/worst) hunger does not require patients to do a mathematical computation (as does average hunger) and peak hunger is inherently meaningful and	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
active treatment baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment for patients in the not cognitively impaired ≥12yo pivotal FAS populatio n										conceptually equivalent to standard assessment of other symptom, therefore it is considered the most appropriate among the 3 daily hunger scores. 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025	
Third key secondary	≥12yo FAS, pivotal, not	16	N/A	62.5	(35.4, 84.8)	<0.0001	N/A	N/A	N/A	Based on psychometric analysis, the most appropriate,	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
endpoint: Proportion of not cognitively impaired ≥12yo patients in the pivotal FAS population who achieve a ≥25% improvement from active treatment baseline in the weekly average of the daily hunger score, versus an	cognitively impaired									meaningful, within-patient threshold for most/worst hunger score is a reduction of 1 to 2 points across the populations in whom setmelanotide has been tested in pivotal trials. 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025	

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
historical untreated proportion of 10%.											
Secondary endpoint: Body weight percent change from baseline at 14 weeks in the pivotal ≥12yo PCAS population	Setmelanotide	16	Mean (SD): -2.41 (4.752)	-2.10	-4.92, 0.42	0.0516	N/A	N/A	N/A	All body weight measurements were to be done in triplicate at each timepoint. Whenever possible, the same scale was to be used throughout the study, including the Screening Visit, and calibrated on a regular basis. Weight was to be measured at approximately the same time at each visit and after fasting for at least 8 hours. Patients were to be in light clothing or underwear, with no shoes and have emptied their bladder. If an in-person study visit was not possible due to COVID-19 restrictions, a scale was provided for use at the patient's home to provide	[40]
	Placebo	17	Mean (SD): -0.32 (2.253)								[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										accurate and consistent measurements; weight was measured under direct visual observation during telehealth visits, and the weight data were electronically transmitted to the study site. For critical visits (Weeks 15, 53, and 66), weight assessments may have been obtained at a doctor's office near the patient's home.	
Secondary endpoint (post-hoc analysis): Body weight percent change from baseline at 14 weeks in the	Setmelanotide	10	Mean (SD) -3.93 (3.788)	-3.59	(-6.26, -0.93)	0.0054	N/A	N/A	N/A	In all patients (pivotal and supplemental) aged ≥18 years, treatment with setmelanotide over 14 weeks resulted in significantly greater reduction in body weight from the placebo-controlled period baseline compared with placebo-treated patients. 95% CI and p-value are based on Rubin's Rule. p-value is one-	[40]
	Placebo	12	Mean (SD), 0.34 (2.106)								[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
pivotal ≥18yo PCAS populatio n										sided and compared with alpha = 0.025	
Secondary endpoint: Weekly average daily hunger score percent change from baseline at 14 weeks in the not cognitively impaired pivotal ≥12 years old PCAS	Setmelanotide	7	Mean (SD): -33.38 (15.564)	-20.27	(-35.72, -4.82)	0.0051	N/A	N/A	N/A	Most/worst hunger over 24 hours, based on psychometric analysis. 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025	[40]
	Placebo	10	Mean (SD): -13.11 (15.918)								[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
population											
Exploratory endpoints: 14 weeks											
BMI at PCPB	Setmelanotide	22	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	All body weight measurements were to be done in triplicate at each timepoint. Whenever possible, the same scale was to be used throughout the study, including the Screening Visit, and calibrated on a regular basis. Weight was to be measured at approximately the same time at each visit and after fasting for at least 8 hours. Patients were to be in light clothing or underwear, with no shoes and have emptied their bladder. If an in-person study visit was not possible due to COVID-19 restrictions, a scale was provided for use at the patient's home to provide	[40]
	Placebo	22	[redacted]								[40]
Change in BMI after 14 weeks (kg/m2) after 14 weeks of setmelanotide treatment	Setmelanotide	22	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA		[40]
	Placebo	22	[redacted]								[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Percentage change in BMI after 14 weeks of setmelanotide treatment	Setmelanotide	22	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	accurate and consistent measurements; weight was measured under direct visual observation during telehealth visits, and the weight data were electronically transmitted to the study site. For critical visits (Weeks 15, 53, and 66), weight assessments may have been obtained at a doctor's office near the patient's home. Height (cm) was to be measured, without shoes, using a wall-mounted stadiometer. All measurements were to be done in triplicate at each timepoint. Height was used along with body weight to determine BMI.	[40]
	Placebo	22	[redacted]								[40]
Exploratory endpoints at 52 weeks											

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Percentage of the BMI 95th percentile score at ATB	All patients	16	Mean (SD): 144.47 (35.806)	NA	NA	NA	NA	NA	NA		[40]
Percentage of the BMI 95th percentile score at Week 52	All patients	14	Mean (SD): 126.82 (37.059)	NA	NA	NA	NA	NA	NA		[40]
Change after 52 weeks	All patients	14	NA	Mean (SD): -17.30 (7.674)	-21.73, -12.87	<0.0001	NA	NA	NA		[40]
BMI at ATB (kg/m^2)	Patients <18 years	16	Mean (SD): 37.44 (9.439)	NA	NA	NA	NA	NA	NA	See above.	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
BMI at ATB (kg/m^2)	Patients ≥18 years	15	Mean (SD): 46.35 (5.857)	NA	NA	NA	NA	NA	NA	Subgroup analysis.	[40]
Change in BMI after 52 weeks (kg/m^2)	Patients <18 years	14	NA	Mean (SD): -3.36 (2.070)	-4.55, -2.16	<0.0001	NA	NA	NA		[40]
Change in BMI after 52 weeks (kg/m^2)	Patients ≥18 years	12	NA	Mean (SD): -4.22 (3.335)	-6.34, -2.10	0.0005	NA	NA	NA		[40]
Percent change in BMI after 52 weeks	Patients <18 years	14	NA	Mean (SD): -9.50 (6.440)	-13.22, -5.78	<0.0001	NA	NA	NA		[40]
Percent change in BMI after 52 weeks	Patients ≥18 years	12	NA	Mean (SD): -9.09 (6.760)	-13.39, -4.80	0.0003	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Body fat at ATB (kg)	Pivotal patients	29	Mean (SD): 51.1 (18.9)	NA	NA	NA	NA	NA	NA	Body composition measurements (total body weight, fat, non-bone lean mass) were performed using an appropriate methodology used at the site (e.g., dual-energy X-ray absorptiometry [DXA] scans, bioelectrical impedance analysis [BIA]) to assess changes in body composition during treatment with setmelanotide or placebo. For DXA methodology, which uses low dose x-rays to non-invasively assess skeletal and soft tissue density, half-body scans were permitted for patients who extended beyond the scanning area. For severely obese patients who could not be measured in the available DXA scanner due to practical limitations (size of DXA machine), then other methodologies were to be	[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										considered (i.e., BIA). DXA should have been added at a time when patients had lost enough weight to do adequate DXA measurements (as DXA may provide additional information above BIA, for example).	
Lean muscle mass at ATB (kg)	Pivotal patients	29	Mean (SD): 58.9 (14.1)	NA	NA	NA	NA	NA	NA		[40]
Change in body fat after 52 weeks (kg)	Pivotal patients	18	NA	Mean (SD): -5.6 (12.0)	NA	NA	NA	NA	NA		[40]
Change in lean muscle mass after	Pivotal patients	18	NA	Mean (SD): -1.2 (3.9)	NA	NA	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
52 weeks (kg)											
Percentage change in body fat after 52 weeks (kg)	Pivotal patients	18	NA	Mean (SD): -11.3 (26.3)	NA	NA	NA	NA	NA		[40]
Percentage change in lean muscle mass after 52 weeks (kg)	Pivotal patients	18	NA	Mean (SD): -2.0 (6.5)	NA	NA	NA	NA	NA		[40]
Waist circumference at ATB (cm)	FAS	31	Mean (SD): 117.89 (18.022)	NA	NA	NA	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in waist circumference after 52 weeks (cm)	FAS	25	NA	Mean (SD): -7.18 (7.402)	-10.236, -4.124	NA	NA	NA	NA		[40]
Percent change in waist circumference after 52 weeks	FAS	25	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA		[40]
Total cholesterol (mmol/L) at ATB	FAS	31	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	The lipid profile included total cholesterol, high-density lipoprotein (HDL) cholesterol, lowdensity lipoprotein (LDL) cholesterol and triglycerides. Blood samples were to be collected when the patient was in the fasted state.	[40]
Change in total	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
cholesterol (mmol/L) after 52 weeks				[redacted]							
Percent change in total cholesterol (mmol/L) after 52 weeks	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]
High-density lipoprotein (mmol/L) at ATB	FAS	31	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]
Change in high-density lipoprotein	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(mmol/L) after 52 weeks											
Percent change in high-density lipoprotein (mmol/L) after 52 weeks	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]
Low-density lipoprotein (mmol/L) at ATB	FAS	31	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]
Change in low-density lipoprotei	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
n (mmol/L) after 52 weeks											
Percent change in low-density lipoprotein (mmol/L) after 52 weeks	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]
Triglycerides (mmol/L) at ATB	FAS	31	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]
Change in triglycerides (mmol/L)	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]

Results of Study RM-493-023 (NCT03746522)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
after 52 weeks											
Percent change in triglycerides (mmol/L) after 52 weeks	FAS	23	[redacted]	[redacted]	NA	NA	NA	NA	NA		[40]

B.1.1 Additional endpoints RM-493-023

Below are additional endpoints from RM-493-023

Table 74. BMI shift data for individual patients aged ≥18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients)

Obesity class	BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50+				[redacted]	[redacted]		
IV	45 to <50		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
III	40 to <45	[redacted]	[redacted]				[redacted]	
II	35 to <40	[redacted]		[redacted]				[redacted]
I	30 to < 35			[redacted]				
Over weight	25 to <30							
Class change		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Light grey shading = baseline value; dark grey shading = end of study value

Table 75. BMI Z-score shift data for individual patients aged <18 years who were classified as 52-week responders (Study RM-493-023, pivotal patients)

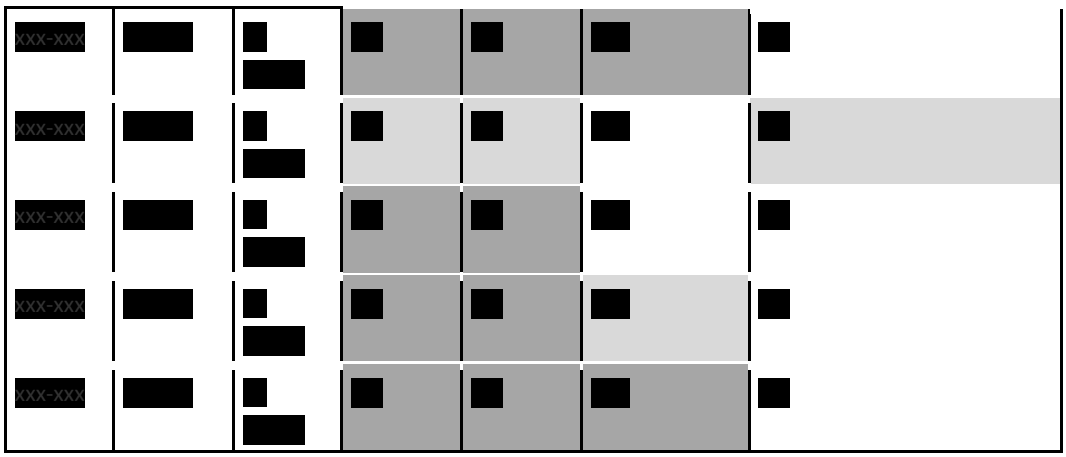
BMI Z-score [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4+		[redacted]		[redacted]		[redacted]			[redacted]			
3.5 to <4					[redacted]					[redacted]		[redacted]
3 to <3.5				[redacted]			[redacted]					
2.5 to <3	xxx				[redacted]					[redacted]		[redacted]
2 to <2.5			[redacted]				[redacted]	[redacted]				
1 to <2	xxx										[redacted]	
<1			[redacted]								[redacted]	

Class change	x											

Light grey shading = baseline value; dark grey shading = end of study value

Table 76. Symptom improvement in patients with BBS aged ≥18 years after 52 weeks of setmelanotide treatment (Study RM-493-023)

Patient	Age at study entry	Time on study	Weight change (%)	Change in BMI (%)	Change in most/ worst hunger (%)	Quality of life improvement
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						
XXX-XXX						



Light grey shading = disease stabilisation; dark grey shading = clinically-meaningful improvement

Table 77 Symptom improvement in patients with BBS aged <18 years after 52 weeks of setmelanotide treatment (Study RM-493-023)

Patient	Age at study entry	Time on study	Change in BMI Z-score	Change in BMI 95th percentile	Quality of life improvement
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Light grey shading = disease stabilisation; dark grey shading = clinically-meaningful improvement

B.2 Results per study RM-493-022

Table 78 show the results of the outcomes in study RM-493-022.

Table 78 Results per study

Results of Study RM-493-022 (NCT03651765)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
BMI at index study baseline (kg/m^2)	Setmelanotide responders	30	Mean (SD): 39.65 (8.97); 90% CI: 36.87, 42.44	NA	NA	NA	NA	NA	NA	All body weight measurements were to be done in triplicate at each timepoint. Whenever possible, the same scale was to be used throughout the study, including the Screening Visit, and calibrated on a regular basis. Weight was to be measured at approximately the same time at each visit and after fasting for at least 8 hours. Patients were to be in light clothing or underwear, with no shoes and have emptied their bladder. If an in-	[94]
Change in BMI after 12 months (kg/m^2)	Setmelanotide responders	30	NA	Mean (SD): -5.53 (2.26)	90% CI: -6.23, -4.82	NA	NA	NA	NA		[94]
Percent change in BMI after 12 months	Setmelanotide responders	30	NA	Mean (SD): -13.78 (4.58)	90% CI: -15.20, -12.36	NA	NA	NA	NA		[94]

Results of Study RM-493-022 (NCT03651765)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in BMI after 18 months (kg/m^2)	Setmelanotide responders	29	NA	Mean (SD): -4.76 (4.11)	90% CI: -6.06, -3.46	NA	NA	NA	NA	person study visit was not possible due to COVID-19 restrictions, a scale was provided for use at the patient's home to provide accurate and consistent measurements; weight was measured under direct visual observation during telehealth visits, and the weight data were electronically transmitted to the study site. For critical visits (Weeks 15, 53, and 66), weight assessments may have been obtained at a doctor's office near the patient's home. Height (cm) was to be measured, without shoes, using a wall-mounted stadiometer. All measurements were to be done in triplicate at each timepoint. Height was used	[94]
Percent change in BMI after 18 months	Setmelanotide responders	29	NA	Mean (SD): -11.97 (9.33)	90% CI: -14.91, -9.02	NA	NA	NA	NA		[94]
Change in BMI after 24 months (kg/m^2)	Setmelanotide responders	24	NA	Mean (SD): -4.35 (5.26)	90% CI: -6.19, -2.51	NA	NA	NA	NA		[94]
Percent change in BMI after 24 months	Setmelanotide responders	24	NA	Mean (SD): -10.74 (12.24)	90% CI: -15.02, -6.45	NA	NA	NA	NA		[94]
Change in BMI after 36 months (kg/m^2)	Setmelanotide responders	12	NA	Mean (SD): -5.45 (6.84)	90% CI: -9.00, -1.91	NA	NA	NA	NA		[94]

Results of Study RM-493-022 (NCT03651765)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Percent change in BMI after 36 months	Setmelanotide responders	12	NA	[redacted]	[redacted]	NA	NA	NA	NA	along with body weight to determine BMI.	[94]

B.2.1 Additional endpoints RM-493-022

Table 79 and Table 80 summarize additional information from the RM-493-022.

Table 79 BMI shift data for individual patients aged ≥18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients)

Obesity class	BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50+				[redacted]	[redacted]		
IV	45 to <50		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
III	40 to <45	[redacted]	[redacted]				[redacted]	
II	35 to <40	[redacted]		[redacted]				[redacted]
I	30 to < 35			[redacted]				
Over weight	25 to <30							
Class change		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Light grey shading = baseline value; dark grey shading = end of study value

Table 80 BMI Z-score shift data for individual patients aged <18 years who were classified as 52-week responders (Study RM-493-023, pivotal patients)

BMI Z-score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4+		[redacted]		[redacted]		[redacted]			[redacted]			
3.5 to <4					[redacted]					[redacted]		[redacted]
3 to <3.5				[redacted]			[redacted]					
2.5 to <3	[redacted]				[redacted]					[redacted]		[redacted]
2 to <2.5			[redacted]				[redacted]	[redacted]				
1 to <2	[redacted]										[redacted]	
<1			[redacted]								[redacted]	
Class change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Light grey shading = baseline value; dark grey shading = end of study value

Appendix C. Comparative analysis of efficacy - not applicable

Not applicable.

Table 81 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] – not applicable

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median overall survival		NA	NA	NA					
Example: 1-year survival									
Example: HRQoL									

Appendix D. Extrapolation – not applicable

Not applicable.

Appendix E. Serious adverse events

All serious adverse events occurred during study RM-493-023 (at 14 and 52 weeks) are presented in Section 9.1.

Appendix F. Health-related quality of life

As the health economic model did not consider the HRQoL in study RM-493, these results were not included in the main body. These main results are presented in the tables below.

Table 82. Impact of setmelanotide in adult participants with BBS (≥18yo) with available baseline and 52-week health related quality of life data

Adult participants with BBS (≥18yo)	
Patients	N=11[a]
IWQOL-Lite total score at baseline, mean (SD)	74.9 (12.6)
Change in IWQOL-Lite total score at 1 year, mean (SD)	+12.0 (10.8)
BMI, % change at 1 year, mean (SD)	−9.4% (7.0%)

Note: [a]IWQOL-Lite is 31-item, self-reported, obesity-specific, quality of life questionnaire which includes domains of physical function, self-esteem, sex life, public distress, and work. The results are reported on 0-100 scale where 100 represents the best quality of life
Abbreviations: IWQOL-Lite, Impact of Weight on Quality of Life-Lite; BMI, body mass index; SD, standard deviation.
Source: Forsythe et al ObesityWeek 2021 Virtual Conference 32

Table 83. Impact of setmelanotide in paediatric participants with BBS (8-17 yo; self-reported) with available baseline and 52-week HRQoL data

Adult participants with BBS (≥18yo)	
Patients	n 9
PedsQL total score at baseline, mean (SD)	67.2 (18.9)
Change in PedsQL total score at 1 year, mean (SD)	+ 11.2 (14.4)
BMI Z score change at 1 year, mean (SD)	−0.7 (0.5)

Note: PedsQL, Paediatric Quality of Life Inventory; BMI, body mass index; BMI Z-score, BMI standard-deviation score SD, standard deviation. Source: Forsythe et al Obesity Week 2021 Virtual Conference 32

EQ-5D-5L scores in the pivotal patients aged ≥16 years without cognitive impairment (n=13) are presented in Table 84. Additionally, Table 85 shows the mean utilities and change in EQ-5D-5L from baseline for subjects ≥12 years old with EQ-5D-5L recorded at all three visits (n=19).

Table 84. Effect of setmelanotide on EQ-5D-5L score in patients aged ≥16 years with and without cognitive impairment (Study RM-493-023, pivotal patients)

	Active-treatment baseline (n=13)	Change from baseline to Week 52 (n=13)
Mobility score, mean (SD)	[redacted]	[redacted]
Self-care score, mean (SD)	[redacted]	[redacted]
Usual activities score, mean (SD)	[redacted]	[redacted]
Pain/discomfort score, mean (SD)	[redacted]	[redacted]
Anxiety/depression score, mean (SD)	[redacted]	[redacted]
VAS, mean (SD)	[redacted]	[redacted]

Note: There were 6 patients with cognitive impairment and 7 without cognitive impairment.

Table 85. Mean EQ-5D-5L utility by weeks using setmelanotide in patients ≥12 years old.

Time on treatment	Mean	Change from baseline		
		Percent change	Mean change	95% CI
Active treatment baseline	[redacted]	[redacted]	[redacted]	[redacted]
14 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]
1 year of treatment	[redacted]	[redacted]	[redacted]	[redacted]

Note: Only include subjects with EQ-5D-5L recorded at all three visits (n=19). The difference at week 52 relative to baseline is significant at 5% confidence level (p-value 0.011)

Appendix G. Probabilistic sensitivity analyses

Table 86 summarizes the parameters used in the PSA.

Table 86. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Baseline BMI Z-score distribution				
0.0-1.0	0%	0%	100%	Dirichlet
1.0-2.0	6%	0%	100%	Dirichlet
2.0-2.5	6%	0%	100%	Dirichlet
2.5-3.0	13%	0%	100%	Dirichlet
3.0-3.5	19%	0%	100%	Dirichlet
3.5-4.0	19%	0%	100%	Dirichlet
≥4.0	38%	0%	100%	Dirichlet
Baseline BMI distribution				
20-25	0%	0%	100%	Dirichlet
25-30	0%	0%	100%	Dirichlet
30-35	6%	0%	100%	Dirichlet
35-40	13%	0%	100%	Dirichlet
40-45	38%	0%	100%	Dirichlet
45-50	19%	0%	100%	Dirichlet
≥50	25%	0%	100%	Dirichlet
Setmelanotide Efficacy				

Response rate-paediatric	86%	0%	100%	Beta
Response rate-adult	47%	0%	100%	Beta
Treatment discontinuation	1%	0%	100%	Beta
SMRs				
SMR for setmelanotide	1.00	0	-	Lognormal
Utility				
Utility by BMI Z-score				
0.0-1.0	0.89	0	1	Beta
1.0-2.0	0.87	0	1	Beta
2.0-2.5	0.86	0	1	Beta
2.5-3.0	0.85	0	1	Beta
3.0-3.5	0.83	0	1	Beta
3.5-4.0	0.82	0	1	Beta
≥4.0	0.81	0	1	Beta
Utility by BMI: 18-30				
20-25	0.91	0	1	Beta
25-30	0.91	0	1	Beta
30-35	0.89	0	1	Beta
35-40	0.88	0	1	Beta
40-45	0.84	0	1	Beta

45-50	0.84	0	1	Beta
≥50	0.80	0	1	Beta
Utility by BMI: 31-40				
20-25	0.89	0	1	Beta
25-30	0.89	0	1	Beta
30-35	0.86	0	1	Beta
35-40	0.83	0	1	Beta
40-45	0.82	0	1	Beta
45-50	0.82	0	1	Beta
≥50	0.77	0	1	Beta
Utility by BMI: 41-50				
20-25	0.86	0	1	Beta
25-30	0.86	0	1	Beta
30-35	0.82	0	1	Beta
35-40	0.79	0	1	Beta
40-45	0.75	0	1	Beta
45-50	0.75	0	1	Beta
≥50	0.70	0	1	Beta
Utility by BMI: 51-60				
20-25	0.83	0	1	Beta
25-30	0.83	0	1	Beta
30-35	0.80	0	1	Beta
35-40	0.77	0	1	Beta

40-45	0.73	0	1	Beta
45-50	0.73	0	1	Beta
≥50	0.69	0	1	Beta
Utility by BMI: 61-70				
20-25	0.81	0	1	Beta
25-30	0.81	0	1	Beta
30-35	0.79	0	1	Beta
35-40	0.76	0	1	Beta
40-45	0.71	0	1	Beta
45-50	0.71	0	1	Beta
≥50	0.66	0	1	Beta
Utility by BMI: >70				
20-25	0.79	0	1	Beta
25-30	0.79	0	1	Beta
30-35	0.76	0	1	Beta
35-40	0.74	0	1	Beta
40-45	0.69	0	1	Beta
45-50	0.69	0	1	Beta
≥50	0.66	0	1	Beta
Hyperphagia Utility Multiplier				
Mild	0.909	0	1	Beta
Moderate	0.72	0	1	Beta
Severe	[redacted]	0	1	Beta

BBS utility decrement multiplier	0.8	0	1	Gamma
Setmelanotide treatment effect on utility	1.000	0	1	Gamma
Nausea/Vomiting				
Disutility	-0.040	0	-1	Beta
Probability	25%	0%	100%	Beta
Injection site reaction				
Disutility	-0.011	0	-1	Beta
Probability	45.5%	0%	100%	Beta
Sleep Apnoea (disutility)				
1.0-2.0	-0.02	0	-1	Normal
2.0-2.5	-0.03	0	-1	Normal
2.5-3.0	-0.03	0	-1	Normal
3.0-3.5	-0.04	0	-1	Normal
3.5-4.0	-0.05	0	-1	Normal
≥4.0	-0.06	0	-1	Normal
Osteoarthritis (disutility)				
1.0-2.0	-0.06	0	-1	Normal
2.0-2.5	-0.10	0	-1	Normal
2.5-3.0	-0.15	0	-1	Normal
3.0-3.5	-0.24	0	-1	Normal
3.5-4.0	-0.38	0	-1	Normal

≥4.0	-0.61	0	-1	Normal
T2DM (disutility)				
1.0-2.0	-0.03	0	-1	Normal
2.0-2.5	-0.03	0	-1	Normal
2.5-3.0	-0.04	0	-1	Normal
3.0-3.5	-0.05	0	-1	Normal
3.5-4.0	-0.06	0	-1	Normal
≥4.0	-0.08	0	-1	Normal
CV Events (disutility)				
1.0-2.0	-0.03	0	-1	Normal
2.0-2.5	-0.04	0	-1	Normal
2.5-3.0	-0.06	0	-1	Normal
3.0-3.5	-0.08	0	-1	Normal
3.5-4.0	-0.11	0	-1	Normal
≥4.0	-0.15	0	-1	Normal
Costs				
BMIz-Related Health Care Costs (Paediatric)				
1.0-2.0	DKK 37,083.12	0	-	Gamma
2.0-2.5	DKK 41,325.24	0	-	Gamma
2.5-3.0	DKK 45,567.36	0	-	Gamma
3.0-3.5	DKK 45,619.55	0	-	Gamma
3.5-4.0	DKK 45,619.55	0	-	Gamma
≥4.0	DKK 45,619.55	0	-	Gamma

BMI-Related Health Care Costs: 18-30				
25-30	DKK 37,083.12	0	-	Gamma
30-35	DKK 41,325.24	0	-	Gamma
35-40	DKK 45,567.36	0	-	Gamma
40-45	DKK 45,619.55	0	-	Gamma
45-50	DKK 45,619.55	0	-	Gamma
≥50	DKK 45,619.55	0	-	Gamma
BMI-Related Health Care Costs: 31-40				
25-30	DKK 37,083.12	0	-	Gamma
30-35	DKK 41,325.24	0	-	Gamma
35-40	DKK 45,567.36	0	-	Gamma
40-45	DKK 45,619.55	0	-	Gamma
45-50	DKK 45,619.55	0	-	Gamma
≥50	DKK 45,619.55	0	-	Gamma
BMI-Related Health Care Costs: 41-50				
25-30	DKK 37,083.12	0	-	Gamma
30-35	DKK 41,325.24	0	-	Gamma
35-40	DKK 45,567.36	0	-	Gamma
40-45	DKK 45,619.55	0	-	Gamma
45-50	DKK 45,619.55	0	-	Gamma
≥50	DKK 45,619.55	0	-	Gamma
BMI-Related Health Care Costs: 51-60				
25-30	DKK 37,083.12	0	-	Gamma

30-35	DKK 41,325.24	0	-	Gamma
35-40	DKK 45,567.36	0	-	Gamma
40-45	DKK 45,619.55	0	-	Gamma
45-50	DKK 45,619.55	0	-	Gamma
≥50	DKK 45,619.55	0	-	Gamma
BMI-Related Health Care Costs: 61-70				
25-30	DKK 37,083.12	0	-	Gamma
30-35	DKK 41,325.24	0	-	Gamma
35-40	DKK 45,567.36	0	-	Gamma
40-45	DKK 45,619.55	0	-	Gamma
45-50	DKK 45,619.55	0	-	Gamma
≥50	DKK 45,619.55	0	-	Gamma
BMI-Related Health Care Costs: >70				
25-30	DKK 37,083.12	0	-	Gamma
30-35	DKK 41,325.24	0	-	Gamma
35-40	DKK 45,567.36	0	-	Gamma
40-45	DKK 45,619.55	0	-	Gamma
45-50	DKK 45,619.55	0	-	Gamma
≥50	DKK 45,619.55	0	-	Gamma
Treatment Costs: Setmelanotide				
Paediatric Year 1	[redacted]	0	-	Gamma
Paediatric Years 2+	[redacted]	0	-	Gamma
Adult Year 1	[redacted]	0	-	Gamma

Adult Years 2+	[redacted]	0	-	Gamma
Monitoring Costs				
Setmelanotide Year 1	DKK 4,348.78	0	-	Gamma
Setmelanotide Years 2+	DKK 1,051.21	0	-	Gamma
BSC Year 1	DKK 2,370.24	0	-	Gamma
BSC Years 2+	DKK 2,370.24	0	-	Gamma
Sleep Apnoea (costs)				
0.0-1.0	8,381.74 DKK	0	-	Normal
1.0-2.0	16,763.48 DKK	0	-	Normal
2.0-2.5	20,954.35 DKK	0	-	Normal
2.5-3.0	25,145.22 DKK	0	-	Normal
3.0-3.5	29,336.09 DKK	0	-	Normal
3.5-4.0	33,526.97 DKK	0	-	Normal
≥4.0	37,717.84 DKK	0	-	Normal
Osteoarthritis (costs)				
0.0-1.0	2,426.75 DKK	0	-	Normal
1.0-2.0	4,853.50 DKK	0	-	Normal
2.0-2.5	6,066.87 DKK	0	-	Normal
2.5-3.0	7,280.24 DKK	0	-	Normal
3.0-3.5	8,493.62 DKK	0	-	Normal
3.5-4.0	9,706.99 DKK	0	-	Normal
≥4.0	10,920.36 DKK	0	-	Normal

NASH (costs)				
0.0-1.0	2,487.46 DKK	0	-	Normal
1.0-2.0	4,974.93 DKK	0	-	Normal
2.0-2.5	6,218.66 DKK	0	-	Normal
2.5-3.0	7,462.39 DKK	0	-	Normal
3.0-3.5	8,706.12 DKK	0	-	Normal
3.5-4.0	9,949.86 DKK	0	-	Normal
≥4.0	11,193.59 DKK	0	-	Normal
T2DM (costs)				
0.0-1.0	16,287.05 DKK	0	-	Normal
1.0-2.0	32,574.10 DKK	0	-	Normal
2.0-2.5	40,717.62 DKK	0	-	Normal
2.5-3.0	48,861.15 DKK	0	-	Normal
3.0-3.5	57,004.67 DKK	0	-	Normal
3.5-4.0	65,148.20 DKK	0	-	Normal
≥4.0	73,291.72 DKK	0	-	Normal
CV Events (costs)				
0.0-1.0	11,746.00 DKK	0	-	Normal
1.0-2.0	23,492.01 DKK	0	-	Normal
2.0-2.5	29,365.01 DKK	0	-	Normal
2.5-3.0	35,238.01 DKK	0	-	Normal
3.0-3.5	41,111.01 DKK	0	-	Normal
3.5-4.0	46,984.01 DKK	0	-	Normal

≥4.0	52,857.01 DKK	0	-	Normal

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

An SLR was conducted to characterize the burden of obesity associated with BBS by collating and synthesizing evidence on: the epidemiology of BBS, patient and caregiver burden, the economic disease burden, and treatment outcomes. Research questions that were investigated to meet the study objective comprised:

- **Epidemiology:** What are the epidemiological outcomes (incidence, prevalence, mortality, and survival rates) in patients with obesity or hyperphagia caused by BBS or AS?
- **Health-related quality of life (HRQoL) burden**:
    - How does the disease affect the quality of life of patients with obesity or hyperphagia caused by BBS and AS and their caregivers?
    - What are the HRQoL outcomes for this population?
    - What utilities/disutilities are associated with this disease?
- **Economic burden**: What is the cost and medical resource use associated with these patients?
- **Economic models**: What are the cost-effectiveness outcomes among patients who receive conventional treatments, including current standards of care (e.g., pharmacological treatments, bariatric surgery)?
- **Clinical outcomes:**
    - What are the real-world treatment outcomes for patients with obesity or hyperphagia caused by BBS and AS who are treated with standard of care or other interventions?
    - What are the efficacy and safety outcomes associated with the treatment of patients with obesity caused by BBS and AS, as investigated in clinical trials?

Initial systematic literature searches were conducted on June 3, 2021, followed by updates on August 4, 2022; January 10, 2023; and February 15, 2023 via Ovid.com in several electronic literature databases. The January and February 2023 literature search updates focused only on the clinical outcomes and humanistic burden among those with BBS. The searches used strategies developed specifically for BBS- and AS-related obesity, including a combination of free-text and controlled vocabulary terms. Recent proceedings (the last three years) from key conferences were also searched for abstracts of relevant studies. Supplemental searches of health technology assessment (HTA) bodies and trial registries were also conducted to identify reimbursement of treatments

for obesity in patients with BBS/AS and ongoing trials for which outcome data have not yet been published. Details of the databases, and conference sources are outlined in Table 87 and Table 89, respectively. Supplemental searches of ClinicalTrials.gov and orpha.net were also conducted to identify ongoing trials for which outcome data had not been published (Table 88).

Table 87 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	OvidSP	No time limit was used	Initial systematic literature searches were conducted on 03 June 2021 and updated on 04 August 2022, 10 January 2023 and 15 February 2023
MEDLINE and MEDLINE In-Process		No time limit was used	
The Cochrane Library (CENTRAL and CDSR)		No time limit was used	
EconLit		No time limit was used	
PsycINFO		No time limit was used	
DARE*		No time limit was used	Initial systematic literature searches were conducted on 03 June 2021
DARE/NHS EED	CRD	No time limit was used	Initial systematic literature searches were conducted on 03 June 2021

*Database of Abstracts of Reviews of Efficacy (DARE) and NHS EED are no longer updated but were searched.

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Efficacy; NHS EED: National Health Service Economic Evaluation Database

Table 88 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinical trials registries	• Clinicaltrials.gov • Orpha.net	Electronic search: Supplemental searches were conducted to identify ongoing trials	Initial searches were conducted on 03 June 2021 and updated on 04 August 2022, 10 January

Source name	Location/source	Search strategy	Date of search
		for which outcome data had not been published.	2023 and 15 February 2023
	• Clinicaltrialsregister.eu		Initial searches were conducted on 04 August 2022, and updated on 10 January 2023 and 15 February 2023
	• World Health Organization International Clinical Trials Registry Platform Search Portal • European Medicines Agency Registry • Drug Information System of the Federal Institute for Drugs and Medical Devices		Initial searches were conducted on 10 January 2023 and updated on 15 February 2023

Table 89 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European Congress of Endocrinology	Conference website	Electronic search 2019 to 2022: Hand searched	According to inclusion criteria	Initial literature searches were conducted on 03 June 2021 and updated on 04 August 2022
European Conference on Rare Disease and Orphan Products		Electronic search 2020 to 2022: Indexed in Embase	According to inclusion criteria	

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Endocrine Society annual meeting		Electronic search 2019 to 2022: Hand searched	According to inclusion criteria	
European Congress on Obesity		Electronic search 2019: Indexed in Embase 2020: Hand searched 2021 to 2022: Indexed in Embase	According to inclusion criteria	
American Association of Clinical Endocrinologists annual congress		Electronic search 2019 to 2020: Hand searched 2021 to 2022: Indexed in Embase	According to inclusion criteria	
European Society for Paediatric Endocrinology		Electronic search 2021–2022: Indexed in Embase	According to inclusion criteria	Initial literature searches were conducted on 04 August 2022
Paediatric Endocrine Society		Electronic search 2021 to 2022: Indexed in Embase	According to inclusion criteria	
The Obesity Society		Electronic search 2021 to 2022: Indexed in Embase	According to inclusion criteria	
American College of Medical Genetics		Electronic search 2021 to 2022: Indexed in Embase	According to inclusion criteria	

H.1.1 Search strategies

Search terms used for Ovid algorithms are detailed in Table 90.

Table 90. Electronic literature search strategies (2 June 2023)

No.	Query	Results
Embase		
#1	exp alstrom syndrome/	425
#2	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	422
#3	exp bardet biedl syndrome/	1,851
#4	(bardet-biedl adj2 syndrom$).ti,ab.	1,418
#5	or/1-4	2,473
#6	(obes$ or hyperphag$).ti,ab.	476,597
#7	obesity/	450,907
#8	exp hyperphagia/	6,209
#9	or/6-8	601,652
#10	5 and 9	1,033
#11	(exp animal/ or nonhuman/) not exp human/	6,590,082
#12	10 not 11	926
#13	conference abstract.pt.	4,096,658
#14	12 not 13	775
#15	limit 13 to yr="2019-current"	707,263
#16	12 and 15	32
#17	14 or 16	807
Medline		
#1	exp alstrom syndrome/	139
#2	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	295
#3	exp bardet-biedl syndrome/	665

No.	Query	Results
#4	(bardet-biedl adj2 syndrom$).ti,ab.	1,148
#5	or/1-4	1,502
#6	(obes$ or hyperphag$).ti,ab.	322,804
#7	obesity/	189,719
#8	exp hyperphagia/	8,632
#9	or/6-8	370,168
#10	5 and 9	610
#11	exp animals/ not exp humans/	4,836,803
#12	10 not 11	570
Cochrane CENTRAL Register of Controlled Trials		
#1	exp alstrom syndrome/	1
#2	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	5
#3	exp bardet-biedl syndrome/	1
#4	(bardet-biedl adj2 syndrom$).ti,ab.	7
#5	or/1-4	10
#6	(obes$ or hyperphag$).ti,ab.	41,160
#7	obesity/	11,899
#8	exp hyperphagia/	722
#9	or/6-8	43,543
#10	5 and 9	4
#11	exp animals/ not exp humans/	12
#12	10 not 11	4
Cochrane Database of Systematic Reviews		
#1	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	0
#2	(bardet-biedl adj2 syndrom$).ti,ab.	0

No.	Query	Results
#3	1 or 2	0
PsycInfo		
#1	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	7
#2	(bardet-biedl adj2 syndrom$).ti,ab.	31
#3	1 or 2	35
#4	(obes$ or hyperphag$).ti,ab.	41,871
#5	obesity/	25,744
#6	exp hyperphagia/	532
#7	or/4-6	44,188
#8	3 and 7	16
EconLit		
#1	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	0
#2	(bardet-biedl adj2 syndrom$).ti,ab.	0
#3	1 or 2	0

Table 91. Conferences search strategies (2 June 2023)

No.	Query	Results
#1	exp alstrom syndrome/	425
#2	((alstrom or Alstrom-Hallgren) adj2 syndrom$).ti,ab.	422
#3	exp bardet biedl syndrome/	1,851
#4	(bardet-biedl adj2 syndrom$).ti,ab.	1,418
#5	or/1-4	2,473
#6	(obes$ or hyperphag$).ti,ab.	476,597
#7	obesity/	450,907
#8	exp hyperphagia/	6,209

No.	Query	Results
#9	or/6-8	601,652
#10	5 and 9	1,033
#11	(exp animal/ or nonhuman/) not exp human/	6,590,082
#12	10 not 11	926
#13	european congress on obesity.cf,cg.	6,340
#14	ecrd.cf,cg.	189
#15	american association of clinical endocrinologists.cf,cg.	973
#16	or/13-15	7,502
#17	limit 16 to yr="2019-current"	1,218
#18	12 and 17	0

Furthermore, the results of the latest search update (15 February 2023) are presented in Table 92.

Table 92. Electronic literature search strategies (15 February 2023)

No.	Query	Results
Embase		
#1	exp bardet biedl syndrome/	2102
#2	(bardet-biedl adj2 syndrom$).ti,ab.	1637
#3	1 or 2	2372
#4	(obes$ or hyperphag$ or overweight or polyphag$ or overeating or appetite or overweight or hunger or hungry).ti,ab.	624897
#5	obesity/	515128
#6	exp hyperphagia/	7042
#7	or/4-6	747513
#8	3 and 7	969
#9	(exp animal/ or nonhuman/) not exp human/	7043724

No.	Query	Results
#10	8 not 9	870
#11	conference abstract.pt.	4675284
#12	10 not 11	710
#13	limit 11 to yr="2019-current"	1275910
#14	10 and 13	62
#15	12 or 14	772
Medline		
#1	exp bardet-biedl syndrome/	757
#2	(bardet-biedl adj2 syndrom$).ti,ab.	1283
#3	or/1-2	1376
#4	(obes$ or hyperphag$ or overweight or polyphag$ or overeating or appetite or overweight or hunger or hungry).ti,ab.	422399
#5	obesity/	211692
#6	exp hyperphagia/	9153
#7	or/4-6	466700
#8	3 and 7	533
#9	exp animals/ not exp humans/	5094353
#10	8 not 9	484
Cochrane CENTRAL Register of Controlled Trials		
#1	exp bardet-biedl syndrome/	3
#2	(bardet-biedl adj2 syndrom$).ti,ab.	12
#3	or/1-2	12
#4	(obes$ or hyperphag$ or overweight or polyphag$ or overeating or appetite or overweight or hunger or hungry).ti,ab.	57177
#5	obesity/	146799
#6	exp hyperphagia/	809

No.	Query	Results
#7	or/4-6	59211
#8	3 and 7	11
#9	exp animals/ not exp humans/	2683
#10	8 not 9	11
Cochrane Database of Systematic Reviews		
#1	(bardet-biedl adj2 syndrom$).ti,ab.	0
PsycInfo		
#1	(bardet-biedl adj2 syndrom$).ti,ab.	33
#2	(obes$ or hyperphag$ or overweight or polyphag$ or overeating or appetite or overweight or hunger or hungry).ti,ab.	63650
#3	obesity/	28102
#4	exp hyperphagia/	554
#5	or/2-4	65189
#6	1 and 5	16
EconLit		
#1	(bardet-biedl adj2 syndrom$).ti,ab.	0

H.1.2 Systematic selection of studies

Studies were selected for inclusion in the SLR based on the PICOS: populations, interventions, comparators, outcomes, and study design (PICOS) framework as shown in Table 93 and Table 94 (January 2023 and February 2023 search).

Table 93. PICOS selection criteria for the systematic literature review (June 2021 and August 2022 Search)

Epidemiology	Humanistic burden	Economic burden	Treatment outcomes	Exclusion criteria
Population				
Pediatrics and adults with obesity or hyperphagia caused by one of the following: AS BBS plus the following obesity markers:				• Patients younger than 6 years old

Adults aged 18 years and over: BMI > 30 kg/m^2 • Pediatrics aged ≥17: weight ≥97th percentile for age on growth chart assessment or BMI z-score ≥+2SD for children ages 5-19, ≥+3SD for children under 5				• Patients with obesity due to other genetic deficiencies or syndromes, or those not meeting the age-specified obesity markers • Mixed populations [1] of patients of interest plus patients not of interest without results reported separately
Intervention/comparator				
No restrictions			Interventions for the treatment of obesity/ hyperphagia	None
Outcomes				
• Incidence • Prevalence • Mortality • Survival	• Patient HRQoL, PROs,[2] utilities/ disutilities • Caregiver HRQoL, PROs,[2] utilities/ disutilities • Impact of comorbidities on patients HRQoL, PROs,[2] utilities/ disutilities	<u>Economic burden of disease</u> • Healthcare resource utilisation (e.g., doctor visits, hospitalisation, ICU stays, length of stay, ER visits) • Direct costs • Indirect costs <u>Cost-effectiveness models</u> • Economic model structure • ICERs based on QALYs, LY, budget impact per member per month, etc.	<u>Real-world evidence</u> • Efficacy or safety outcomes reported from real-world treatment studies <u>Clinical trial evidence</u> • Efficacy and safety outcomes reported from clinical trials	• Studies that do not report any outcomes related to the SLR objectives • Case studies describing only case presentation, diagnostic odyssey, comorbidities, and treatment outcomes

Study design				
• Any epidemiological study designs • Any genomic investigation studies	• Observational studies including case series/case reports • Clinical trials reporting the humanistic burden of disease	<u>Economic burden of disease</u> • Clinical trials (randomised controlled trials, single-arm) • Observational studies (including case studies and case series) <u>Cost-effectiveness models</u> • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • Budget-impact analyses	<u>Real-world evidence</u> • Any observational real-world evidence study reporting treatment outcomes (excluding case studies/ case series) <u>Clinical Trial Evidence</u> • Any clinical trial investigating the efficacy and safety of treatment	• Letters to the editor, editorials, comments, opinions, notes, narrative reviews • SLR/meta-analysis/network meta-analysis published in 2018 or earlier

Note: Best supportive care included: behavioural interventions, psychological interventions, and strategies to reduce calorie intake and/or to increase physical activity, among others. Pharmacological therapies including setmelanotide, orlistat, and methylcellulose were also included in the SLR.

All PROs were captured, including disease-related measures of HRQoL.

ER: emergency room; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; LY: life-year; PRO: patient-reported outcome; QALY: quality-adjusted life-year

[1] The 80% threshold is in line with recommendations by the Institute for Quality and Efficiency in Health Care (IQWiG), a German HTA body.
[2] All PROs will be captured, including any disease-related measure of HRQoL.

Table 94 PICOS selection criteria for the systematic literature review (January 2023 and February 2023 Search)

	Clinical Outcomes	Humanistic Burden	Exclusion Criteria
Population	Pediatrics and adults with obesity or hyperphagia caused by genetically confirmed Bardet-Biedl syndrome		Patients younger than 6 years old

			Patients with obesity due to other genetic deficiencies or syndromes Mixed populations of patients of interest plus patients not of interest without results reported separately
Intervention	Interventions for the treatment of obesity/hyperphagia	None	None
Comparator	Any or none	Any or none	None
Outcomes	Real-world Evidence Efficacy or safety outcomes reported from real-world treatment studies Clinical Trial Evidence Efficacy and safety outcomes reported from clinical trials	Patient HRQoL, PROs,[1] utilities/ disutilities Caregiver HRQoL, PROs,[1] utilities/ disutilities Impact of comorbidities on patients' HRQoL, PROs,[1] utilities/ disutilities	Studies that do not report any outcomes related to the SLR objectives Case studies describing only case presentation, diagnostic odyssey, comorbidities, and treatment outcomes
Study Design	Real-world Evidence Any observational real-world evidence study reporting treatment outcomes (excluding case studies/ case series) Clinical Trial Evidence Any clinical trial investigating the efficacy and safety of treatment	Observational studies including case series/case reports Clinical trials reporting humanistic burden of disease	Letters to the editor, editorials, comments, opinions, notes, narrative reviews SLR/MA/NMA published in 2018 or earlier

Abbreviations: HRQoL = health-related quality of life; MA = meta-analysis; NMA = network meta-analysis; PRO = patient-reported outcome; SLR = systematic literature review
1 All PROs will be captured, including any disease-related measure of HRQoL.

A two-step approach was used for article selection: screening of titles and abstracts, followed by screening of full texts using Distiller Systematic Review software (Evidence Partners, Ottawa, Ontario, Canada), a web-based application that facilitates collaboration among reviewers during the study-selection process.

Standardized forms were used to screen the evidence at the first (title and abstract) and second (full-text) levels. These forms were developed based on the review inclusion and exclusion criteria and were piloted prior to the start of screening to ensure consistency and clarity among reviewers. Each publication was independently screened at both levels by two reviewers trained in the objectives of the project and familiar with the review protocol.

Any disagreements between reviewers about screening decisions were resolved by a third, senior researcher. Extraction of data from included studies into a pre-specified Microsoft Excel® template was conducted by one investigator and independently validated by a second, more senior researcher to ensure accuracy and consistency. Extraction of data from included studies into a pre-specified Microsoft Excel® template was conducted by one investigator and independently validated by a second, more senior researcher to ensure accuracy and consistency.

For studies with multiple publications, the most recent results, records with the longest follow-up period, or results reported in the primary full-text publication were extracted and summarized.

H.1.2.1 **Results**

In the original literature search, the database searches identified 1,397 records, of which 889 unique records were screened after removing duplicates. After screening the titles and abstracts for each record, 96 articles were selected for full-text review. Ultimately, 11 studies identified through the database searches met the SLR inclusion criteria. An additional two studies were identified through searches of relevant conference proceedings. Thirteen studies reporting on 10 unique studies were included in the SLR from the original literature search.

In the August 2022 literature search update, the database searches identified an additional 123 records, from which 86 unique records were screened after removing duplicates. After the title/abstract screening, eight full-text articles were reviewed. Four records identified through the database searches met the SLR inclusion criteria. All four records were related publications of a phase III trial (NCT03746522) that was included in the original literature search. An additional relevant study was identified through searches of relevant conference proceedings. This study was an open-label, long-term extension (LTE) of the phase II (NCT03013543) and phase III (NCT03746522) trials that were included in the original literature search.

In the January 2023 literature search update, the database searches identified 1,235 records, which encompassed literature up to the date of search (including literature from the original and August 2022 search update). Of those, 44 unique, new records were screened after removing duplicates. After the title/abstract screening, two full-text records were reviewed. Both records met the SLR inclusion criteria and were related publications of the phase III trial (NCT03746522) that was included in the previous literature searches.

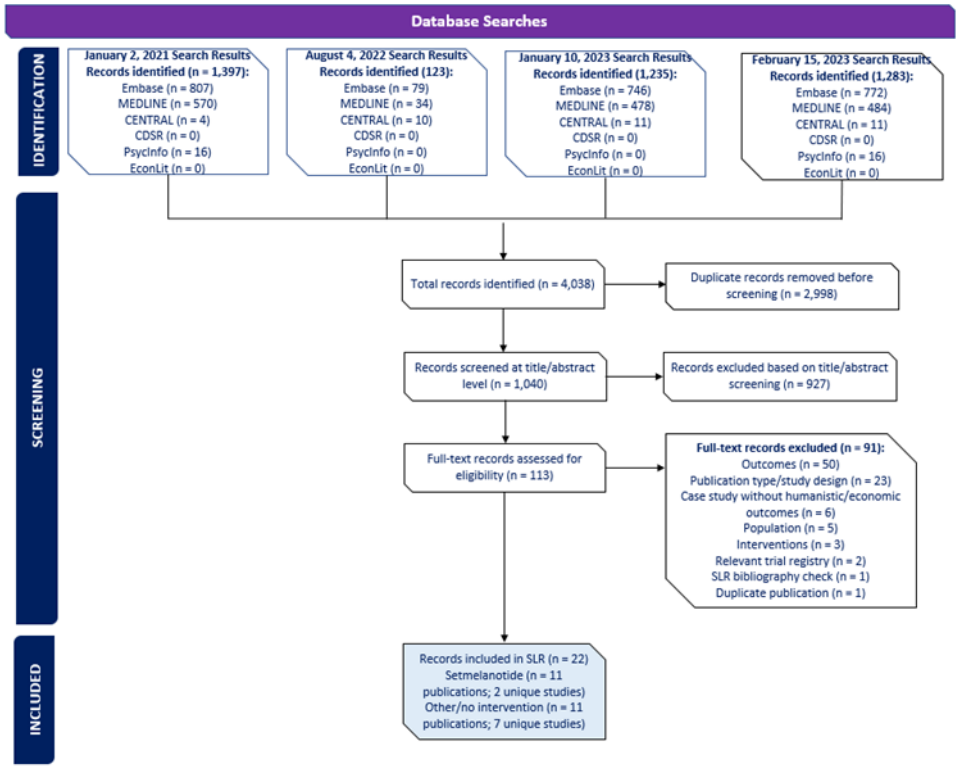
In the February 2023 literature search update, the database searches identified 1,283 records which encompassed literature up to the date of search (including literature from the original, August 2022, and January 2023 search updates). Of those, 21 unique, new

records were screened after removing duplicates. After the title/abstract screening, seven full-text records were reviewed. Five records identified through the database searches met the SLR inclusion criteria. Three records were related publications of the phase III trial (NCT03746522) that was included in the previous literature searches. The remaining two records were cross-sectional surveys reporting on HRQoL outcomes.

Ultimately, 25 studies reporting on 11 unique studies were included in the SLR.A PRISMA diagram of studies included and excluded at each stage of the SLR is presented in

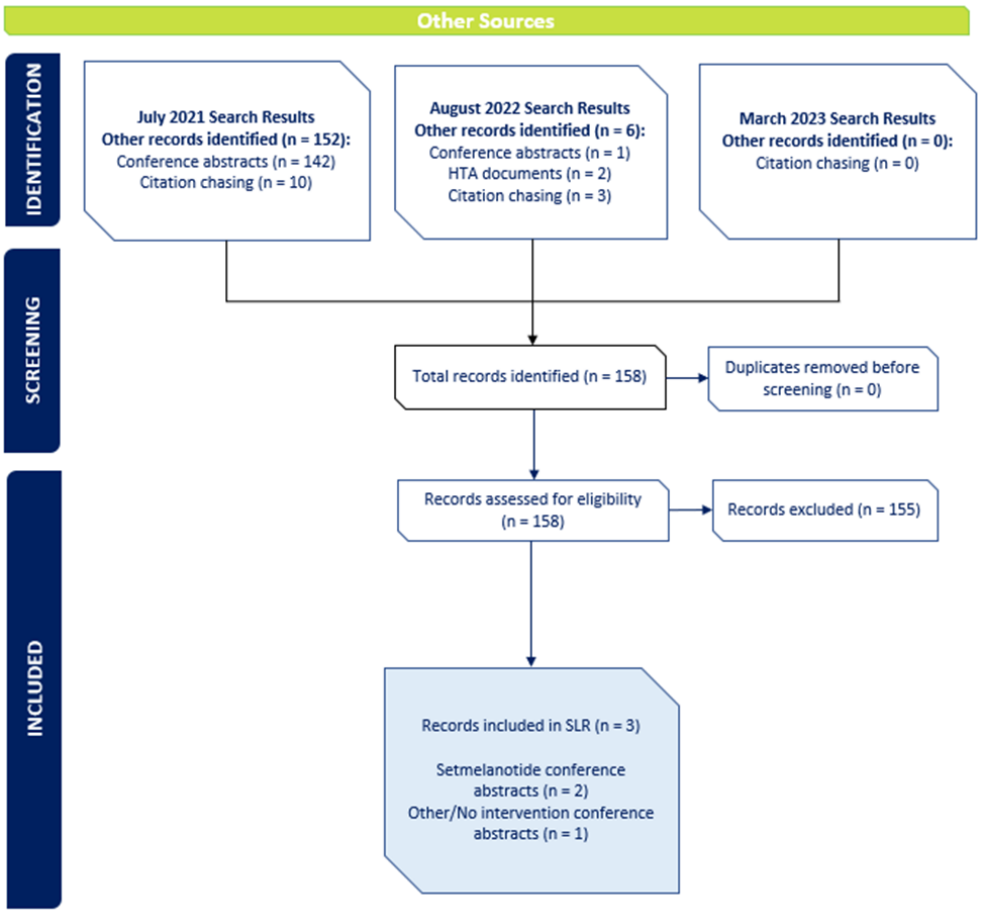
Figure 15 (database searches) and Figure 16 (grey literature searches).

Figure 15. PRISMA diagram (database searches)



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review.

Figure 16. PRISMA diagram (grey literature searches)



Abbreviations: HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review.

Of the 11 articles that met the inclusion criteria, five were epidemiology studies, one was an LTE trial reporting on clinical outcomes of setmelanotide, three were observational studies reporting only on humanistic outcomes of interest, and two were trials reporting clinical outcomes and information related to the humanistic burden of disease (Table 95).

Table 95. Outcomes by study

Study	Epidemiology Outcomes	Treatment Outcomes	Treatment and Humanistic Outcomes	Humanistic Outcomes
M'hamdi 2011[95]	Y			
Reinehr 2007[96]	Y			

Webb 2009[97, 98]	Y					
Haws 2020 [62]				Y		
Hamlington 2015[99]					Y	
Argente 2022 [64]			Y			
Saeed 2020[100]*	Y					
Martos-Moreno 2020[101]*	Y					
Haws 2021 [63, 66, 102, 103]*				Y		
Han 2018[104]*					Y	
Forsythe 2022[105]					Y	

*Included AS populations or a mixed population of BBS and AS.

Table 96 summarises the studies identified throught he SLR that were included in this application.

Table 96. Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Haws 2020 [62]	To report an analysis of one year of setmelanotide treatment for obesity and hunger, as well as metabolic and cardiac	Phase II, open-label, single-arm, basket-design pilot study	Individuals with BBS	Setmelanotide (n = 10)	Follow-up: 12-week treatment phase; 52-week treatment extension phase	Endpoints: Body weight, BMI, body fat mass, total body mass, waist circumference, cholesterol, heart rate, TEAEs

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	outcomes, in individuals with BBS					
Haws 2021[39, 63, 65-67, 102, 103, 106-109]*	To evaluate the effect of setmelanotide, a melanocortin 4 receptor agonist on weight loss, hunger reduction, and safety outcomes in individuals (aged ≥6 years) with obesity and a genetically confirmed diagnosis of BBS or AS	Phase III, randomized, placebo-controlled, double-blind, with an open-label extension	Individuals (aged ≥6 years) with obesity and a genetically confirmed diagnosis of BBS or AS	Setmelanotide (n = 38)	Follow-up: 52 weeks	Endpoints: Body weight, BMI z-score, BMI, Serious TEAE
Argente 2022 [64]	To assess the continued long-term efficacy of setmelanotide treatment in patients with BBS over ~2 years	Open-label LTE	Patients with BBS who completed phase II (NCT03013543) and phase III (NCT03746522) index trials	Setmelanotide vs Placebo (n = 54)	Follow-up: 2 years	Endpoint: Body weight, BMI, BMI z-score, Serious drug-related AE, TEAE

Finally, the list of excluded studies is presented in Table 97.

Table 97 List of excluded studies at full-text screening

Search Date	Bibliography	Reasons for exclusion
June 2, 2021	Asaad, N., Volcotrub, E., Bhangoo, A., Ten, S.. Heterozygous Polymorphism in Bardet-Biedl Syndrome (BBS) Genes was Associated with Early Onset Morbid Obesity, Metabolic Syndrome and Low Leptin Levels. American Heart Journal. 2020. 229:161-162	No outcomes of interest
June 2, 2021	Asaad, N., Volcotrub, E., Bhangoo, A., Ten, S.. Heterozygous polymorphism in Bardet-Biedl syndrome (BBS) genes was associated with early onset morbid obesity and low leptin levels. Hormone Research in Paediatrics. 2020. 93 (SUPPL 1):9-10	Publication type/ study design not of interest
June 2, 2021	Baig, S., Veeranna, V., Bolton, S., Edwards, N., Tomlinson, J. W., Manolopoulos, K., Moran, J., Steeds, R. P., Geberhiwot, T.. Treatment with PBI-4050 in patients with Alstrom syndrome: Study protocol for a phase 2, single-Centre, single-arm, open-label trial. BMC Endocrine Disorders. 2018. 18:	Population not of interest
June 2, 2021	Alqahtani, A. R., Elahmedi, M., Alqahtani, Y. A.. Bariatric surgery in monogenic and syndromic forms of obesity. Seminars in Pediatric Surgery. 2014. 23:37-42	Publication type/ study design not of interest
June 2, 2021	Alqahtani, A., Alamri, H., Elahmedi, M., Mohammed, R.. Laparoscopic sleeve gastrectomy in adult and pediatric obese patients: A comparative study. Surgical Endoscopy. 2012. 26:3094-3100	No outcomes of interest
June 2, 2021	Al-Adsani, A., Gader, F. A.. Combined occurrence of diabetes mellitus and retinitis pigmentosa. Annals of Saudi Medicine. 2010. 30:70-75	Case study without humanistic/ economic outcomes
June 2, 2021	Anonymous. Bardet Biedl syndrome: New discoveries!. [French]. Medecine/Sciences. 2004. 20:969	Publication type/ study design not of interest
June 2, 2021	Aloulou, H., Cheikhrouhou, H., Belguith, N., Ben Ameur, S., Ben Mansour, L., Chabchoub, I., Kammoun, T., Hachicha, M.. [Bardet - Biedl syndrome in the child. A study of 11 cases]. Tunisie Medicale. 2011. 89:31-6	No outcomes of interest
June 2, 2021	Andersen, K. L., Echwald, S. M., Larsen, L. H., Hamid, Y. H., Glumer, C., Jorgensen, T., Borch-Johnsen, K., Andersen, T., Sorensen, T. I., Hansen, T., Pedersen, O.. Variation of the McKusick-Kaufman gene and studies	No outcomes of interest

	of relationships with common forms of obesity. Journal of Clinical Endocrinology & Metabolism. 2005. 90:225-30	
June 2, 2021	Alstrom, C. H., Hallgren, B., Nilsson, L. B., Asander, H.. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree. Acta Psychiatrica et Neurologica Scandinavica Supplementum. 1959. 129:1-35	Population not of interest
June 2, 2021	Battin, J.. Clinical forms of obesity in children. [French]. Journal de Pediatrie et de Puericulture. 2000. 13:72-81	Publication type/ study design not of interest
June 2, 2021	Beales, P. L., Elcioglu, N., Woolf, A. S., Parker, D., Flinter, F. A.. New criteria for improved diagnosis of Bardet-Biedl syndrome: Results of a population survey. Journal of Medical Genetics. 1999. 36:437-446	No outcomes of interest
June 2, 2021	Benzinou, M., Walley, A., Lobbens, S., Charles, M. A., Jouret, B., Fumeron, F., Balkau, B., Meyre, D., Froguel, P.. Bardet-Biedl syndrome gene variants are associated with both childhood and adult common obesity in French Caucasians. Diabetes. 2006. 55:2876-2882	Publication type/ study design not of interest
June 2, 2021	Bettini, V., Maffei, P., Pagano, C., Romano, S., Milan, G., Favaretto, F., Marshall, J. D., Paisey, R., Scolari, F., Greggio, N. A., Tosetto, I., Naggert, J. K., Sicolo, N., Vettor, R.. The progression from obesity to type 2 diabetes in Alstrom syndrome. Pediatric Diabetes. 2012. 13:59-67	No outcomes of interest
June 2, 2021	Bingham, N. C., Rose, S. R., Inge, T. H.. Bariatric surgery in hypothalamic obesity. Frontiers in Endocrinology. 2012. 3:23	Publication type/ study design not of interest
June 2, 2021	Branfield Day, L., Quammie, C., Heon, E., Bhan, A., Batmanabane, V., Dai, T., Kamath, B. M.. Liver anomalies as a phenotype parameter of Bardet-Biedl syndrome. Clinical Genetics. 2016. 89:507-509	Publication type/ study design not of interest
June 2, 2021	Brauner, R.. Organic cause of obesity. [French]. Journal de Pediatrie et de Puericulture. 2000. 13:487	Publication type/ study design not of interest
June 2, 2021	Buscher, A. K., Cetiner, M., Buscher, R., Wingen, A. M., Hauffa, B. P., Hoyer, P. F.. Obesity in patients with Bardet-Biedl syndrome: Influence of appetite-regulating hormones. Pediatric Nephrology. 2012. 27:2065-2071	No outcomes of interest

June 2, 2021	Cerqueira, F., Peres, E.. [Laurence-Moon-Bardet-Biedl syndrome]. Arquivo de Patologia. 1968. 40:55-63	No outcomes of interest
June 2, 2021	Charalambides, M., Barrett, T., Kershaw, M.. Audit of national health service England (NHSE) specialised service for alstrom (children) shows that a declining renal function over time is associated with poorer glycaemic control. Diabetic Medicine. 2019. 36 (Supplement 1):58	No outcomes of interest
June 2, 2021	Charalambides, M., Kershaw, M., Pemberton, J., Brock, K., Barrett, T.. Audit and quality improvement of the nationalhealth service England (NHSE) specialised service forchildren with alstrom syndrome. Archives of Disease in Childhood. 2020. 105 (SUPPL 1):A158	No outcomes of interest
June 2, 2021	Chessa Ricotti, G., Giovannucci Uzielli, M. L., Martini, R., Pietraperzia, M.. The Laurence-Moon-Biedl syndrome. [Italian]. Rivista Italiana di Pediatria. 1982. 8:227-229	Case study without humanistic/ economic outcomes
June 2, 2021	Coburn, B.. Two new genes have been identified for the obesity disorder Bardet-Biedl syndrome. Clinical genetics. 2001. 60:176-177	Publication type/ study design not of interest
June 2, 2021	Dassie, F., Favaretto, F., Bettini, S., Parolin, M., Valenti, M., Reschke, F., Danne, T., Vettor, R., Milan, G., Maffei, P.. Alstrom syndrome: an ultra-rare monogenic disorder as a model for insulin resistance, type 2 diabetes mellitus and obesity. Endocrine. 2021. 71:618-625	Publication type/ study design not of interest
June 2, 2021	Delrue, M. A., Michaud, J. L.. Fat chance: Genetic syndromes with obesity. Clinical Genetics. 2004. 66:83-93	Publication type/ study design not of interest
June 2, 2021	Devarajan, P.. Obesity and genitourinary anomalies in Bardet-Biedl syndrome after renal transplantation. Pediatric Nephrology. 1995. 9:397-8	Publication type/ study design not of interest
June 2, 2021	Eissa, M. A. H., Gunner, K. B.. Evaluation and management of obesity in children and adolescents. Journal of Pediatric Health Care. 2004. 18:35-38	Publication type/ study design not of interest
June 2, 2021	Euctr, E. S.. Setmelanotide (RM-493) trial in Bardet-Biedl Syndrome (BBS) and AlstrC6m syndrome (AS) Patients with Moderate to Severe Obesity. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018. 2018. #volume#:#pages#	Relevant trial registry

June 2, 2021	Fan, Y., Rahman, P., Peddle, L., Hefferton, D., Gladney, N., Moore, S. J., Green, J. S., Parfrey, P. S., Davidson, W. S.. Bardet-Biedl syndrome 1 genotype and obesity in the Newfoundland population. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 2004. 28:680-4	No outcomes of interest
June 2, 2021	Fendler, W., Borowiec, M., Baranowska-Jazwiecka, A., Szadkowska, A., Skala-Zamorowska, E., Deja, G., Jarosz-Chobot, P., Techmanska, I., Bautembach-Minkowska, J., Mysliwiec, M., Zmyslowska, A., Pietrzak, I., Malecki, M. T., Mlynarski, W.. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia. 2012. 55:2631-2635	Population not of interest
June 2, 2021	Feuillan, P. P., Ng, D., Han, J. C., Sapp, J. C., Wetsch, K., Spaulding, E., Zheng, Y. C., Caruso, R. C., Brooks, B. P., Johnston, J. J., Yanovski, J. A., Biesecker, L. G.. Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance. Journal of Clinical Endocrinology & Metabolism. 2011. 96:E528-35	No outcomes of interest
June 2, 2021	Fieggen, K., Milligan, C., Henderson, B., Esterhuizen, A. I.. Bardet Biedl syndrome in South Africa: A single founder mutation. South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde. 2016. 106:S72-4	No outcomes of interest
June 2, 2021	Forsythe, E., Sparks, K., Best, S., Borrows, S., Hoskins, B., Sabir, A., Barrett, T., Williams, D., Mohammed, S., Goldsmith, D., Milford, D. V., Bockenhauer, D., Foggensteiner, L., Beales, P. L.. Risk factors for severe renal disease in bardet-biedl syndrome. Journal of the American Society of Nephrology. 2017. 28:963-970	No outcomes of interest
June 2, 2021	Garg, R. A., Singh, J., Mathur, B. B.. Alstrom syndrome. Indian pediatrics. 1991. 28:799-801	Case study without humanistic/ economic outcomes
June 2, 2021	Gillessen-Kaesbach, G.. Syndromale Formen geistiger Behinderung. [German]. Medizinische Genetik. 2009. 21:209-216	Publication type/ study design not of interest
June 2, 2021	Gouronc, A., Zilliox, V., Jacquemont, M. L., Darcel, F., Leuvrey, A. S., Nourisson, E., Antin, M., Alessandri, J. L., Doray, B., Gueguen, P., Payet, F., Randrianaivo, H., Stoetzel, C., Scheidecker, S., Flodrops, H., Dollfus, H., Muller, J.. High prevalence of Bardet-Biedl syndrome in La Reunion Island is due to a founder variant in ARL6/BBS3. Clinical Genetics. 2020. 98:166-171	No outcomes of interest

June 2, 2021	Grace, C., Beales, P., Summerbell, C., Jebb, S. A., Wright, A., Parker, D., Kopelman, P.. Energy metabolism in Bardet-Biedl syndrome. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 2003. 27:1319-24	No outcomes of interest
June 2, 2021	Hainerova, I. A.. [Genetics of obesity]. Vnitrni Lekarstvi. 2010. 56:1035-42	Publication type/ study design not of interest
June 2, 2021	Harville, H. M., Held, S., Diaz-Font, A., Davis, E. E., Diplas, B. H., Lewis, R. A., Borochowitz, Z. U., Zhou, W., Chaki, M., MacDonald, J., Kayserili, H., Beales, P. L., Katsanis, N., Otto, E., Hildebrandt, F.. Identification of 11 novel mutations in eight BBS genes by high-resolution homozygosity mapping. Journal of Medical Genetics. 2010. 47:262-267	Publication type/ study design not of interest
June 2, 2021	Haws, R. M., Joshi, A., Shah, S. A., Alkandari, O., Turman, M. A.. Renal transplantation in Bardet-Biedl Syndrome. Pediatric Nephrology. 2016. 31:2153-2161	Interventions not of interest (i.e., not intended to treat obesity)
June 2, 2021	Hirano, M., Satake, W., Ihara, K., Tsuge, I., Kondo, S., Saida, K., Betsui, H., Okubo, K., Sakamoto, H., Ueno, S., Ikuno, Y., Ishihara, R., Iwahashi, H., Ohishi, M., Mano, T., Yamashita, T., Suzuki, Y., Nakamura, Y., Kusunoki, S., Toda, T.. The first nationwide survey and genetic analyses of bardet-biedl syndrome in Japan. PLoS ONE. 2015. 10:#pages#	No outcomes of interest
June 2, 2021	Huvenne, H., Dubern, B., Clement, K., Poitou, C.. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. Obesity Facts. 2016. 9:158-173	Publication type/ study design not of interest
June 2, 2021	Isabelle, K., Manuel, M., Nadia, M., Jean-Jacques, B., Catherine, C., Jean, M., Anna, Z. B., Nathalie, G., Helene, D., Sylvie, R.. Reproduction function in male patients with bardet biedl syndrome. Journal of Clinical Endocrinology and Metabolism. 2020. 105:#pages#	No outcomes of interest
June 2, 2021	Keith, C. G.. Bardet-Biedl syndrome. Australian Journal of Ophthalmology. 1984. 12:143-148	No outcomes of interest
June 2, 2021	Kleinendorst, L., Massink, M. P. G., Cooiman, M. I., Savas, M., Van Der Baan-Slootweg, O. H., Roelants, R. J., Janssen, I. C. M., Meijers-Heijboer, H. J., Knoers, N. V. A. M., Ploos Van Amstel, H. K., Van Rossum, E. F. C., Van Den Akker, E. L. T., Van Haaften, G., Van Der Zwaag, B., Van Haelst, M. M.. Genetic obesity: Next-generation sequencing results of 1230 patients with obesity. Journal of Medical Genetics. 2018. 55:578-586	No outcomes of interest

June 2, 2021	Labrune, M., Gaux, J. C., Brault, B.. Laurence Moon Bardet Biedl syndrome: urographic signs. [French]. Annales de Radiologie. 1974. 17:385-389	No outcomes of interest
June 2, 2021	Lim, E. T., Liu, Y. P., Chan, Y., Tiinamaija, T., Karajamaki, A., Madsen, E., Go, T. D. Consortium, Altshuler, D. M., Raychaudhuri, S., Groop, L., Flannick, J., Hirschhorn, J. N., Katsanis, N., Daly, M. J.. A novel test for recessive contributions to complex diseases implicates Bardet-Biedl syndrome gene BBS10 in idiopathic type 2 diabetes and obesity. American Journal of Human Genetics. 2014. 95:509-20	Publication type/ study design not of interest
June 2, 2021	Liu, G. C., Hannon, T. S.. Reasons for the prevalence of childhood obesity: Genetic predisposition and environmental influences. Endocrinologist. 2005. 15:49-55	Publication type/ study design not of interest
June 2, 2021	Lofterod, B., Riise, R., Skuseth, T., Storhaug, K.. [Laurence-Moon-Bardet-Biedl syndrome]. Nordisk Medicin. 1990. 105:146-8	No outcomes of interest
June 2, 2021	Lovisetto, P., Biarese, V., Trenta, N., Rizzi, G.. Laurence Moon Bardet Biedl disease. Clinical data. [French]. Annales d'Endocrinologie. 1974. 35:547-561	No outcomes of interest
June 2, 2021	Markham, A.. Setmelanotide: First Approval. Drugs. 2021. 81:397-403	Publication type/ study design not of interest
June 2, 2021	Marshall, J. D., Bronson, R. T., Collin, G. B., Nordstrom, A. D., Maffei, P., Paisey, R. B., Carey, C., MacDermott, S., Russell-Eggitt, I., Shea, S. E., Davis, J., Beck, S., Shatirishvili, G., Mihai, C. M., Hoeltzenbein, M., Pozzan, G. B., Hopkinson, I., Sicolo, N., Naggert, J. K., Nishina, P. M.. New Alstrom syndrome phenotypes based on the evaluation of 182 cases. Archives of Internal Medicine. 2005. 165:675-683	No outcomes of interest
June 2, 2021	Marshall, J. D., Ludman, M. D., Shea, S. E., Salisbury, S. R., Willi, S. M., Laroche, R. G., Nishina, P. M.. Genealogy, natural history, and phenotype of Alstrom Syndrome in a large Acadian kindred and three additional families. American Journal of Medical Genetics. 1997. 73:150-161	No outcomes of interest
June 2, 2021	Mason, K., Page, L., Balikcioglu, P. G.. Screening for hormonal, monogenic, and syndromic disorders in obese infants and children. Pediatric annals. 2014. 43:e218-e224	Publication type/ study design not of interest
June 2, 2021	Minton, J. A., Owen, K. R., Ricketts, C. J., Crabtree, N., Shaikh, G., Ehtisham, S., Porter, J. R., Carey, C., Hodge, D., Paisey, R., Walker, M., Barrett, T. G.. Syndromic obesity and diabetes: changes in body composition with age and mutation analysis of ALMS1 in 12 United	No outcomes of interest

	Kingdom kindreds with Alstrom syndrome. Journal of Clinical Endocrinology & Metabolism. 2006. 91:3110-6	
June 2, 2021	Mokashi, A., Cummings, E. A.. Presentation and course of diabetes in children and adolescents with Alstrom syndrome. Pediatric Diabetes. 2011. 12:270-275	Interventions not of interest (i.e., not intended to treat obesity)
June 2, 2021	Molnar, D., Erhardt, E.. Severe childhood obesity: What are the keys for management?. International Journal of Pediatric Obesity. 2008. 3:9-14	No outcomes of interest
June 2, 2021	Mujahid, S., Hunt, K. F., Cheah, Y. S., Forsythe, E., Hazlehurst, J. M., Sparks, K., Mohammed, S., Tomlinson, J. W., Amiel, S. A., Carroll, P. V., Beales, P. L., Huda, M. S. B., McGowan, B. M.. The Endocrine and Metabolic Characteristics of a Large Bardet-Biedl Syndrome Clinic Population. Journal of Clinical Endocrinology and Metabolism. 2018. 103:1834-1841	No outcomes of interest
June 2, 2021	Narayanan, H. S., Rao, B. S. S. R., Reddy, G. N. N.. Laurence-Moon-Biedl-Bardet syndrome: Review of 14 cases. Indian Journal of Medical Sciences. 1977. 31:30-32	No outcomes of interest
June 2, 2021	Nct. Setmelanotide (RM-493), Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alstrom Syndrome (AS) Patients With Moderate to Severe Obesity. https://clinicaltrials.gov/show/NCT03746522. 2018. #volume#:#pages#	Relevant trial registry
June 2, 2021	Oehme, J.. Early detection and early treatment. Immunizations. Metabolic disorders in children. [German]. Monatskurse fur die Arztliche Fortbildung. 1975. 25:424-427	No outcomes of interest
June 2, 2021	Ozanturk, A., Marshall, J. D., Collin, G. B., Duzenli, S., Marshall, R. P., Candan, S., Tos, T., Esen, I., Taskesen, M., Cayir, A., Ozturk, S., Ustun, I., Ataman, E., Ozdemir, T. R., Erol, I., Erotlu, F. K., Torun, D., Pariltay, E., Yilmaz-Gulec, E., Karaca, E., Atabek, M. E., Elciotlu, N., Satman, I., Moller, C., Muller, J., Naggert, J. K., Ozgul, R. K.. The phenotypic and molecular genetic spectrum of Alstrom syndrome in 44 Turkish kindreds and a literature review of Alstrom syndrome in Turkey. Journal of Human Genetics. 2015. 60:1-9	No outcomes of interest
June 2, 2021	Ozer, G., Yuksel, B., Suleymanova, D., Alhan, E., Demircan, N., Onenli, N.. Clinical features of Bardet-Biedl syndrome. Acta Paediatrica Japonica. 1995. 37:233-6	Case study without humanistic/ economic outcomes

June 2, 2021	Paisey, R. B., Barrett, T., Carey, C. M., Hiwot, T., Cramb, R., White, A., Seymour, R., Bunce, S., Waterson, M., Rockett, C., Vogler, K., Williams, K., Parkinson, K., Kenny, T.. Rare disorders presenting in the diabetic clinic: An example using audit of the NSCT adult Alstrom clinics. Practical Diabetes. 2011. 28:340-343	No outcomes of interest
June 2, 2021	Paisey, R. B., Carey, C. M., Bower, L., Marshall, J., Taylor, P., Maffei, P., Mansell, P.. Hypertriglyceridaemia in Alstrom's syndrome: Causes and associations in 37 cases. Clinical Endocrinology. 2004. 60:228-231	No outcomes of interest
June 2, 2021	Paolacci, S., Maltese, P. E., Manara, E., Iarossi, G., Ziccardi, L., Colombo, L., Falsini, B., Bertelli, M.. Next generation sequencing analysis of patients with Mendelian obesity. Journal of Biotechnology. 2019. 305 (Supplement):S7	No outcomes of interest
June 2, 2021	Poitou, C., Lubrano-Berthelier, C., Clement, K.. Genetic forms of obesity associated with hypogonadism. [French]. Medecine Therapeutique Medecine de la Reproduction. 2005. 7:240-248	Publication type/ study design not of interest
June 2, 2021	Pomeroy, J., Krentz, A. D., Richardson, J. G., Berg, R. L., VanWormer, J. J., Haws, R. M.. Bardet-Biedl syndrome: Weight patterns and genetics in a rare obesity syndrome. Pediatric Obesity. 2021. 16:#pages#	No outcomes of interest
June 2, 2021	Ramirez, N., Marrero, L., Carlo, S., Cornier, A. S.. Orthopaedic manifestations of Bardet-Biedl syndrome. Journal of Pediatric Orthopedics. 2004. 24:92-6	No outcomes of interest
June 2, 2021	Riise, R.. Visual function in Laurence-Moon-Bardet-Biedl syndrome - A survey of 26 cases. Acta Ophthalmologica. 1987. 65:128-131	No outcomes of interest
June 2, 2021	Riise, R.. Laurence-Moon-Bardet-Biedl syndrome. Clinical, electrophysiological and genetic aspects. Acta Ophthalmologica Scandinavica, Supplement. 1998. 76:1-28	No outcomes of interest
June 2, 2021	Riise, R., Andreasson, S., Borgastrom, M. K., Wright, A. F., Tommerup, N., Rosenberg, T., Tornqvist, K.. Intrafamilial variation of the phenotype in Bardet-Biedl syndrome. British Journal of Ophthalmology. 1997. 81:378-85	No outcomes of interest
June 2, 2021	Riise, R., Tornqvist, K., Wright, A. F., Mykytyn, K., Sheffield, V. C.. The phenotype in Norwegian patients with Bardet-Biedl syndrome with mutations in the BBS4 gene. Archives of Ophthalmology. 2002. 120:1364-1367	No outcomes of interest
June 2, 2021	Russell-Eggitt, I. M., Clayton, P. T., Coffey, R., Kriss, A., Taylor, D. S., Taylor, J. F.. Alstrom syndrome. Report of 22 cases and literature review. Ophthalmology. 1998. 105:1274-80	No outcomes of interest

June 2, 2021	Scheinfeldt, L. B., Biswas, S., Madeoy, J., Connelly, C. F., Schadt, E. E., Akey, J. M.. Population genomic analysis of ALMS1 in humans reveals a surprisingly complex evolutionary history. Molecular Biology & Evolution. 2009. 26:1357-67	Publication type/ study design not of interest
June 2, 2021	Seringe, P., Allaneau, C., Fores, C., Guimbaud, P.. [Bardet-Biedl syndrome and its endocrine disorders]. Annales d Endocrinologie. 1969. 30:641-57	Case study without humanistic/ economic outcomes
June 2, 2021	Sharifian, M., Dadkhah-Chimeh, M., Einollahi, B., Nafar, M., Simforoush, N., Basiri, A., Otukesh, H.. Renal transplantation in patients with Bardet-Biedl syndrome. Archives of Iranian Medicine. 2007. 10:339-342	Interventions not of interest (i.e., not intended to treat obesity)
June 2, 2021	Sherafat-Kazemzadeh, R., Ivey, L., Kahn, S. R., Sapp, J. C., Hicks, M. D., Kim, R. C., Krause, A. J., Shomaker, L. B., Biesecker, L. G., Han, J. C., Yanovski, J. A.. Hyperphagia among patients with Bardet-Biedl syndrome. Pediatric Obesity. 2013. 8:E64-E67	No outcomes of interest
June 2, 2021	Stahel, P., Sud, S. K., Lee, S. J., Jackson, T., Urbach, D. R., Okrainec, A., Allard, J. P., Bassett, A. S., Paterson, A. D., Sockalingam, S., Dash, S.. Phenotypic and genetic analysis of an adult cohort with extreme obesity. International Journal of Obesity. 2019. 43:2057-2065	Population not of interest
June 2, 2021	Tahani, N., Choudhary, S., Boivin, C., Dawson, C., Gittoes, N., Geberhiwot, T.. Very high bone mineral density in a monogenic form of obesity-associated insulin resistance. Bone. 2021. 143 (no pagination):#pages#	No outcomes of interest
June 2, 2021	Viggiano, D., Santoriello, C., Ferretti, A., Malgieri, G., Polverino, F., Polverino, M.. First description of obstructive sleep apnea and its clinical consequences on quality of life in Bardet-Biedl syndrome. Respiratory Medicine CME. 2008. 1:182-184	Case study without humanistic/ economic outcomes
June 2, 2021	Yeung, J. C., Katwa, U. A., Lee, G. S.. Sleep disordered breathing in Bardet-Biedl Syndrome. International Journal of Pediatric Otorhinolaryngology. 2017. 102:127-132	No outcomes of interest
June 2, 2021	Tahani, N., Maffei, P., Dollfus, H., Paisey, R., Valverde, D., Milan, G., Han, J. C., Favaretto, F., Madathil, S. C., Dawson, C., Armstrong, M. J., Warfield, A. T., Duzenli, S., Francomano, C. A., Gunay-Aygun, M., Dassie, F., Marion, V., Valenti, M., Leeson-Beevers, K., Chivers, A., Steeds, R., Barrett, T., Geberhiwot, T.. Consensus clinical management guidelines for Alstrom syndrome. Orphanet Journal of Rare Diseases. 2020. 15:#pages#	SLR/ NMA/ Guideline

June 2, 2021	Faraci, C., Galmozzi, A., Sesini, E.. Laurence Moon Biedl Bardet, a polymorphous syndrome. [Italian]. Pediatria Medica e Chirurgica. 1984. 6:529-534	No outcomes of interest
June 2, 2021	Paisey, R. B., Hodge, D., Williams, K.. Body fat distribution, serum glucose, lipid and insulin response to meals in Alstrom syndrome. Journal of Human Nutrition & Dietetics. 2008. 21:268-74	No outcomes of interest
August 4, 2022	Day, S. E., Muller, Y. L., Koroglu, C., Kobes, S., Wiedrich, K., Mahkee, D., Kim, H. I., Van Hout, C., Gosalia, N., Ye, B., Shuldiner, A. R., Knowler, W. C., Hanson, R. L., Bogardus, C., Baier, L. J.. Exome Sequencing of 21 Bardet-Biedl Syndrome (BBS) Genes to Identify Obesity Variants in 6,851 American Indians. Obesity. 2021. 29(4):748-754	No outcomes of interest
August 4, 2022	Dormegny, L., Velizarova, R., Schroder, C. M., Kilic-Huck, U., Comtet, H., Dollfus, H., Bourgin, P., Ruppert, E.. Sleep-Disordered Breathing, Quality of Sleep and Chronotype in a Cohort of Adult Patients with Bardet-Biedl Syndrome. Nature & Science of Sleep. 2021. 13:1913-1919	Population not of interest
August 4, 2022	Haws, R., Brady, S., Davis, E., Fletty, K., Yuan, G., Gordon, G., Stewart, M., Yanovski, J.. Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. Diabetes, Obesity and Metabolism. 2020. 22(11):2133-2140	Duplicate publication
August 4, 2022	Pomeroy, J., VanWormer, J. J., Meilahn, J. R., Maki, T., Murali, H. R., Haws, R. M.. Sleep and physical activity patterns in adults and children with Bardet-Biedl syndrome. Orphanet Journal Of Rare Diseases. 2021. 16:276	No outcomes of interest
February 15, 2023	Haws, R. M., Haqq, A. M., Clement, K., Chung, W. K., Dollfus, H., Forsythe, E., Martos-Moreno, G. A., Yanovski, J. A., Mittleman, R. S., Yuan, G., Argente, J.. Impact of Setmelanotide Treatment on Lipid Parameters and Vital Signs in Patients With Bardet-Biedl Syndrome in a Phase 3 Trial. Hormone Research in Paediatrics. 2022. 95(Supplement 1):148-149	No outcomes of interest
February 15, 2023	Touzani, A., Drai, J., Balafrej, A., Gaouzi, A., Chabraoui, L.. Leptinemia and cardiometabolic risk factors in genetic obesity syndromic in children: Prader Willi and Bardet Biedl. Hormone Research in Paediatrics. 2022. 95(Supplement 2):487	No outcomes of interest

H.1.3 Quality assessment

Quality assessments were performed for all interventional studies and economic evaluations, published as full-text articles, and deemed suitable for inclusion in the SLR. Studies published only as abstracts were deemed unsuitable for critical assessment because of the lack of details required to perform an accurate assessment of study quality. Randomized controlled trials (RCTs) and other randomized trial designs were critically

appraised using the Cochrane Risk of Bias Assessment Tool 2.0, as required by the Federal Joint Committee (G-BA). Non-randomized and non-controlled studies were assessed using the Critical Appraisal Skills Programme (CASP) tool. The Drummond's Quality Assessment Tool was planned to be used to appraise any identified economic evaluations, but no studies with this design were included. Quality assessment was conducted by one reviewer and validated by a second reviewer.

H.1.4 Unpublished data

No relevant unpublished data were identified by the SLR.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The SLR conducted (see section Appendix H) aimed at gathering both clinical and HRQoL data. Therefore, not all of the following sections are applicable.

Table 98 Bibliographic databases included in the literature search – not applicable

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A		
Medline	N/A		
Specific health economics databases[1]	N/A		

Abbreviations:

Table 99 Other sources included in the literature search – not applicable

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A		
ScHARRHUD	N/A		

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Table 100 Conference material included in the literature search – not applicable

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A			
	N/A			

I.1.1 Search strategies

Table 101 Search strategy for [name of database] – not applicable

No.	Query	Results
#1		
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9	#7 OR #8	
#10	#3 AND #6 AND #9	

Of the 11 articles that met the inclusion criteria, five studies [62, 63, 99, 104, 105] reported HRQoL or patient-/caregiver-reported outcomes related to obesity in BBS or AS (Table 102). In one study, the primary aim was to investigate the humanistic burden of disease via evaluation of the stigma surrounding obesity in children with BBS.[99] This qualitative study interviewed 28 caregivers from 20 families with a child with a genetically confirmed BBS diagnosis and conducted a thematic analysis of caregiver experiences.[99] A second, prospective, case-control study characterized the endocrine and metabolic features of AS.[104] It included 38 patients who fulfilled the clinical diagnosis criteria for AS with confirmed ALMS1 mutations and 76 body mass index (BMI)-matched control subjects, and compared hyperphagia scores (assessed using Dykens et al., 2007[110]) in the two populations.[104] A third cross-sectional survey characterized the burden experienced by

242 caregivers of individuals with BBS. The survey included several observer- and caregiver-reported instruments for adult caregivers who had cared for ≥6 month old individuals with BBS who had obesity (or were in the ≥95th weight percentile) and hyperphagia [105].

Finally, the two clinical trials investigating the efficacy and safety of setmelanotide described earlier-reported hunger scores at baseline and throughout the treatment period [62, 63]. The phase II trial assessed maximal hunger, morning hunger, and average daily hunger using a Likert-type scale to generate a hunger score. The phase III trial also assessed maximal hunger and average daily hunger score, although it was not explicitly stated whether the same Likert-scoring system was used. The phase III trial also examined the Impact of Weight on Quality-of-Life Questionnaire-Lite (IWQOL-Lite) among adults aged ≥18 years and the Pediatric Quality of Life Inventory (PedsQL) among children aged ≤17 years. No studies reporting on the quality-of-life impact of obesity in AS were identified.

Table 102. Characteristics of studies informing on health-related quality of life in patients with BBS

Publication	Study aim	Study methods	Data source	Trial identifier	Country	Accrual years	Study follow-up duration	Population description	Number enrolled	Outcomes related to BBS or AS
Hamlington, 2015[99]	To characterize caregivers' experiences of stigma and courtesy stigma surrounding obesity in children with BBS	Prospective observational study: qualitative interview study	National Institutes of Health (NHGRI protocol 04-HG-0123).	NA	US	NA	NA	Caregivers of children ≤18 years old with genetically confirmed BBS	28 caregivers from 20 families with a child with BBS	BBS

Han, 2018[104]	To characterize the endocrine and metabolic features of AS while accounting for obesity as a confounder by comparing patients with AS to BMI-matched controls	Case-control: Single-center prospective evaluation	Patients were recruited through AS International, a support group for families and healthcare providers of patients with AS, and were referred to the NIH Clinical Center	NCT00068224	US	February 2013 to June 2014	NA	Patients who fulfilled the clinical diagnostic criteria for AS and had confirmed ALMS1 mutations and a matched-control sample of subjects with no known genetic disorder	38 AS patients and 76 matched-control subjects	AS
Forsythe, 2022[105, 111]	To characterize the burden experienced by caregivers of individuals with BBS	Cross-sectional survey	Survey	NA	International	NR	NR	Caregivers of individuals with BBS	242 caregivers	BBS

Abbreviations: AS = Alström syndrome; BBS = Bardet-Biedl syndrome; HRQoL = health-related quality of life; LTE = long-term extension; NA = not applicable; NIH= National Institute of Health; NR = not reported; US = United States.

Literature search results included in the model/analysis:

The HRQoL literature search results were considered to be not relevant and therefore were not used in the model/analysis. Alternatively, targeted searches were done to identify utility values for the general obese population. The utility values used and accepted by the NICE in HST21 [112], were considered representative for the Danish patient population.

I.1.2 Quality assessment and generalizability of estimates

Not applicable

I.1.3 Unpublished data

Not applicable

Appendix J. Literature searches for input to the health economic model -not applicable

J.1 External literature for input to the health economic model

J.1.1 Ex. Systematic search for […]

Not applicable.

Table 103 Sources included in the search – not applicable

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A		
Medline			
CENTRAL			

Abbreviations:

J.1.2 Ex. Targeted literature search for [estimates]

Not applicable.

Table 104 Sources included in the targeted literature search – not applicable

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Appendix K. Early Onset of Obesity Model: Initial situation

K.1 Summary

The obesity epidemic is a global issue characterized by excessive body fat and associated with various chronic diseases. Driven by unhealthy eating habits and sedentary lifestyles, obesity has doubled since 1980, affecting over one billion people worldwide.

This report focuses on early-onset obesity, which is associated with greater long-term weight gain and higher risk of remaining obese. Due to diverse individual and health factors, quantifying the impact of early-onset obesity on morbidity and mortality is complex. To address this challenge, the Early-Onset of Obesity-Model (EOObesity-Model) was developed, integrating data from clinical studies and demographic information. This model provides insights into the effects of early-onset obesity and its relation to long-term morbidity and mortality, particularly cardiovascular health. Factors such as obesity level, age, and obesity duration influence the risk of comorbidities and mortality, with recent studies suggesting that reducing obesity duration can lower the long-term risk and severity of comorbidities[2].

This research assesses the consequences of obesity based on age, weight, and obesity duration. Data was extracted from studies that sufficiently quantified outcomes for incorporation into the EOObesity-Model. The study information was classified into three groups: Prevalence Information, Mortality Risk Information, and Duration Information.

Data on prevalence and mortality risk of various comorbidities such as Type 2 Diabetes, Cardiovascular Events, Non-Alcoholic Fatty Liver Disease, Cancer, Asthma, and Sleep Apnea were gathered for ages 0-100 years and BMI-Z 0.0-4.5. Impact of obesity duration information was collected for its effects on comorbidities and mortality risk. Prevalence and mortality risk information for all ages and weight classifications were tabulated, with missing information interpolated from existing data. Obesity duration tables were developed, containing risk increase Hazard Ratios for each year of obesity duration and obesity level. Irreversible risk accumulation due to obesity duration was also modeled based on studies assessing the effects of weight loss on comorbidity risk.

Comorbidity risk for each age is derived from by modifying prevalence with comorbidity-specific duration factors, further adjusted for irreversible risk accumulation to obtain a new risk profile following treatment for obesity (BMI reduction). This approach enables

[2] Norris et al. 2020, Duration of obesity exposure between ages 10 and 40 years and its relationship with cardiometabolic disease risk factors: A cohort study

BMI-Z = body mass index z score

the estimation of comorbidity risks and life expectancy based on changing the weight trajectory, with comorbidity risks used to calculate disability-adjusted life years (DALYs).

The model creates two weight trajectories for each case: one without change in obesity severity/duration and one with a modified weight trajectory, allowing for assessment of the impact of this change on future comorbidity risks, life expectancy, and DALYs. These trajectories are “plotted” onto a three-dimensional risk landscape, influenced by individual patient factors such as comorbidity prevalence, mortality risk, obesity duration, and irreversible risk accumulation, and shift according to changes in obesity severity and duration, enabling precise estimations of obesity-related morbidity and mortality over the patient’s lifetime.

This model is unique in combining the currently best available evidence to allow for assessing the impact of early-onset obesity on mortality and morbidity, confirming the substantial impact of early-onset obesity on life expectancy and the benefits of early weight loss.

The model's capability lies in its systematic evaluation of a wide range of patient cases, validating findings for diverse scenarios. It reflects that increased weight and age, coupled with longer obesity duration, heighten the risk of comorbidities and mortality. The model's other ability is in assessing the risk reduction resulting from weight / BMI loss, linking greater and earlier weight / BMI loss to a larger reduction in comorbidity risk. This risk reduction decreases for each year of delay in change of weight trajectory, confirming the need for rapid diagnosis and intervention in early-onset obesity.

K.2 Initial situation

The obesity epidemic is a global crisis that transcends borders, cultures, and socio-economic classes. Characterized by an excessive accumulation of body fat, obesity is not merely a cosmetic concern but a complex medical problem. It has more than doubled since 1980 and now affects over 650 million adults worldwide. At its core, the epidemic is driven by a modern lifestyle that often promotes unhealthy eating habits and sedentary behavior. The accessibility of high-calorie, low-nutrient food, and a shift away from physical labor have played significant roles in the rise of this public health challenge. The consequences of obesity are severe, leading to various chronic diseases like heart disease, diabetes, and certain cancers.

This work focuses primarily on a relatively under-researched form of early-onset obesity. With increasing level of obesity and early-onset, obesity related risks are increasing as well. Thus, an earlier onset of severe obesity also accelerates the development of comorbidities, leading to an earlier onset of severe consequences of obesity compared to patients with later onsets of obesity. An early-onset of obesity is also tending to lead to a higher level of obesity itself in patients compared to same age patients with a later onset of obesity. This early and greater long-term weight gain also leads to a higher risk of

remaining obese compared to those with a later onset of obesity.[3] There is a paucity of work quantifying the impact of early-onset obesity on morbidity and mortality, especially on the long-term consequences, as the vast majority of work has been on general obesity and adult obesity, focusing on adulthood onsets and consequences in later adulthood.

Estimating the consequences of early-onset of obesity is a deeply intricate task that encompasses a broad spectrum of individual, health, economic, social, and methodological considerations. On the individual level, obesity's effects can vary widely due to different factors like genetics and lifestyle choices, making specific predictions difficult. Health-wise, obesity is linked to a diverse range of conditions, from heart disease and diabetes to certain types of cancer, complicating the task of estimating exact risks and interactions.

The economic impact, encompassing both direct costs like healthcare and indirect ones like productivity loss, requires nuanced understanding of various economic structures and societal values. The social and psychological facets of obesity, influenced by cultural norms and personal attitudes, add a layer of subjectivity that can be challenging to quantify. Further complexity arises from the necessity to differentiate between immediate and long-term consequences, as well as the complications introduced by co-morbidity with other health conditions. Lifestyle factors, such as diet and exercise, and the effectiveness of various interventions, can further muddy the waters in isolating obesity's consequences.

Finally, inconsistencies in defining and measuring obesity, such as the limitations of Body Mass Index (BMI), can lead to misclassification and challenges in assessing associated risks. In sum, the multi-dimensional nature of obesity, interwoven with various biological, psychological, economic, and societal factors, makes the task of estimating its consequences a complex and nuanced endeavor.

This technical report describes the innovative process by which we built a comprehensive model to estimate the effect of early onset of obesity on comorbidities and mortality risk. The Early-Onset of Obesity-Model (EOObesity-Model) adopts a multidisciplinary approach, synthesizing data from clinical studies and demographic information. The model is designed to navigate the inherent complexities and individual variations tied to obesity.

The subsequent sections detail the methodology, data sources, model architecture, validation processes, and key findings. This model was designed to serve not only as a sophisticated tool for healthcare professionals but also to inform Health Economic Modelling, as well as a foundation for future research in obesity's multifaceted consequences. Recent studies suggest that the long-term risk and severity of comorbidities linked to early onset obesity is lowered by reducing the duration of obesity[108]. Therefore, the main goal was to develop a disease estimation model to qualify and quantify the impact of early-onset obesity and its reduction on long-term morbidity and mortality with a specific focus on cardiovascular health & related diseases. In order to assess the consequences of early onset obesity in the light of all these factors and based

[3] Geserick et al. 2018, Acceleration of BMI in Early Childhood and Risk of Sustained Obesity

on current research, the first step was to identify obesity related factors that have been best studied and shown to influence mortality and comorbidity.

- The first and most obvious factor is the level of obesity[25], which is measured by various methods in studies. Most common type of measurement is the BMI value, as well as the BMI Z-score in children and adolescents and the resulting percentile. Waist circumference and abdominal obesity have also been added recently. Although waist circumference and abdominal obesity are sometimes more accurate in assessing long-term risks, the overwhelming majority of studies measure BMI. In order to be able to draw on a larger pool of study results, BMI measurement was also chosen for the EOObesity-Model. The severity of obesity is directly related to an increase in the risk of comorbidities and an increase in the risk of mortality, therefore measuring the level of obesity allows a measurement of resulting risk increase in comorbidity risk as well as mortality risk.

- The second important factor is age[1]. Age in combination with weight defines a patient's risk of developing a certain comorbidity as well as their overall mortality risk. Being obese in old age increases these factors by a lot more than being obese in young adulthood.

- The combination of weight level and age directly leads to the third important factor, obesity duration. Besides the degree of obesity, the duration of obesity is important as well in developing comorbidities and increasing the mortality risk[108]. Someone who has been obese for 20 years has a significantly higher risk profile than someone of the same age and weight who has been obese for only 10 years. In order to better understand the effect of duration of obesity, numerous studies have been published in recent years that have precisely investigated this influence of duration.

- Living with severe obesity for a long period of time also leads to another development, namely the accumulation of irreversible processes that harm the organism and increase comorbidity risk. Juonala et al. (2014)[42] showed that these accumulated risks are irreversible when reducing the weight to average weight again. Thus, reducing the duration of obesity also decreases the time of this accumulation of irreversible risks, leading directly to smaller long-term risk.

K.2.1 Methodical approach

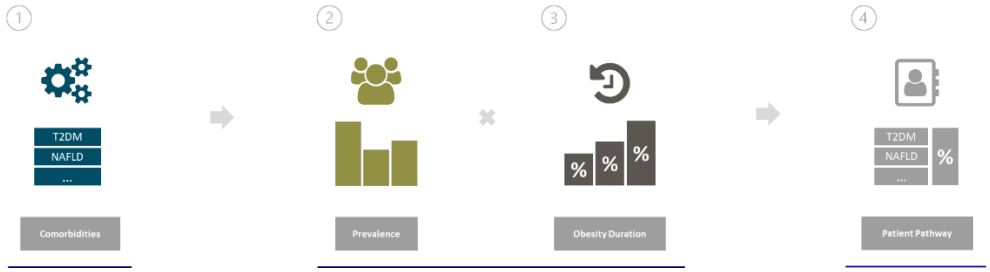
Below is a pictorial representation of the methodical approach used to determine the influence of the aforementioned factors on life expectancy and comorbidity risk. We have chosen two different approaches for the model, one for life expectancy and a separate approach for comorbidity risk determination. The reason for this is that a sufficient number of studies have quantified the impact of obesity on mortality and thus provide an accurate picture of the situation to provide the model with accurate information. In order to keep this mortality assessment as precise as possible, the comorbidity risk is assessed separately. Figure 17 shows the approach to modelling the impact of all the previously mentioned factors on mortality and thus on life expectancy. Figure 18 shows the approach

to modelling the impact of all the above factors on the risk of developing comorbidities across the lifespan.

Figure 17. Methodical approach to model the mortality effect of early onset obesity

The first step is to gather all relevant patient information. This information yields comorbidity prevalence figures and mortality risks, which are combined to get one patient individual All-Comorbidity related Mortality risk. By further modifying this Mortality Risk with obesity duration, a patient individual trajectory is created that determines the Average and Maximum Life-Expectancy.

Figure 18. Methodical approach to model the morbidity effect of early onset obesity



In the second approach the previously gathered information on prevalence is directly modified with the effect of obesity duration, yielding another patient trajectory only representing the comorbidity risk development of the patient's life course.

K.3 Sources and Data Extraction

To assess the consequences of obesity based on age, weight as well as duration of obesity, we only considered studies that have quantified the resulting outcomes sufficiently enough to incorporate them into a model. Studies assessing the prevalence of comorbidities in relation to BMI (BMI-Z Score) and age, as well as studies assessing the duration of obesity in relation to the severity of obesity were selected to extract data. The data generated in this way, is the cornerstone of all estimates, as the estimation process itself only combines these data sets to produce a case-specific estimate of mortality and morbidity. The study information was classified in three groups: Prevalence Information, Mortality Risk Information and Duration Information. For technical reasons, the model works with BMI-Z Score for all age groups. Most studies report the weight of study participants over 18 years of age in BMI and that of those under 18 years of age in BMI-Z Score. In order to have a uniform weight unit for the entire life span, the BMI relevant study results were converted into BMI-Z score equivalents. As an intermediate step in this

conversion, the BMI percentiles were added in order to obtain a uniform comparative value and to be able to assign BMI over 18 to the respective BMI-Z Scores. The weight range studied is between BMI 20 and BMI 50, which corresponds to a BMI-Z score range of 0.0 - 4.5. The reason for this weight range is a technical one, namely that most studies investigating obesity have investigated BMI 30 to 40 and very few studies have investigated and quantified increased obesity. Due to a lack of reliable study results, it was decided to determine a BMI of up to 50. Conversely, this means that patients with a BMI above 50 have at least the same comorbidity risk as BMI 50 patients.

For the Prevalence Information, data for Type 2 Diabetes (T2DM), Cardiovascular Events (CV) (Fatal non-fatal Events, Cardiovascular disease, coronary heart disease), Non-Alcoholic fatty Liver Disease (NAFLD) (NAFLD+ Non-Alcoholic Steatohepatitis), Cancer (all-cancer), Asthma, and Sleep Apnea were gathered for ages 0-100 years and BMI-Z 0.0-4.5. For the Mortality Risk Information, data for Type 2 Diabetes, Cardiovascular Events (Fatal non-fatal Events, Cardiovascular disease, coronary heart disease), Non-Alcoholic fatty Liver Disease (NAFLD+NASH), Cancer (all-cancer), Asthma, and Sleep Apnea was gathered for ages 0-100 years and BMI-Z 0.0-4.5.

Impact of obesity duration information was gathered for impact of duration on comorbidities and impact of duration on mortality risk. For the impact of duration on comorbidities, only studies for T2DM, CV, and cancer were available. Information for obesity duration between 0-20 years was available and one study provided risk increase data for each additional two years of obesity. Prevalence Information was needed for all ages 0-100 and all BMI-Z 0.0-4.5. Data extracted from the studies (Prevalence in %, Incidence in %, Hazard Ratios for BMI Classifications) was put into a table and missing information was interpolated only between given study results.

To create these fundamental tables showing comorbidity development in relation to age and weight, a prevalence figure is needed for each weight classification times each age from 0 to 100 years. To ensure that this information is as accurate as possible, careful attention was paid to the cohorts that the included studies examined. The main focus was thereby on the exact age and weight of the groups studied.

To explain the procedure to create these comorbidity risk tables in more detail, the NAFLD prevalence table is used as an example. Five studies were selected for NAFLD prevalence data extraction because they provided sufficient information on age and weight differences.

Anderson et al. (2015)[15] quantifies the differences of NAFLD prevalence in young age, from 0-19 years of Age, and in relation to weight differences, normal/average to obese levels. Age groups were characterized from 0 ≤ 15 and ≥ 15 years. Weight classifications were Normal weight, Overweight and Obesity. These figures were then combined to create the NAFLD comorbidity risk for ages 0 until 19 years and their corresponding weight category differences. For verry high obesity, the obesity weight category upper Confidence Interval (CI) figure was taken. The underlying rationale is that the confidence interval range reflects the NAFLD risk development within the assessed weight range. Thus, the lower CI represents the risk at the beginning of the obesity range and the upper CI the NAFLD Risk at the end of this obesity range. Next step was the integration of risk quantifications

assessing older ages and same corresponding weight classifications. For the next group, in this case 20 until 29 years, results from Arshad et al. (2021)[17] were taken for low weight categories and for high obesity categories data from Mummadi et al. (2008)[16] was chosen. Arshad et al. (2021)[17] assessed the impact of weight differences on the NAFLD risk between the ages 12 and 29 years. Age classifications were 12-17, 18-24, and 25-29 years. The last two age groups were included, representing the risk developments for the ages 20-24 years and 25-29 years. In these age groups the risk differs between the weight classifications but not between exact ages, meaning risk at 26 is the same as 29 years of age. Obesity was classified as BMI: ≥30Kg/m2 in Arshad et al. (2021)[17]. Another study was needed for a more precise risk assessment, providing data for the higher obesity realm. Mummadi et al. (2008)[16] is providing information on NAFLD risk for the higher obesity realm (BMI: 35-50) and was integrated as risk for the adult population for these weight categories. The same approach of data selection and integration was done for the remaining studies to create the whole NAFLD prevalence table.

A similar approach was applied to all comorbidities in order to map the development of the comorbidity risk as accurately as possible, based on available study data. If no data was available for an age group or weight classification, this gap was closed by interpolation. For example, data were available for 20 and 40 years and all corresponding weight classifications, but not for 30 years. In this case, interpolation was used to generate data for all weight classifications in the 30 years group. All prevalence figures are therefore directly related to study results and can be justified accordingly. For this reason, the same approach was used to create the mortality risk tables, with the difference that hazard ratios were increasingly used to model the impact of weight differences on mortality risk.

With the above-described approach, all risk tables on which the model is built on were created. The prevalence and mortality risk table creation process itself can therefore be described as a selection, integration, and combination process of already existing risks figures, in which missing risks were mathematically interpolated. This resulted in a table giving comorbidity prevalence information for all combinations of age and weight classifications required for modelling. For filling out the missing information in this table only interpolation was used and no extrapolation, to ensure the credibility of the results. The same approach was used to build the mortality risk tables for all comorbidities. For obesity duration only information for the years of being obese and the level of obesity was needed. The tables were therefore filled with a risk increase Hazard Ratio for each year of obesity duration combined with the level of obesity in that year. In addition to pure risk increase due to duration of obesity, an irreversible risk accumulation was modelled as well. Information was available for T2DM and CV from studies assessing the effect of weight loss on comorbidity risk. In the following section, each information extracted from study results is listed with a rationale for why which study was selected for data extraction.

K.3.1 T2DM Prevalence

For the risk numbers at normal weight the DIABETES Surveillance of the Robert Koch Institute was used for ages 35 between 54. Tanamas et al. (2018)[1] was used to get information on younger ages and high BMI values. This Study was chosen as it provides prevalence and incidence numbers (5-year and 10-year incidence) for verry young and

obese individuals, as well as a long follow up period until 45 years of age. Ahmad et al. (2014)[2] was chosen as it depicts the prevalence in young adulthood for both sexes and obese individuals. Bjerregaard et al. (2018)[3] was chosen as it has a big number of participants (n = 62,565), therefore depicting age and BMI specific prevalence numbers most accurately. It also includes a verry long follow up period until 30-60 years of age. (For the resulting risk plane, see Graphic 1 at the end).

Figure 19. T2DM Prevalence Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	Prevalence (%)	"	"	"	"	"	"
Hu 2014[1]	US	NHS	30-55 years	24 years follow up	Only Women	61,821	Can be used to "calibrate" for lower BMI values				3%	8%	-
Hu 2014[1]	US	NHS II	25-42 years	20 years follow up	Only Women	63,653	-	-	-	-	1%	3%	-
Ahmad 2014[2]	UK	HSE 2006	≥18 years	-	Both	9,425	-	-	17%	9%	3%	-	-
Tirosh 2011[3]	IL	MELANY	≥25 years	mean follow-up, 17.4 years	Only Men	37,674	-	-	-	-	-	7%	-
Luo 2019[4]	AU	ALSWH	18-23 years	19 years follow up	Only Women	11,192	Studies selected			-	-	7%	3%	3%
Abdullah 2010[5]	US	FHS	28–62 years	48 years follow up	Both	1,256	-	-	-	-	22%	-	-
Tanamas 2018[6]	US	American Indians	5-18	until 45 years Age	Both	7,045	-	17%	15%	6%	3%	-	-
Bjerregaard 2018[7]	DK	CSHRR	7-13 years	until 30-60 years Age	Only Men	62,565	-	-	-	-	31%	18%	14%

1) Hu et al. Duration of Obesity and Overweight and Risk of Type 2 Diabetes Among US Women, 2014 2) Ahmad et al. Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey, 2014 3)Tirosh et al. Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis, 2011 4) Luo et al. Age of obesity onset, cumulative obesity exposure over early adulthood and risk of type 2 diabetes, 2019 5) Abdullah et al. The duration of obesity and the risk of type 2 diabetes, 2010 6) Tanamas et al. Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population, 2018 7) Bjerregaard et al. Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes, 2018

K.3.2 Cardiovascular Event Prevalence

First study included is Ahmad et al. (2014)[2], due to its information on highly obese individuals of both sexes. Second study, containing most information is Baker et al. (2007)[10]. This study included 276,835 individuals from the Danish CRS databank. Individuals from 7 to 60 years are included and all obesity classifications are included for both sexes. (For the resulting risk plane, see Graphic 2 at the end).

Figure 20. CV Event Prevalence Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	Prevalence (%)	"	"	"	"	"	"
Ahmad 2014[1]	UK	HSE 2006	≥18 years	-	Both	9,425	-	-	11%	8%	4%	-	-
Baker 2007[2]	DK	Danish CRS	7-13 years 25-60 years	46 years of follow up	Both	276,835	(increase in Relative Risk = 1.17 (CI 1.15-1.20) or 1.9%per 5.6 Kg weight increase) 40%	36%	32%	26%	23%	19%	15%
Kim 2021[3]	Meta-Analysis 12 systematic reviews, 53 meta-analyses (501 non-overlapping cohort studies) and 12 MR studies (25 cohorts)						(increase in risk of cardiovascular event per BMI 5 Units = 1.4) 41%	37%	29,4%	26,6%	21%	-	-
Sierra-Johnson 2005[4]	DE	-	62 ±11 years	6.4 ±1.8 years	Both	389	-	-	-	-	26%	29%	16%
Liu 2019[5]	CN	-	51.5 ± 11.1 years	2006-2015	Both	18,703	-	-	-	-	-	HR 1.3	HR 1
Li 2006[6]	SE	MDC	48-67	7.6±1.7 years	Both	27,007	-	-	-	HR 2.04/2.14	HR 1.67/1.69	HR 1.2/1.4	HR1
Khan 2018[7]	US	10 Cohorts	20-79	1964-2015	Men/Women	190,672	-	-	65%/47%	47%/38%	47%/38%	37%/28%	32%/20%

1) Ahmad et al. Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey, 2014 2) Baker et al. Childhood Body-Mass Index and the Risk of Coronary Heart Disease in Adulthood, 2007 3) Kim et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies, 2021 4) Sierra-Johnson et al. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation, 2005 5) Liu et al. Joint association of body mass index and central obesity with cardiovascular events and all-cause mortality in prediabetic population: A prospective cohort study, 2019 6) Li et al. Sex differences in the relationships between BMI, WHR and incidence of cardiovascular disease: a population-based cohort study, 2006 7) Khan et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity, 2018

K.3.3 NAFLD Prevalence

For childhood ages Anderson et al. (2015)[15] was used as it included children from 1 to 19 years of age and nearly all obesity classifications. Schwimmer et al. (2006)[51] and Arshad et al. (2021)[17] were taken to model the prevalence at young adulthood as they included participants between 2 and 29 years of age. Data from Younossi et al. (2016)[18] provided information for all ages between 30 and 79 years of age, but no information on BMI

differences. To model the BMI differences as well, Information from Mummadi et al. (2008)[16] was included as it depicted the prevalence of NAFLD in highly obese adult individuals. (For the resulting risk plane, see Graphic 3 at the end).

Figure 21. NAFLD Prevalence Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Prevalence (%)	"	"	"	"	"	"
Anderson 2015[1]	corresponding to 76 independent study populations		1-19 years	Systematic Review/Meta Analysis of 74 Studies			-	-	49%	36%	25%	17%	9%
Schwimmer 2006[2]	US	SCALE	2-19 years	1993-2003	Both	742	-	-	-	-	38%	20%	17%
Arshad 2021[3]	US	NHANES	12-29 years	2007-2016	Both	4,654	-	-	-	-	-	-	12%/25%/ 22%
Younossi 2014[4]	meta-analysis		30-79 years of Age		Both	8,515,431	Only Age specific Data available 30-79 years 30-39=22%; 40-49=26%; 50-59=27%; 60-69=29%; 70-79=34%						
Mummadi 2008[5]	electronic literature search of published articles on bariatric surgery and liver histology (total of 15 studies (766 paired liver biopsies))						-	95%	85%	70%	-	-	-
Le 2017[6]	US	NHANES	18+ years	1999-2012	Both	6000	-	-	90%	80%	-	30%	20%
Stefan 2018[7]	Citing Anderson 2015 and Younossi 2014												
Vernon 2011[8]	Systematic review 1980-2010						-	-	-	-	98%	57%	25%

1) Anderson et al. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis, 2015 2) Schwimmer et al. Prevalence of Fatty Liver in Children and Adolescents, 2006 3) Arshad et al. Nonalcoholic Fatty Liver Disease Prevalence Trends Among Adolescents and Young Adults in the United States, 2007-2016, 2021 4) Younossi et al. Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes, 2016 5) Mummadi et al. Effect of Bariatric Surgery on Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis, 2008 6) Le et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States, 2017 7) Stefan et al. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies, 2018 8) Vernon et al. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults, 2011

K.3.4 Cancer Prevalence

For childhood prevalence number, information from Ward et al. (2014)[24] was extracted and used to model the cancer prevalence for children and adolescents. This study provided a big part of the US population (SEER+NAACCR Cohorts) from birth onwards. For adulthood Yao et al. (2022)[25] was used as the study provides prevalence information for all ages between 20 and 90 years with a total cohort of n = 503,060. To model the differences caused by BMI classifications, Hazard Ratios were extracted from Jee et al. (2008)[26]. This study included 1,213,829 patients and therefore precisely depicts the impact of weight on cancer risk. (For the resulting risk plane, see Graphic 4 at the end).

Figure 22. Cancer Prevalence Study Selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Prevalence (%) or HR	"	"	"	"	"	"
Ward 2014[1]	US	SEER	Birth	1975 and 2010	Both	28% of US population	-	-	-	-	-	-	0,35%/0,25%
Ward 2014[1]	US	NAACCR	Birth	1975 and 2010	Both	95% of US population	-	-	-	-	-	-	0,35%/0,25%
Yao 2022[2]	CA	CCR	all	2013-2018	Both	503,060 cases the past 5-years	Only Age specific Data available 20-90 years 20-29= 0,3% 30-39= 0.83%; 40-49=1,89%; 50-59=4,22%; 60-69=8,44%; 70-79=13,6% 80-89=14,63% 90+=11,13%						
Jee 2008[3]	KR	NHIC	30-95 years	1992-1995	Both	1,213,829	-	-	HR 1.49	HR 1.33	HR 1.19	HR 1.03	HR 1
RKI 2021[4]	DE	-	-	2017-2018	Men/Women	90%+ of Germany	Only Age specific Data available 45-85 years 45= 2.2%/1.2% 55 = 4.8%/3.3% 65 = 8.2%/9.7% 75 = 12.8%/20% 85 = 16.2%/26.7%						
Wang 2020[5]	CN	CKB	51.47±10.67	median: 8.95 years	Both	508,362	-	-	-	-	HR 1.13	HR 1	HR 1
Wang 2020[5]	CN	CKB	51.47±10.67	median: 8.95 years	Both	508,362	-	-	-	-	-	4,2%	4.2%

1) Ward et al. Childhood and Adolescent Cancer Statistics, 2014, 2014 2) Yao et al. Short-term cancer prevalence in Canada, 2018, 2022 3) Jee et al. Body mass index and cancer risk in Korean men and women, 2008 4) Robert Koch-Institut, Krebs in Deutschland für 2017/2018, Zentrum für Krebsregisterdaten, 13. Ausgabe, Berlin, 2021 5) Wang et al. Cancer incidence in relation to body fatness among 0.5 million men and women: Findings from the China Kadoorie Biobank, 2020

K.3.5 Asthma Prevalence

Information from the CDC Most recent national Asthma data 2020[30] was used to model the Asthma prevalence at normal weight from ages 0-65 years of age. For later ages Chen et al. (1999)[31] was used, as it provides information until 70 years of age. To model the differences caused by BMI classifications, Hazard Ratios from Kim et al. (2003)[32] were used. This study assessed the impact of BMI on the development of asthma in 45,973 individuals until a BMI of 45. (For the resulting risk plane, see Graphic 5 at the end).

Figure 23. Asthma Prevalence Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50) Prevalence (%) or HR	(BMI 45-50) "	(BMI 40-45) "	(BMI 35-40) "	(BMI 30-35) "	(BMI 25-30) "	(BMI 20-25) "
Kim 2003[1]	US	2000 BRFSS	18-34 years	-	Both	45,973	-	HR 4.9	HR 3.19	HR 2.28	HR 1.79	HR 1.51	HR 1
Camargo 1999[2]	US	NHS II	24-44 years	191-1995	Women	116,678	-	-	HR 3.1	HR 2.6	HR 2.3	HR 1.5	HR 1
Nystad 2004[3]	NO	Screening Programm	14–60 years	1963–2002	Both	135,405	-	-	-	HR 2.34	HR 1.78	HR 1.27	HR 1
KIM 2003[1]	US	2000 BRFSS	18-34 years	-	Both	45,973	-	-	-	-	-	-	8%
Chen 1999[4]	CA	NPHS	≥12 years	1994-1995	Women	17,605	(Age specific Prevalence 12-70+ years) 12-24 years = 10.4%; 25-39 = 5.8%; 40-54 = 4.1%; 55-69 = 4.9%; 70+ = 4.5 %						
Zhang 2022[5]	204 countries	GBD	1-19 years	1990-2019	Both	-	(Age specific Prevalence 1-19 years) 1-4 years= 44.2%; 5-9 years = 28.4%; 10-14 years= 16.7% 15-19 years= 10.8%						
CDC[6] Most Recent National Asthma Data Prevalence 2020							(Age specific Prevalence 0-65+ years) 0-4=2%; 5-11=5.9%; 12-14= 8.1%; 15-19=9.3%; 20-24=10.3%; 25-34=8.1%; 35-64=8.3%; 65+=7.8%						
Huisstede 2013[7]	NL	pre-operative screening before bariatric surgery	18-60 years	2009-2011	Both	86	-	42%	-	-	-	-	-

1) Kim et al. Sex-race Differences in the Relationship between Obesity and Asthma: The Behavioral Risk Factor Surveillance System, 2000, 2003 2) Camargo et al. Sex-race Differences in the Relationship between Obesity and Asthma: The Behavioral Risk Factor Surveillance System, 2000, 2003, 1999 3) Nystad et al. Body Mass Index in Relation to Adult Asthma among 135,000 Norwegian Men and Women, 2004 4) Chen et al. Increased Effects of Smoking and Obesity on Asthma among Female Canadians: The National Population Health Survey, 1994-1995, 1999 5) Zhang et al. The Burden of Childhood Asthma by Age Group, 1990–2019: A Systematic Analysis of Global Burden of Disease 2019 Data, 2022 6) Centers for Disease Control. Most recent national asthma data 2020 7) Huisstede et al. Underdiagnosis and overdiagnosis of asthma in the morbidly obese, 2013

K.3.6 Sleep Apnea Prevalence

Verlhust et al. (2007)[36] provides an overview of obese children affected by Sleep Apnea. For modelling Adulthood ages Lopez et al. (2008)[37] and Young et al. (2002)[35] were used. Lopez provides data on all BMI classifications needed for modelling and Young provides all information needed for all ages after childhood. (For the resulting risk plane, see Graphic 6 at the end).

Figure 24. Sleep Apnea Prevalence Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50) Prevalence (%) or HR	(BMI 45-50) "	(BMI 40-45) "	(BMI 35-40) "	(BMI 30-35) "	(BMI 25-30) "	(BMI 20-25) "
Verlhust 2007[3]	BE	Pediatric Clinic	6-16 years	2002-2005	both	91	-	-	-	-	47%	44%	-
Lopez 2008[2]	US	Clinic Database	17-75 years	5 years	both	290	77%	73%	73%	71%	33%	33%	-
Young 2002[1]	US	SHHS	40-98 years	questionnaire	both	5615	(Age specific prevalence 40-85 years) 39-49=10%; 50-59=16%; 60-69=19%; 70-79=21%; 80-99=20%						
Young 2002[1]	US	SHHS	40-98 years	questionnaire	both	5615	(Severetiy differences in OSA) Mild OSA=3-28%; Severe OSA=1-14%						

1) Young et al. Epidemiology of Obstructive Sleep Apnea A Population Health Perspective, 2002 2) Lopez et al. Prevalence of Sleep Apnea in Morbidly Obese Patients Who Presented for Weight Loss Surgery Evaluation: More Evidence for Routine Screening for Obstructive Sleep Apnea before Weight Loss Surgery, 2008 3) Verhulst et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution, 2007

K.3.7 T2DM Mortality Risk

Carstensen et al. (2020)[4] and Salehidoost et al. (2018)[5] provides a broad spectrum of patient information regarding age and mortality risk due to diabetes. It assessed the mortality risk of 448,445 diabetic patients in Denmark and was chosen to model the age differences in mortality risk. To Modell the BMI differences Mulnier et al. (2005)[6] was used. This study provides data for all BMI Classifications and a broad diabetic cohort (n = 44,230) and a reference group without diabetes (n = 219,797). The mortality risk was adjusted by 58% for (Cardiovascular mortality 44% + Cancer 14%) based on Liu et al. (2019)[7], to tackle double counting in the modelling. (For the resulting risk plane, see Graphic 7 at the end).

Figure 25. T2DM Mortality Risk Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Mortality (%) or HR	„	„	„	„	„	„
Carstensen 2020[1]	DK	entire Danish population	0-100 years	1996-2016	both	448,445 diabetics	Only Age specific Data available 0-80+ Age 10-45 = 0,05%-0,5%; 50-80 = 0,7%-7%; 85-100 = 10%-75%						
Salehidoost 2018[2]	IR	database of the Iranian Endocrine and Metabolism Research Center	Mean Age 49.4-56.0	1992-2010	both	2,383	-	-	HR 1.17	HR 0.68	HR 0.8	HR 0.82	HR 1
Mulnier 2005[3]	UK	GPRD	35 – 89 years	1992-1999	both	44,230 diabetics + 219,797 reference	HR 1.59	HR 1.43	HR 1.28	HR 1.22	HR 1.13	HR 0.97	HR 1
Shan 2020[4]	CN	From: Tianjin, Shenyang, Taiyuan, Rizhao.	Mean Age 44.12 years	12-years observation	both	39,054	-	-	-	-	-	-	0,14%
Lin 2012[5]	TW	DCMP	30-94 years	Median 4.02 years	both	5,686	-	-	-	-	-	-	0.5%

1) Carstensen et al. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016, 2020 2) Salehidoost et al. Body mass index and the all-cause mortality rate in patients with type 2 diabetes mellitus, 2018 3) Mulnier et al. Mortality in people with Type 2 diabetes in the UK, 2005Source: Exemplary literature screen for relationship of Early Onset Obesity and Prevalence of T2DM 4) Shan et al. Associations between the incidence and mortality rates of type 2 diabetes mellitus and long-term exposure to ambient air pollution: A 12-year cohort study in northern China, 2020 5) Lin et al. Impact of Lifestyle-Related Factors on All-Cause and Cause-Specific Mortality in Patients With Type 2 Diabetes, 2012

K.3.8 Cardiovascular Event Mortality Risk

Data for all ages (0-70+) was provided by the Global burden of disease study 2019[11,12]. Information from Furer et al. (2018)[13] was taken to model the differences in mortality risk caused by increased BMI level. Furer included 2,294,139 patients to assess the impact of BMI on cardiovascular mortality risk between 1967 until 2010 (For the resulting risk plane, see Graphic 8 at the end).

Figure 26. Cardiovascular Event Mortality Risk Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Mortality (%) or HR	„	„	„	„	„	„
GBD 2019[1]	all	-	-	1990-2019	both	Global	Only Age specific Data available 0-70+ 5-14 years = 0.001%; 15-49 years = 0.04%; 50-69 years = 0.5%; 70+ years = 3.56%						
Furer 2018[2]	IL	All Military examination	17 years	1967-2010	both	2,294,139	-	-	HR 7.5/6.7	HR 4.2/5.7	HR 2.4/4.8	HR 2.3/3.1	HR 1/1
Gunnel 1998[3]	US	Boyd Orr	2-14 years	1948-1995	both	2,399	-	-	-	-	-	HR 2.6	-
Gunnel 1998[3]	US	Boyd Orr	2-14 years	1948-1995	both	2,399	-	-	-	-	-	-	0,3%
Lin 2012[4]	TW	DCMP	30-94 years	median 4.02 years	both	5,686	-	-	-	-	-	-	0.4%
Sierra-Johnson 2005[5]	DE	-	62 ±11 years	6.4 ±1.8 years	both	389	-	-	-	-	2%	8%	10%
Khan 2018[6]	US	10 Cohorts	20-39	1964-2015	Male/Female	190,672	-	-	3.8%/0%	1.7%/1%	1.7%/1%	0.9%/0.4%	0.6%/0.4%
Khan 2018[6]	US	10 Cohorts	40-59	1964-2015	Male/Female	190,672	-	-	35%/19.5%	24%/18.3%	24%/18.3%	18.2%/12%	16.2%/8.9%

1) Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME) 2) Furer et al. Sex-specific associations between adolescent categories of BMI with cardiovascular and non-cardiovascular mortality in midlife, 2018 3) Gunnel et al. Childhood obesity and adult cardiovascular mortality: a 57-y follow-up study based on the Boyd Orr cohort, 1998 4) Lin et al. Impact of Lifestyle-Related Factors on All-Cause and Cause-Specific Mortality in Patients With Type 2 Diabetes, 2012 5) Sierra-Johnson et al. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation, 2005 6) Khan et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity, 2018

K.3.9 NAFLD Mortality Risk

Le et al. (2017)[22] and Simon et al. (2021)[21] were used to model age differences in mortality risk due to NAFLD, as all ages are covered by these two studies. To model the additional differences caused by BMI, information from Golabi et al. (2020)[23] is taken as it provides data for patients aged 20-74 years and uses data from NHANES III. (For the resulting risk plane, see Graphic 9 at the end).

Figure 27. NAFLD Mortality Risk Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50) Mortality (%) or HR	(BMI 45-50) „	(BMI 40-45) „	(BMI 35-40) „	(BMI 30-35) „	(BMI 25-30) „	(BMI 20-25) „
Le 2017[1]	US	NHANES	18+ years	1999-2012	both	6000	-	-	-	-	-	-	0,5%
Simon 2021[2]	SE	ESPRESSO	≤25 years	1966–2017	both	718	-	-	-	-	-	-	0,39%
Golabi 2020[3]	US	NHANES III	20-74 years	18.7-22.4 years follow up	both	9,341	-	-	-	HR 2.48	HR 1.84	HR 2.54	HR 1
Younossi 2014[4]	meta-analysis		30-79 years of Age		both	8,515,431	-	-	-	-	-	1%	-
Rafiq 2009[5]	US	CCF+CLD	50.2 ±14.5 years	28.5 years	both	173	-	-	-	-	2.7%	-	-

1) Le et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States, 2017 2) Simon et al. Non-alcoholic fatty liver disease in children and young adults is associated with increased long-term mortality, 2021 3) Golabi et al. Mortality of NAFLD According to the Body Composition and Presence of Metabolic Abnormalities, 2020 4) Younossi et al. Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes, 2016 5) Rafiq et al. Long-Term Follow-Up of Patients With Nonalcoholic Fatty Liver, 2009

K.3.10 Cancer Mortality Risk

Miller et al. (2020)[27] covers around 28% of US population with its study results and depicts the mortality risk for all ages needed for modelling. Calle et al. (2003)[28] was chosen for modelling the BMI differences because here too the cohort (n = 900,053) is exceptionally big, depicting a precises picture of BMI differences on cancer related mortality risk. (For the resulting risk plane, see Graphic 10 at the end).

Figure 28. Cancer Mortality Risk Study Selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50) Mortality (%) or HR	(BMI 45-50) „	(BMI 40-45) „	(BMI 35-40) „	(BMI 30-35) „	(BMI 25-30) „	(BMI 20-25) „
Miller 2020[1]	US	SEER	15-39 years	1975-2016	both	28% of US population	Only Age specific Data available 15-40+ years 15-19 years = 3%; 20-29 years = 2.8% 30-39 years = 3.4%; 40+ = 6,8%						
Calle 2003[2]	US	Cancer Prevention Study II	30+ years	1982- 16 years of follow up	both	900,053		HR 2.05	HR 1.52	HR 1.2	HR 1.09	HR 0.97	HR 1
RKI 2021[3]	DE	-	-	2017-2018	Women/Men	90%+ of Germany	-	-	-	-	-	-	7.8%
Bhaskaran 2018[4]	UK	CPRD	16 years and older	1998-2016	both	1 969 648	-	-	HR 1.45	HR 1.24	HR 1.11	HR 1.06	HR 1
Bhaskaran 2018[4]	UK	CPRD	16 years and older	1998-2016	both	1 969 648	-	-	-	-	20%/12%/5.6 %/2%	19.6%/11%/4. 7%/1.8%	17.6%/9.8%/4. 2%/1.7%

1) Miller et al. Cancer Statistics for Adolescents and Young Adults, 2020, 2020 2) Calle et al. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults, 2003 3) Robert Koch-Institut, Krebs in Deutschland für 2017/2018, Zentrum für Krebsregisterdaten, 13. Ausgabe, Berlin, 2021 4) Bhaskaran et al. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK, 2018

K.3.11 Asthma Mortality Risk

Data on Asthma Mortality Risk for Age was gathered from the Supplementary material provided by Lemmetyinen et al. (2018)[34] and BMI specific data from Whitlock et al. (2009)[33]. The difference in mortality risk due to BMI was assessed based on a collaborative analysis of 57 prospective studies combining 894,576 patients. (For the resulting risk plane, see Graphic 11 at the end).

Figure 29. Asthma Mortality Risk Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Prevalence (%) or HR	"	"	"	"	"	"
Jordan 2010[1]	US	NHANES III	17-80+ years	1988-1994	both	2439	-	-	HR 5.78	HR 1.69	HR 1	HR 1.25	HR 1.45
Zhang 2022[2]	204 countries	GBD	1-19 years	1990-2019	both	-	(Age specific Mortality all Population 1-19 years) 1-4 = 0,0012%; 5-9 = 0,0003%; 10-14 = 0,0003%; 15-19 = 0,0005%						
Lemmetyinen 2018[3]	FI	questionnaire in 1997	30 years	Mean 15.6 years	both	1052	-	-	-	-	-	-	0,012%
Whitlock 2009[4]	Collaborative analysis of 57 prospective studies				both	894,576	-	-	-	HR 1.39	HR 1.15	HR 0.94	HR 1
CDC[5] Most Recent National Asthma Data Mortality 2020							(Age specific Mortality all Population 0-65+ years 0-4=-; 5-11=0,00032%; 12-17=0.00039%; 25-43=0,00076%; 35-64=0,0013%; 65+= 0,003%						

1) Jordan et al. Obesity and Mortality in Persons with Obstructive Lung Disease Using Data from the NHANES III, 2010 2) Zhang et al. The Burden of Childhood Asthma by Age Group, 1990–2019: A Systematic Analysis of Global Burden of Disease 2019 Data, 2022 3) Lemmetyinen et al. Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort, 2018 4) Whitlock et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies, 2009 5) Centers for Disease Control. Most recent national asthma data 2020

K.3.12 Obesity Duration impact on Mortality Risk

Abdullah et al. (2011)[38] provides a detailed analysis of the duration of obesity and the impact on all-cause mortality risk. It assesses under one year of duration until over 25 years of obesity duration and assessed obese individuals from 28 years until 62 years of age. (For the resulting risk plane, see Graphic 12 at the end).

Figure 30. Obesity Duration impact on Mortality Risk Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
							HR	"	"	"	"
Abdullah 2011[1]	US	FHS	28-62	48 years	Both	5036	1	1.51	1.94	2.25	2.52
Abdullah 2011[1]	US	FHS	28-62	48 years	Both	5036	1	1.06	1.16	1.29	1.25

1) Abdullah et al. The number of years lived with obesity and the risk of all-cause and cause-specific mortality, 2011

K.3.13 Obesity Duration impact on T2DM Risk

Hu et al. (2015)[39] assessed the impact of duration of obesity on the development of T2DM in 125,474 individuals (NHS+NHSII). The study adjusted results for all BMI classifications leaving only the effect of duration for observation. Hazard Ratios from this study were used to increase T2DM risk correspondingly to duration of obesity. (For the resulting risk plane, see Graphic 13 at the end).

Figure 31. Duration impact on T2DM Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
							HR	"	"	"	"
Hu 2015[1]	US	NHS / NHSII	25-55	1984-2011	Women	125,474	1	1.58	1.43	1.11	1.11
Hu 2015[1]	US	NHS / NHSII	25-55	1984-2011	Women	125,474	1	1.04	1.14	1.26	1.34

1) Hu et al. Duration of obesity and overweight and risk of type 2 diabetes among US women, 2015

K.3.14 Obesity Duration impact on Cardiovascular Event Risk

In 48 years of observation Abdullah et al. (2014)[40] made clear, that the duration of obesity has a significant impact of on the development of Cardiovascular Events in obese

individuals. Hazard ratios were extracted and used to increase the risk accordingly to specific obesity durations. (For the resulting risk plane, see Graphic 14 at the end).

Figure 32. Duration impact on Cardiovascular Event Study selection

							>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	HR	"	"	"	"
Abdullah 2014[1]	US	FHS	28-62	48 years	Both	5036	1	1.28	1.31	1.5	1.59

1) Arnold et al. Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States, 2016

K.3.15 Obesity Duration impact on Cancer Risk

Arnold et al. (2016)[41] assessed the development of all cancer types linked to obesity duration in 73,913 individuals from the WHI cohort between 1993-1998. Hazard Ratios were extracted as well and considered when modelling the effect obesity duration. (For the resulting risk plane, see Graphic 15 at the end).

Figure 33. Duration impact on Cancer Study selection

							>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	HR	"	"	"	"
Arnold 2016[1]	US	WHI	50-79	1993-1998	Women	73,913	1	1	1.09	1.18	1.22

1) Arnold et al. Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States, 2016

K.3.16 Irreversible Risk Accumulation Integration

Juonala et al. (2008)[42] assessed the impact of weight loss on the cardiometabolic risk profile of 6328 participants. For T2DM and CV Events the risk profile of patients that have lost weight was higher than that of patients that were never obese, indicating a risk accumulation that is nonreversible. To Get Hazard Ratios needed for modelling, we compared those cases to the known impact of obesity duration and conservatively took the difference as new hazard ratios to be able to model the impact of varying durations of obesity and the resulting irreversible accumulated risk in that period. These new Hazard Ratios describing the irreversible risk accumulation share of comorbidity risks over time were implemented into the modelling process of estimating the case specific comorbidity burden. Risk accumulation for NAFLD was based on one study assessing effect of bariatric surgery by Mummadi et al. (2008)[46] (Graphics 16,17,18 at the end).

K.4 Model Framework

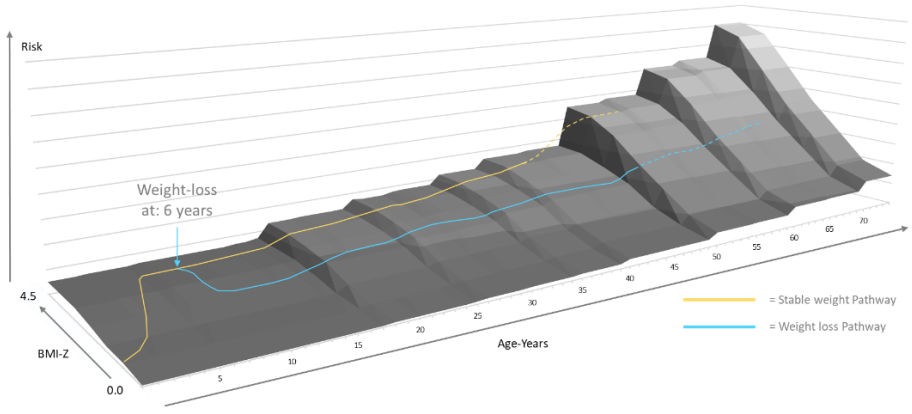
K.4.1 Methodology of modelling outcomes of obesity and weight development

The data tables described above allow access to all the information needed to generate all combinations of weight (BMI-Z 0.0-4.5), age (0-100 years) and duration of obesity (0-100 years). These combinations allow the generation of patient specific trajectories and to assess future comorbidity risks and the corresponding life expectancy.

The prevalence and mortality risk tables serve as the basis for these assessments. The combination results in a mortality risk that is further modified by mortality specific duration factors to obtain a life expectancy estimation. By modifying the prevalence only, with comorbidity specific duration factors the comorbidity risk for each specific age is yielded. This comorbidity risk is further adjusted for the irreversible risk accumulated, to obtain the new risk profile after treatment (after weight loss). These processes are always the same and are only influenced by the age and weight development entered into the model. With this approach, it is possible to estimate how the comorbidity risks and life expectancy will develop based on the patient's weight development. The comorbidity risks are needed to further calculate the disability adjusted life years (DALYs).

In order to be able to see an effect resulting from a weight reduction, the model creates two weight development pathways for the same base case. One pathway without weight reduction and one pathway with new weight development. The resulting difference in risk and life expectancy as well as DALYs after weight reduction is the impact that this reduction has on the future development of comorbidity risks and life expectancy. The created pathways are located in a three-dimensional risk landscape. This risk landscape is a direct result of the individual patient factors, namely prevalence, mortality risk as well as obesity duration and irreversible risk accumulation. The pathway shifts on this risk landscape created by the model engine according to its weight development. The following is an example of a Mortality-Risk-Landscape with two different trajectories representing stable weight at BMI-Z 4.0 in yellow and a weight loss scenario to BMI-Z 3.0 represented in blue (Figure 34).

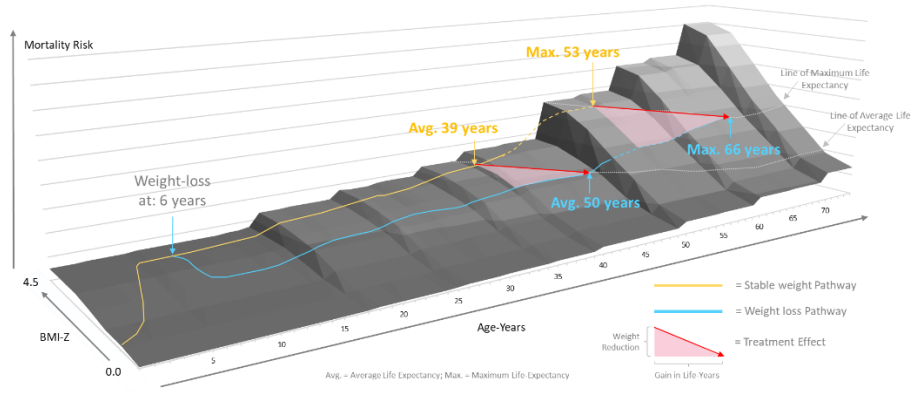
Figure 34. Patient corresponding Mortality-Risk-Landscape



Source: EOObesity-Model

The weight development trajectories are yielding risk information that are used to calculate the mortality risk and the comorbidity risk for all ages. As explained earlier, the difference in the results of the different pathways gives the effect of weight loss on mortality and comorbidity risks. Below is an example where the movement of trajectories on the mortality Risk-Landscape leads to different life expectancies (Figure 35).

Figure 35. Patient corresponding Mortality-Risk-Landscape with Life-Expectancy



Source: EOObesity-Model

K.4.2 Model Step-by-Step assembly

The Actual Model consist of three main bodies: The Interface to create a case specific weight development pathway, the engine that is selecting case specific information based on the provided weight development pathway and calculates comorbidity risks as well as a life expectancy, and the database, which provides all the information extracted by the engine.

First step of building the model was to create the database containing all information needed to model different case scenarios. For each combination of age between 0-100 years and a BMI-Z Score of 0.0-4.5 a comorbidity risk is given. Depending on the onset of obesity for each year of obesity duration and BMI-Z between 0.0-4.5 a specific duration risk increase is given. The Duration Factor Table was created using the Hazard Ratios provided by the afore mentioned studies. These Hazard Ratios were then taken as values for the average study BMI and the upper Confident Intervals were taken as values for the maximum BMI value. The remaining BMI values were interpolated between these data points and no risk increase for BMI-Z of 0.0.

To counter overestimating when modifying the comorbidity risk with duration factors, we adjusted those duration factors for the average obesity duration in the corresponding study cohorts. This step was made based on the assumption, that in a relatively older cohort obesity duration is longer than in a cohort with younger individuals, resulting in an overestimation for the younger and an underestimation for the older patients when taking the same risk value for both age groups. (Graphics 19,20,21,22)

For the comorbidities: T2DM, CV, NAFLD, Cancer, and Asthma Disability Weights are given, needed for DALY calculation. To implement the irreversible risk accumulation of some comorbidities data was created for each age between 0-100 years and all BMI-Z Score 0.0-4.5.

Second step was to create an engine capable of extracting data from the database and calculating Life-Expectancy as well as comorbidity risks for all ages. Another part is the DALYs calculation happening separately. Based on the Age and Weight at that point the

engine is calculating the duration of obesity. With The Age, BMI-Z, and Obesity Duration the engine can fill out all the missing information provided by the database.

The third and final step was to build an interface for data entry and to build an interface between the interface and the engine that generates the weight development paths based on the data entered into the interface. This generated weight development pathway is directly flowing into the engine which provides all the necessary information for the engine to start modelling. The user does not have to leave the interface to see the results, as all information generated by the engine is visible on the interface. In parallel with the data entry, the life expectancy, the DALY overview, and the comorbidity risks for all ages are presented for the treated and untreated patient (No weight loss and weight loss).

This resulting model does not take ethnic and sex differences as well as “healthy-obese” into account.

K.5 Case example

To be able to compare our findings we created a base case example patient with early onset of obesity. Patient conditions were a BMI-Z of 2.5 at 2 years of age and BMI-Z of 4.0 at 4 years of age. This information was used to generate a first patient pathway resembling an untreated patient. With the same weight development at the early stages of life, the patient lost weight at 6 years of Age resulting in a new weight of BMI-Z 3.0, leading to the second Pathway resembling the treated patient. The weight loss at 6 years of Age resulted in a gain in Life-Years of [redacted] years and a reduction of [redacted] DALYs. Later Age years at weight reduction let to diminished treatment effects. Down below is a graphical representation of Three different case Scenarios: Untreated patient, Treatment at 6 years and 20 years:

Figure 36. No Weight reduction

Figure 37. Weight reduction at 6 years of age

Figure 7: Weight reduction at 20 years of age

K.6 Model conclusions

The quantification of the model and the systematic run-through of a wide variety of patient cases is one ability of the model and provides validation for a wide variety of findings. The most important dynamics of the model reflect the findings already discussed in the afore mentioned studies. Increased weight as well as higher age is associated with a higher risk of all comorbidities. This risk increases additionally with higher duration of obesity. An additional dynamic that was not integrated into the model for technical reasons is the increase in risk due to multimorbidity. Having one specific morbidity increases the risk of developing another additional comorbidity, for example the onset of T2DM increases further the risk of CV events. The integration of this additional factor affected all calculations and thus had a severe impact on life expectancy and the overall assessment of comorbidity risk. However, the model results no longer correspond to the clinically verifiable reality, after implementation. Reason for this is double counting a certain number of comorbidities. If you add all prevalence numbers in the model for a certain age and specific weight, sometimes the total comorbidity prevalence exceeds 100%, for example at 15 years of age and a BMI-Z of 3.0 all comorbidities combined yield a prevalence of 120%. This means that at least 100% of all people have 1 comorbidity and at least 20% have 2 comorbidities. The model is already counting in those additional 20% in its equations to estimate comorbidity risk and Life expectancy. These 20% will be double counted when additional factors are implemented to increase the risk further due to multimorbidity factors.

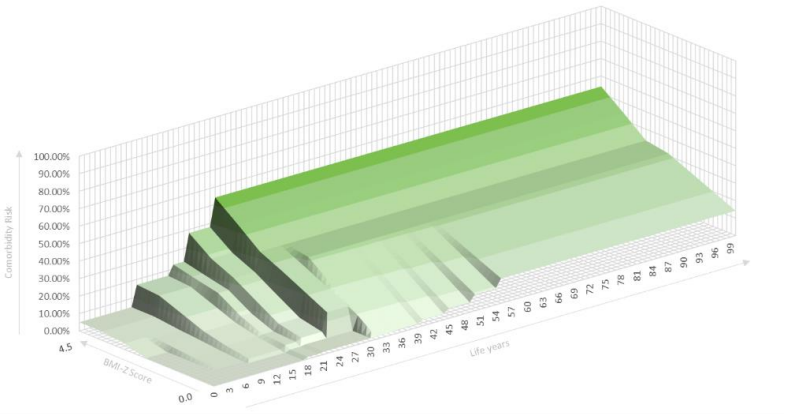
Another capability of the model and one of its main tasks is the assessment of risk reduction resulting from weight loss. Here several dynamics are in play, with the greatest influence on risk reduction being the magnitude of weight reduction. The more weight is reduced, the greater the reduction in the risk of developing comorbidities. Another dynamic of risk reduction is the reduction of obesity duration. by reducing weight at an early stage, the time in which comorbidities can develop due to obesity is reduced, thus a reduction in obesity duration results in a direct decrease in the risk profile. Accordingly, our main finding is that the earlier and more severe you reduce the weight to a healthy level, the greater the risk reduction. This dynamic is influenced by all factors (age, weight, duration) and results in a non-linear progression. For example, the longer you wait to reduce weight, the lower the risk reduction, even if you reduce by the same weight level.

This effect is not linear, i.e. the risk reduction is less for each year of delay in weight loss than it was for the previous year.

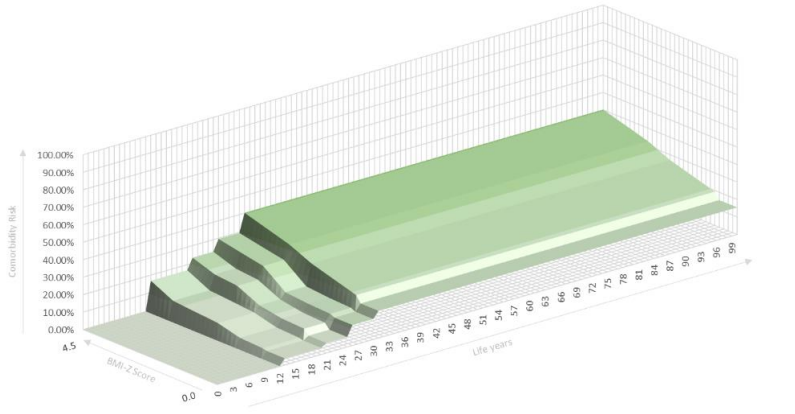
This is the first and only model to assess the impact of early-onset obesity on mortality and morbidity. It confirms the major impact of early-onset obesity on life expectancy and the benefits of losing weight as early as possible.

K.7 Model Graphics

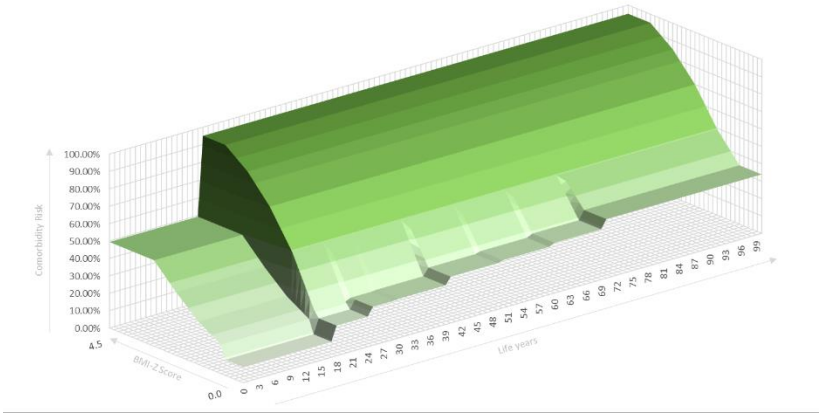
K.7.1 Graphic 1: T2DM Prevalence



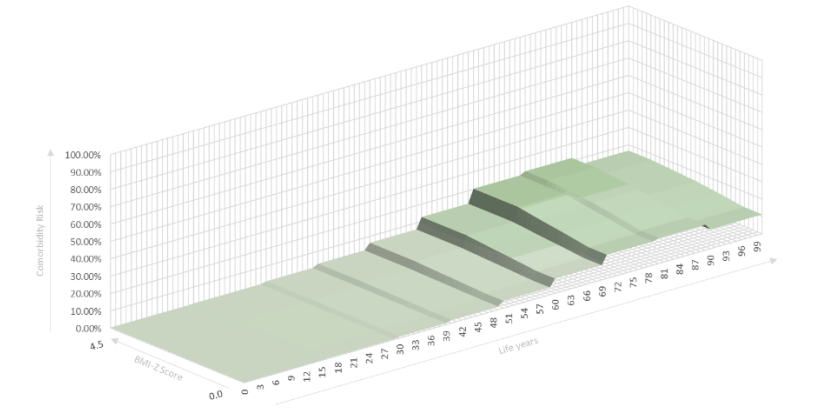
K.7.2 Graphic 2: Cardiovascular Event Prevalence



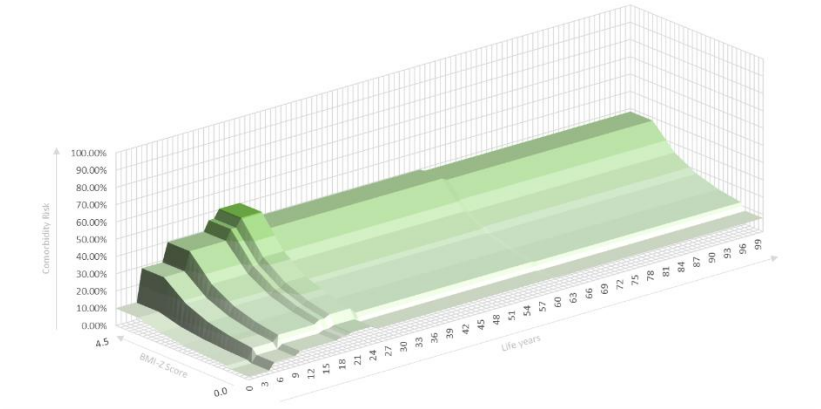
K.7.3 Graphic 3: NAFLD Prevalence



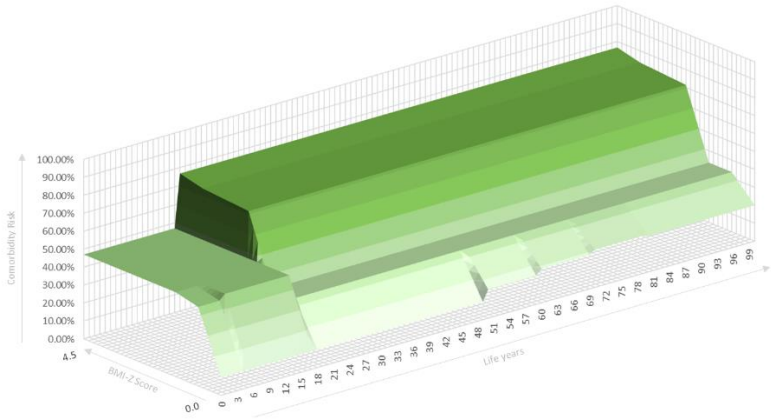
K.7.4 Graphic 4: Cancer Prevalence



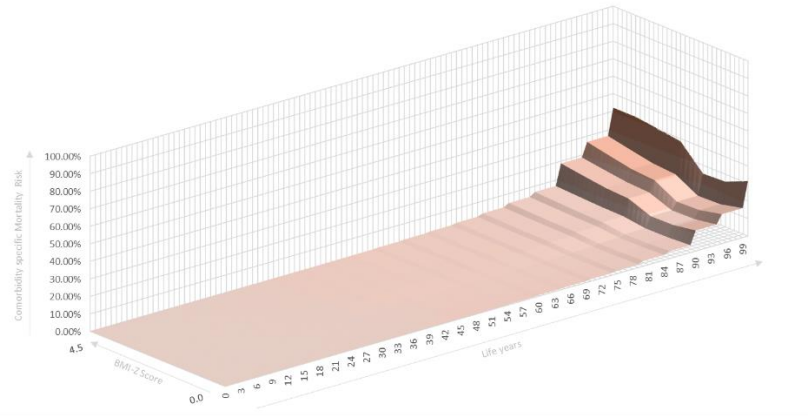
K.7.5 Graphic 5: Asthma Prevalence



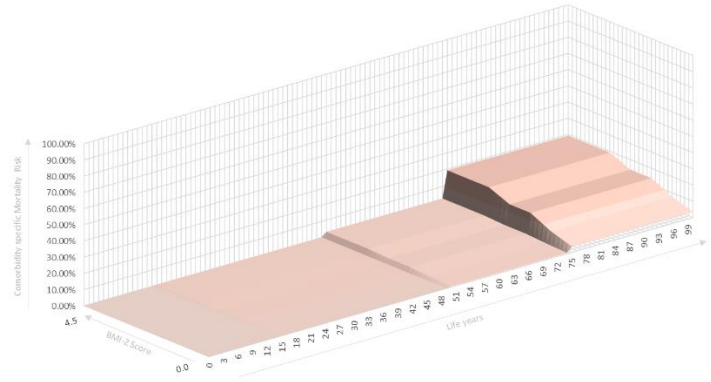
K.7.6 Graphic 6: Sleep Apnea Prevalence



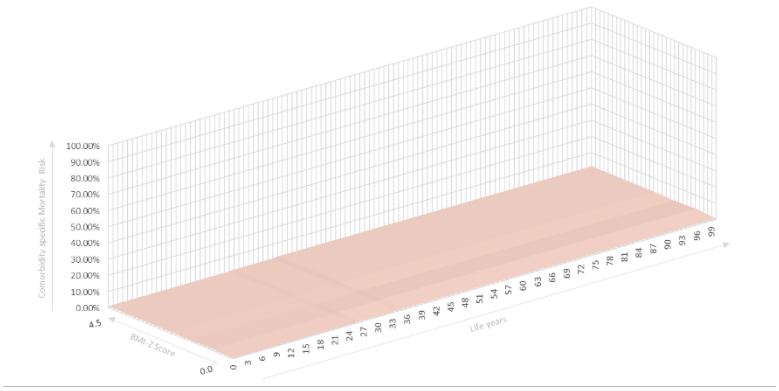
K.7.7 Graphic 7: T2DM Mortality Risk



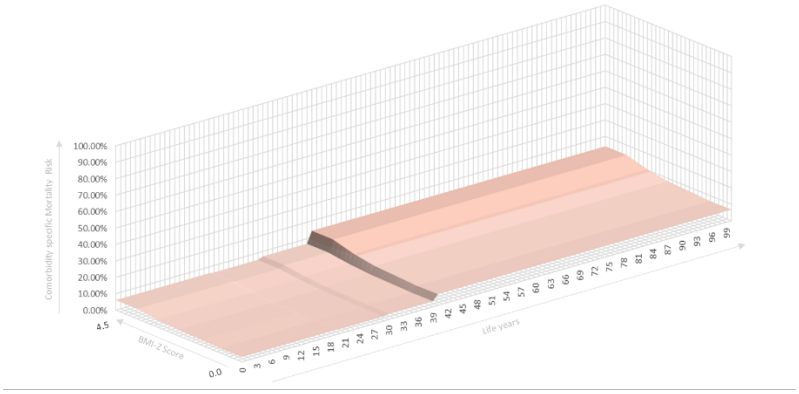
K.7.8 Graphic 8: Cardiovascular Event Mortality Risk



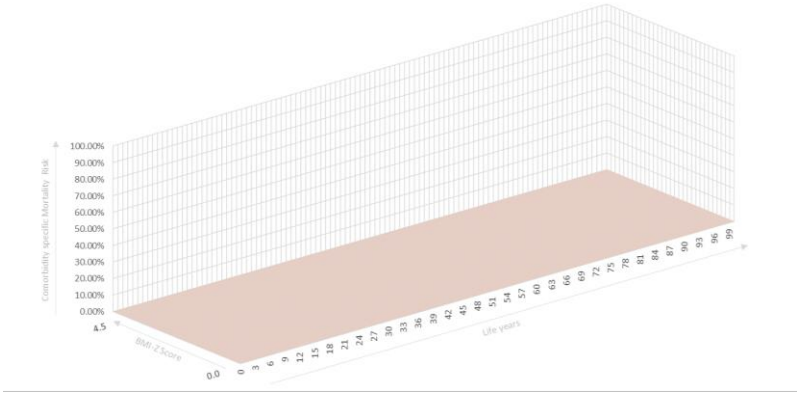
K.7.9 Graphic 9: NAFLD Mortality Risk



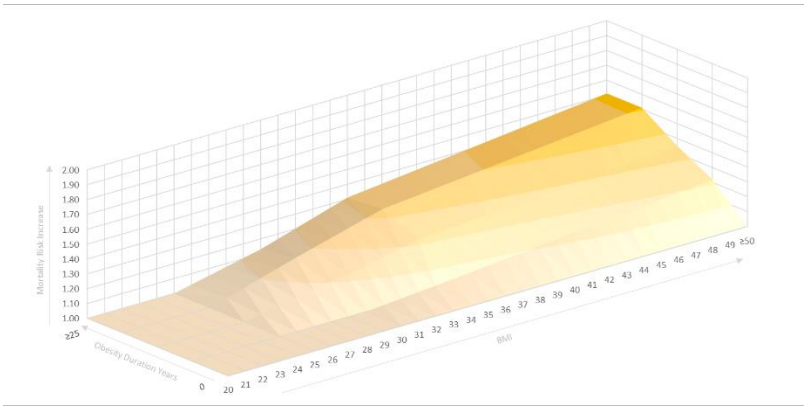
K.7.10 Graphic 10: Cancer Mortality Risk



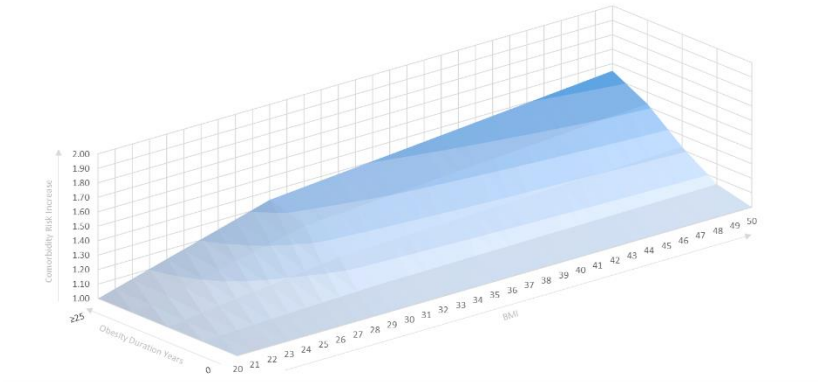
K.7.11 Graphic 11: Asthma Mortality Risk



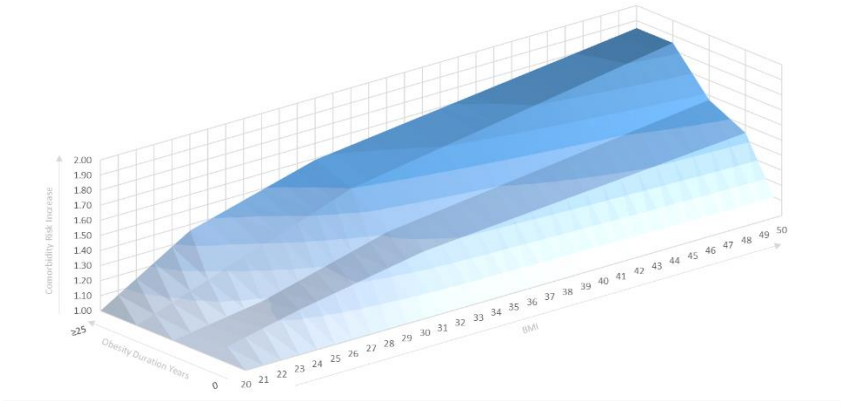
K.7.12 Graphic 12: Obesity Duration impact on Mortality Risk



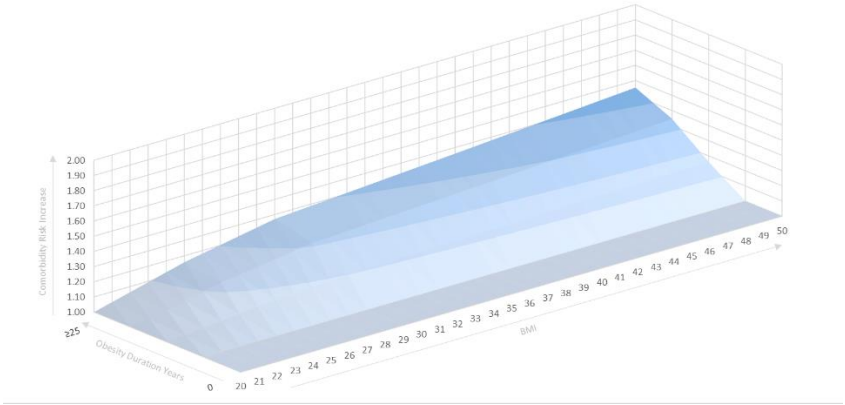
K.7.13 Graphic 13: Obesity Duration impact on T2DM Risk



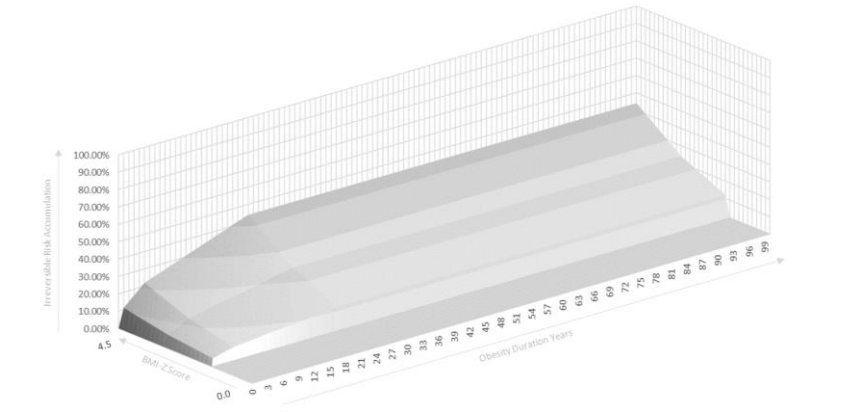
K.7.14 Graphic 14: Obesity Duration impact on Cardiovascular Event Risk



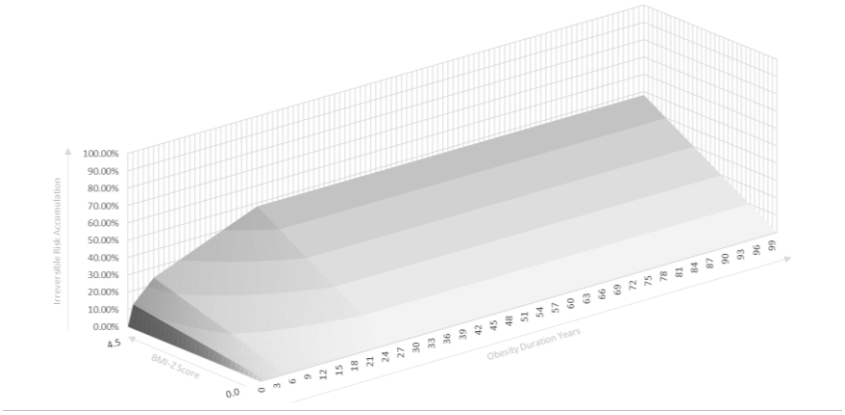
K.7.15 Graphic 15: Obesity Duration impact on Cancer Risk



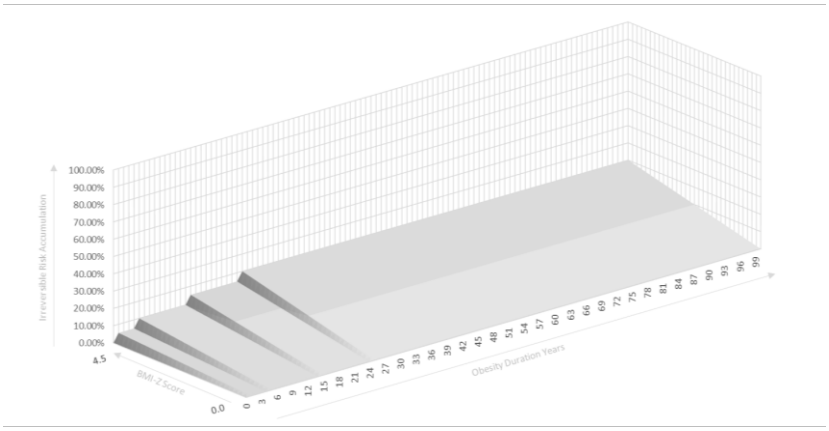
K.7.16 Graphic 16: Irreversible T2DM Risk Accumulation



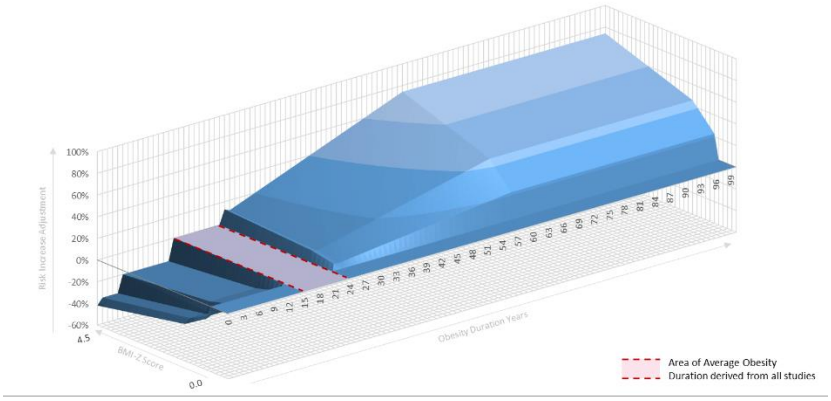
K.7.17 Graphic 17: Irreversible CV Risk Accumulation



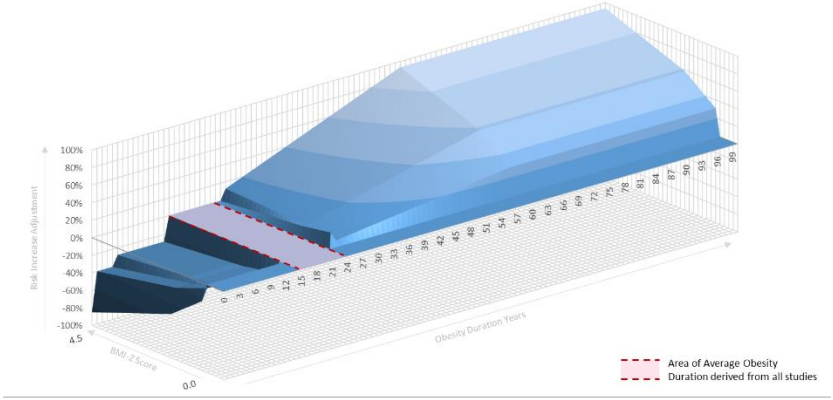
K.7.18 Graphic 18: Irreversible NAFLD Risk Accumulation



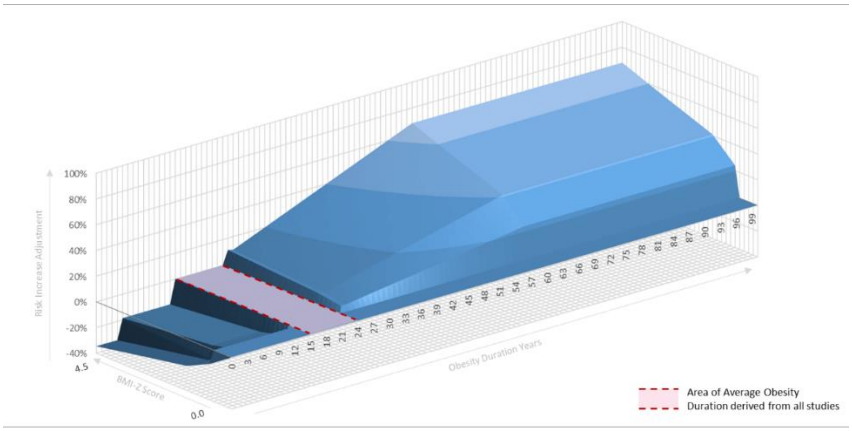
K.7.19 Graphic 19: T2DM Risk adjustment



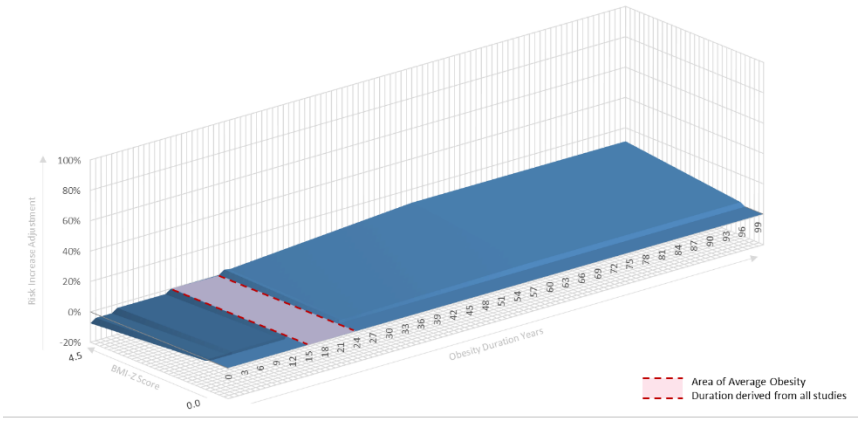
K.7.20 Graphic 20: CV Risk adjustment



K.7.21 Graphic 21: Cancer Risk adjustment



K.7.22 Graphic 22: NAFLD Risk adjustment



K.8 Literature Overview

K.8.1 Studies included

1. Tanamas et al. 2018, Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population
2. Ahmad et al. 2014, Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey
3. Bjerregaard et al. 2018, Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes
4. Carstensen et al. 2020, Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016
5. Salehidoost et al. 2018, Body mass index and the all-cause mortality rate in patients with type 2 diabetes mellitus
6. Mulnier et al. 2005, Mortality in people with Type 2 diabetes in the UK
7. Liu et al. 2019, Cause-Specific Mortality in Multiethnic South East Asians with Type 2 Diabetes Mellitus

8. Hu et al. 2015, Duration of obesity and overweight and risk of type 2 diabetes among US women
9. Ahmad et al. 2014, Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey
10. Baker et al. 2007, Childhood body-mass index and the risk of coronary heart disease in adulthood
11. Institute for Health Metrics and Evaluation, Global Burden of Disease, DEATHS - STROKE - SEX: BOTH - AGE: ALL AGES (RATE), Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME)
12. Institute for Health Metrics and Evaluation, Global Burden of Disease, DEATHS - CARDIOVASCULAR DISEASES - SEX: BOTH - AGE: ALL AGES (RATE), Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME)
13. Furer et al. 2018, Sex-specific associations between adolescent categories of BMI with cardiovascular and non-cardiovascular mortality in midlife, Supplementary Table 4
14. Abdullah et al. 2014, Estimating the risk of cardiovascular disease using an obese-years metric
15. Anderson et al. 2015, The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis
16. Mummadi et al. 2008, Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis
17. Arshad et al. 2021, Nonalcoholic Fatty Liver Disease Prevalence Trends Among Adolescents and Young Adults in the United States, 2007-2016
18. Younossi et al. 2016, Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes
19. Harrison et al. 2021, Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort
20. Clark et al. 2005, Roux-en-Y gastric bypass improves liver histology in patients with non-alcoholic fatty liver disease
21. Simon et al. 2021, Non-alcoholic fatty liver disease in children and young adults is associated with increased long-term mortality
22. Le et al. 2017, Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States
23. Golabi et al. 2020, Mortality of NAFLD According to the Body Composition and Presence of Metabolic Abnormalities
24. Ward et al. 2014, Childhood and Adolescent Cancer Statistics
25. Yao et al. 2022, Short-term cancer prevalence in Canada, 2018
26. Jee et al. 2008, Body mass index and cancer risk in Korean men and women
27. Miller et al. 2020, Cancer Statistics for Adolescence and Young Adults, 2020
28. Calle et al. 2003, Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults
29. Arnold et al. 2026, Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States
30. Centers for Disease Control. Most recent national asthma data 2020
31. Chen et al. 1999, Increased Effects of Smoking and Obesity on Asthma among Female Canadians: The National Population Health Survey, 1994-1995
32. Kim et al. 2003, Sex-race Differences in the Relationship between Obesity and Asthma: The Behavioral Risk Factor Surveillance System, 2000
33. Whitlock et al. 2009, Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies
34. Lemmetyinen et al. 2018, Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort
35. Young et al. 2002 Epidemiology of Obstructive Sleep Apnea A Population Health Perspective
36. Verhulst et al. 2007 Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution
37. Lopez et al. 2008 Prevalence of Sleep Apnea in Morbidly Obese Patients Who Presented for Weight Loss Surgery Evaluation: More Evidence for Routine Screening for Obstructive Sleep Apnea before Weight Loss Surgery
38. Abdullah et al. 2011, The number of years lived with obesity and the risk of all-cause and cause-specific mortality
39. Hu et al. 2015, Duration of obesity and overweight and risk of type 2 diabetes among US women

40. Abdullah et al. 2014, Estimating the risk of cardiovascular disease using an obese-years metric
41. Arnold et al. 2016, Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States
42. Juonala et al. 2011, Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors
43. Hu et al. 2015, Duration of obesity and overweight and risk of type 2 diabetes among US women
44. Abdullah et al. 2014, Estimating the risk of cardiovascular disease using an obese-years metric
45. Mummadi et al. 2008, Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis
46. Juonala et al. 2011, Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors
47. Hu et al. 2015, Duration of obesity and overweight and risk of type 2 diabetes among US women
48. Abdullah et al. 2014, Estimating the risk of cardiovascular disease using an obese-years metric
49. Mummadi et al. 2008, Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis
50. Schwimmer et al. 2006, Prevalence of Fatty Liver in Children and Adolescents

K.8.2 Studies assessed but not included in the modelling

1. Abdullah et al. 2011, The Duration of Obesity and the Risk of Type 2 Diabetes
2. Al-Saeed et al. 2016, An Inverse Relationship Between Age of Type 2 Diabetes Onset and Complication Risk and Mortality
3. Alfredsson et al. 2019, Lifestyle and Environmental Factors in Multiple Sclerosis
4. Aliakbarian et al. 2020, Pre-Operative Predictors of Weight Loss and Weight Regain Following Roux-En-Y Gastric Bypass Surgery
5. Alipoor et al. 2019, Association of Obesity with Morbidity and Mortality in Critically Ill Children
6. Alqahtani et al. 2023, Obesity Burden and Impact of Weight Loss in Saudi Arabia
7. Amini et al. 2021, Trend Analysis of Cardiovascular Disease Mortality, Incidence, and Mortality-to-Incidence Ratio
8. Avdagic-Terzic, et al. 2022, Diabetes Mellitus Type 2 and cardiovascular diseases-Risk Assessment
9. Basen-Engquist et al. 2011, Obesity and Cancer Risk
10. Batsis et al. 2016, Effect of Bariatric Surgery on Cardiometabolic Risk in Elderly Subjects
11. Bendor et al. 2020, Cardiovascular Morbidity, Diabetes and Cancer Risk among Children and Adolescents with Severe Obesity
12. Beuther et al. 2007, Overweight, Obesity, and Incident Asthma
13. Bhaskaran et al. 2018, Association of BMI with overall and cause-specific mortality
14. Bhaskaran et al. 2018, Association of BMI with Overall and Cause-Specific Mortality
15. Boyer et al. 2015, Childhood Body Mass Index Trajectories Predicting Cardiovascular Risk in Adolescence
16. Brara et al. 2012, Pediatric Idiopathic Intracranial Hypertension and Extreme Childhood Obesity
17. Burstein et al. 2019, Mapping 123 million Neonatal, Infant and Child Deaths between 2000 and 2017
18. Burt et al. 2010, Obesity and the Pubertal Transition in Girls and Boys
19. Cali et al. 2009, Primary Defects in Beta-Cell Function Further Exacerbated by Worsening of Insulin Resistance Mark the Development of Impaired Glucose Tolerance in Obese Adolescents
20. Cameron et al. 2002, Critical Periods in Human Growth and Their Relationship to Diseases of Aging
21. Chan et al. 2009, Musculoskeletal Effects of Obesity
22. Chen et al. 2019, Weight Change across Adulthood in Relation to All Cause and Cause Specific Mortality
23. Cheng et al. 2021, Body Mass Index Trajectories during Mid to Late Life and Risks of Mortality and Cardiovascular Outcomes
24. Chiarelli et al. 2008, Insulin Resistance and Obesity in Childhood
25. Cho et al. 2018, Metabolic Risk Factors in Korean Adolescents with Severe Obesity
26. Chung et al. 2017, Growth and Puberty in Obese Children and Implications of Body Composition
27. Chung et al. 2018, Cardiometabolic Risk in Obese Children

28. De et al. 2012, Update on Statural Growth and Pubertal Development in Obese Children
29. Deshmukh-Taskar et al. 2006, Tracking of Overweight Status from Childhood to Young Adulthood
30. Di et al. 2013, Role of Obesity on All-Cause Mortality in Whites with Type 2 Diabetes from Italy
31. DuGoff et al. 2014, Multiple Chronic Conditions and Life Expectancy
32. Eisner et al. 2007, Body composition and functional limitation in COPD
33. Emerging et al. 2015, Association of Cardiometabolic Multimorbidity with Mortality
34. Eriksson et al. 1999, Catch-up Growth in Childhood and Death from Coronary Heart Disease
35. Eriksson et al. 2001, Early Growth and Coronary Heart Disease in Later Life
36. Feldstein et al. 2009, The Natural History of Non-Alcoholic Fatty Liver Disease in Children
37. Field et al. 2005, Weight Status in Childhood as a Predictor of Becoming Overweight or Hypertensive in Early Adulthood
38. Fintini et al. 2020, The Bones of Children with Obesity
39. Franks et al. 2010, Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death
40. Franks et al. 2002, Adult Polycystic Ovary Syndrome Begins in Childhood
41. Franssen et al. 2008, Obesity and the Lung
42. Freedman et al. 2001, Relationship of Childhood Obesity to Coronary Heart Disease Risk Factors in Adulthood
43. Furer et al. 2020, Adolescent Obesity and Midlife Cancer Risk
44. García-García et al. 2019, Neuroanatomical Differences in Obesity
45. Geserick et al. 2018, Acceleration of BMI in Early Childhood and Risk of Sustained Obesity
46. Gunnell et al. 1998, Childhood Obesity and Adult Cardiovascular Mortality
47. Guo et al. 1994, The Predictive Value of Childhood Body Mass Index Values for Overweight at Age 35 y
48. Harding et al. 2014, Mortality Trends among People with Type 1 and Type 2 Diabetes in Australia
49. Harroud et al. 2021, Childhood Obesity and Multiple Sclerosis
50. Haws et al. 2021, The efficacy and safety of Setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome
51. He et al. 2021, Trends in Cardiovascular Risk Factors in US Adults by Race and Ethnicity and Socioeconomic Status, 1999-2018
52. Hong et al. 2021, Cancer Statistics in Korea
53. Horesh et al. 2021, Adolescent and Childhood Obesity and Excess Morbidity and Mortality in Young Adulthood-a Systematic Review
54. Hui et al. 2019, Effect of Obstructive Sleep Apnea on Cardiovascular Function in Obese Youth
55. Huo et al. 2018, Impact of Age at Diagnosis and Duration of Type 2 Diabetes on Mortality in Australia 1997-2011
56. Huovinen et al. 2003, Factors Associated to Lifestyle and Risk of adult-onset Asthma
57. Hyder et al. 2012, Measuring the Health of Populations
58. Hyppönen et al. 2003, Prenatal Growth, BMI, and Risk of Type 2 Diabetes by Early Midlife
59. Ice et al. 2011, Morbidly Obese Diagnosis as an Indicator of Cardiovascular Disease Risk in Children
60. Jacobs et al. 2022, Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events
61. Jayawardene et al. 2017, Clinical Measures of Obesity and Cumulative Cardiometabolic Risk in Adolescents
62. Jordan et al. 2010, Obesity and Mortality in Persons with Obstructive Lung Disease Using Data from the NHANES III
63. Juanola et al. 2021, Non-Alcoholic Fatty Liver Disease
64. Juonala et al. 2011, Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors
65. Juonala et al. 2006, Obesity in Youth Is Not an Independent Predictor of Carotid IMT in Adulthood. The Cardiovascular Risk in Young Finns Study
66. Kansra et al. 2020, Childhood and Adolescent Obesity
67. Khan et al. 2018, Association of Body Mass Index with Lifetime Risk of Cardiovascular Disease and Compression of Morbidity
68. Khera et al. 2018, Effects of Weight Loss Medications on Cardiometabolic Risk Profiles
69. Kim et al. 2021, Association between Adiposity and Cardiovascular Outcomes
70. Kim et al. 2022, DALY Estimation Approaches
71. Kindblom et al. 2018, BMI Change during Puberty and the Risk of Heart Failure
72. Ko et al. 2006, Prediction of Cardiovascular and Total Mortality in Chinese Type 2 Diabetic Patients by the WHO Definition for the Metabolic Syndrome

73. Koskinen et al. 2014, Youth Overweight and Metabolic Disturbances in Predicting Carotid Intima-Media Thickness, Type 2 Diabetes, and Metabolic Syndrome in Adulthood
74. Ku et al. 2020, Trends in Cardiovascular Mortality Among a Cohort of Children and Young Adults Starting Dialysis in 1995 to 2015
75. Kumar et al. 2017, Review of Childhood Obesity
76. Kurth et al. 2002, Body Mass Index and the Risk of Stroke in Men
77. Lai et al. 2014, Impact of Long-Term Burden of Excessive Adiposity and Elevated Blood Pressure from Childhood on Adulthood Left Ventricular Remodeling Patterns
78. Lauby-Secretan et al. 2016, Body Fatness and Cancer--Viewpoint of the IARC Working Group
79. Lavie et al. 2013, Impact of Obesity and the Obesity Paradox on Prevalence and Prognosis in Heart Failure
80. Lavie et al. 2009, Obesity and Cardiovascular Disease
81. Lee et al. 2006, Prevalence and Determinants of Insulin Resistance among U.S. Adolescents
82. Lennon et al. 2016, The Obesity Paradox in Cancer
83. Li et al. 2006, Sex Differences in the Relationships between BMI, WHR and Incidence of Cardiovascular Disease
84. Li et al. 2007, Body Mass Index throughout the Life-Course and Blood Pressure in Mid-Adult Life
85. Li et al. 2016, Cardiometabolic Risk Factors among Severely Obese Children and Adolescents in the United States, 1999-2012
86. Li et al. 2012, Relation of Childhood Obesity/Cardiometabolic Phenotypes to Adult Cardiometabolic Profile
87. Li et al. 2020, The Association between Body Mass Index Trajectories and Cardiometabolic Risk in Young Children
88. Lin et al. 2012, Impact of Lifestyle-Related Factors on All-Cause and Cause-Specific Mortality in Patients with Type 2 Diabetes
89. Lin et al. 2015, Mortality of Patients with Type 2 Diabetes in Taiwan
90. Lindberg et al. 2020, Association of Childhood Obesity with Risk of Early All-Cause and Cause-Specific Mortality
91. Llewellyn et al. 2016, Childhood Obesity as a Predictor of Morbidity in Adulthood
92. Lowe et al. 2020, Adolescent Obesity and Dietary Decision Making-a Brain-Health Perspective
93. Luo et al. 2020, Age of Obesity Onset, Cumulative Obesity Exposure over Early Adulthood and Risk of Type 2 Diabetes
94. Magliano et al. 2020, Young-Onset Type 2 Diabetes Mellitus - Implications for Morbidity and Mortality
95. Manuel et al. 2021, Nutrition, Obesity and Asthma Inception in Children. The Role of Lung Function
96. Marcus et al. 2022, Pediatric obesity—Long-term consequences and effect of weight loss
97. Mayyas et al. 2021, Predictors of Mortality among Patients with Type 2 Diabetes in Jordan
98. McCrindle et al. 2015, Cardiovascular Consequences of Childhood Obesity
99. Medina-Gómez et al. 2018, Mortality from Type 2 Diabetes and Implementation of the PREVENIMSS Program
100. Meurling et al. 2019, Obesity and Sleep
101. Meza et al. 2015, Burden of Type 2 Diabetes in Mexico
102. Mills et al. 2016, Structural Brain Development between Childhood and Adulthood
103. Moran et al. 1999, Insulin Resistance during Puberty
104. Morrison et al. 2010, Childhood Predictors of Adult Type 2 Diabetes at 9- and 26-Year Follow-Ups
105. Munger et al. 2013, Childhood Body Mass Index and Multiple Sclerosis Risk
106. Must et al. 1992, Long-Term Morbidity and Mortality of Overweight Adolescents. A Follow-up of the Harvard Growth Study of 1922 to 1935
107. Nguyen et al. 2021, Differential Clinical Characteristics and Mortality Outcomes in Persons with NAFLD and/or MAFLD
108. Norris et al. 2020, Duration of obesity exposure between ages 10 and 40 years and its relationship with cardiometabolic disease risk factors
109. Olson et al. 2017, Pediatric Markers of Adult Cardiovascular Disease
110. Ortiz-Marrón et al. 2022, Tracking and Risk of Abdominal and General Obesity in Children between 4 and 9 Years of Age. The Longitudinal Childhood Obesity Study (ELOIN)
111. Osmond et al. 2007, Infant Growth and Stroke in Adult Life
112. Park et al. 2019, Incidence-Based versus Prevalence-Based Approaches on Measuring Disability-Adjusted Life Years for Injury

113. Peeters et al. 2011, Age-specific trends in cardiovascular mortality rates in the Netherlands between 1980 and 200
114. Peter et al. 2016, Body Mass Trajectories, Diabetes Mellitus, and Mortality in a Large Cohort of Austrian Adults
115. Petrelli et al. 2021, Association of Obesity with Survival Outcomes in Patients with Cancer
116. Pinhas-Hamiel et al. 2014, Advanced Bone Age and Hyperinsulinemia in Overweight and Obese Children
117. Pomerantz et al. 2010, Injury Patterns in Obese versus Nonobese Children Presenting to a Pediatric Emergency Department
118. Power et al. 2011, Changes in BMI, Duration of Overweight and Obesity, and Glucose Metabolism
119. Prospective et al. 2009, Body-Mass Index and Cause-Specific Mortality in 900 000 Adults
120. Rafiq et al. 2009, Long-Term Follow-up of Patients with Nonalcoholic Fatty Liver
121. Roffi et al. 2013, Gender-Related Mortality Trends among Diabetic Patients with ST-Segment Elevation Myocardial Infarction
122. Rolland-Cachera et al. 2006, Early Adiposity Rebound
123. Rosengren et al. 2017, Body Weight in Adolescence and Long-Term Risk of Early Heart Failure in Adulthood among Men in Sweden
124. Saab et al. 2015, Evaluating the Cause of Death in Obese Individuals
125. Schreiner et al. 2021, Obesity and Multiple Sclerosis-A Multifaceted Association
126. Schroeder et al. 2012, Incidence, prevalence, and hybrid approaches to calculating disability-adjusted life years
127. Sciomer et al. 2020, Role of Gender, Age and BMI in Prognosis of Heart Failure
128. Seferović et al. 2018, Type 2 Diabetes Mellitus and Heart Failure
129. Sharifi et al. 2017, Cost-Effectiveness of a Clinical Childhood Obesity Intervention
130. Sierra-Johnson et al. 2005, Relation of Body Mass Index to Fatal and Nonfatal Cardiovascular Events after Cardiac Rehabilitation
131. Simmonds et al. 2015, The Use of Measures of Obesity in Childhood for Predicting Obesity and the Development of Obesity-Related Diseases in Adulthood
132. Skinner et al. 2015, Cardiometabolic Risks and Severity of Obesity in Children and Young Adults
133. Sopher et al. 2011, Bone Age Advancement in Prepubertal Children with Obesity and Premature Adrenarche
134. Sun et al. 2019, Body Mass Index and All-Cause Mortality in HUNT and UK Biobank Studies
135. The et al. 2013, Timing and Duration of Obesity in Relation to Diabetes
136. Thrainsdottir et al. 2005, The Association between Glucose Abnormalities and Heart Failure in the Population-Based Reykjavik Study
137. Tirosh et al. 2011, Adolescent BMI Trajectory and Risk of Diabetes versus Coronary Disease
138. TODAY et al. 2013, Rapid Rise in Hypertension and Nephropathy in Youth with Type 2 Diabetes
139. Tsoi et al. 2022, Prevalence of Childhood Obesity in the United States in 1999-2018
140. Twig et al. 2020, Adolescent Obesity and Early-Onset Type 2 Diabetes
141. Umer et al. 2017, Childhood Obesity and Adult Cardiovascular Disease Risk Factors
142. Vernon et al. 2011, Systematic Review
143. Volkow et al. 2017, The Dopamine Motive System
144. Wang et al. 2005, Comparison of Abdominal Adiposity and Overall Obesity in Predicting Risk of Type 2 Diabetes among Men
145. Ward et al. 2017, Simulation of Growth Trajectories of Childhood Obesity into Adulthood
146. Weihrauch-Blüher et al. 2018, Risk Factors and Implications of Childhood Obesity
147. Wing et al. 2011, Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals with Type 2 Diabetes
148. Wrzosek et al. 2018, Early Onset of Obesity and Adult Onset of Obesity as Factors Affecting Patient Characteristics Prior to Bariatric Surgery
149. Yoshioka et al. 2020, Effect of Weight Change and Lifestyle Modifications on the Development or Remission of Nonalcoholic Fatty Liver Disease
150. Yu et al. 2019, Prevalence of Nonalcoholic Fatty Liver Disease in Children with Obesity
151. Zhang et al. 2022, The Burden of Childhood Asthma by Age Group, 1990-2019
152. Zhang et al. 2019, Prevalence and the Association of Body Mass Index and Other Risk Factors with Prediabetes and Type 2 Diabetes Among 50,867 Adults in China and Sweden
153. Yang et al. 2021, Trends in Cardiometabolic and Cancer Multimorbidity Prevalence and Its Risk with All-Cause and Cause-Specific Mortality in U.S. Adults: Prospective Cohort Study

154. Xu et al. 2017, Asthma and risk of cardiovascular disease or all-cause mortality: a meta-analysis
155. Simon et al. 2021, Mortality in Biopsy-Confirmed Nonalcoholic Fatty Liver Disease
156. Lee et al. 2013, Mortality of Patients with Obstructive Sleep Apnea in Korea
157. Younossi et al. 2019, The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis
158. Wannamethee et al. 2011, Impact of Diabetes on Cardiovascular Disease Risk and All-Cause Mortality in Older Men
159. Pearson-Stuttard et al. 2021, Type 2 Diabetes and Cancer: An Umbrella Review of Observational and Mendelian Randomization Studies
160. Rayner et al. 2019, The impact of therapy on the risk of asthma in type 2 diabetes
161. Subramanian et al. 2019, Risk of Incident Obstructive Sleep Apnea Among Patients with Type 2 Diabetes
162. Caussy et al. 2021, The Relationship Between Type 2 Diabetes, NAFLD, and Cardiovascular Risk
163. Kim et al. 2008, Fatty liver is an independent risk factor for the development of Type 2 diabetes in Korean adults
164. Sørensen et al. 2003, Risk of Cancer in Patients Hospitalized with Fatty Liver
165. Roh et al. 2022, A nationwide survey of the association between nonalcoholic fatty liver disease and the incidence of asthma in Korean adults
166. Greenlee et al. 2022, Risk of Cardiovascular Disease in Women with and Without Breast Cancer: The Pathways Heart Study
167. George et al. 2023, The Evidence Surrounding Non-Alcoholic Fatty Liver Disease in Individuals with Cancer: A Systematic Literature Review
168. Rayner et al. 2019, Type 2 Diabetes and Asthma: Systematic Review of the Bidirectional Relationship
169. Tattersall et al. 2015, Asthma Predicts Cardiovascular Disease Events: The Multi-Ethnic Study of Atherosclerosis
170. Ioan et al. 2022, Evaluation of obesity and asthma as risk factors for moderate to severe obstructive sleep apnea in children
171. Pashou et al. 2022, Sleep Apnea and Cardiovascular Risk in Patients with Prediabetes and Type 2 Diabetes
172. Huang et al. 2018, A Population-Based Study of the Bidirectional Association Between Obstructive Sleep Apnea and Type 2 Diabetes in Three Prospective U.S. Cohorts
173. Kim et al. 2022, Obstructive Sleep Apnea and Nonalcoholic Fatty Liver Disease in the General Population: A Cross-Sectional Study Using Nationally Representative Data
174. Brenner et al. 2017, Increased Risk for Cancer in Young Patients with Severe Obstructive Sleep Apnea
175. Brinke et al. 2005, Risk factors of frequent exacerbations in difficult-to-treat asthma

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk