Medicinrådet

Bilag til Medicinrådets vurdering af elafibranor til behandling af primær biliær cholangitis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. af elafibranor
2. Amgros' forhandlingsnotat vedr. elafibranor
3. Ansøgning vedr. elafibranor

Comments on the elafibranor assessment report

Ipsen reviewed the assessment report developed by the DMC for the treatment with elafibranor and would like to comment on relevant comparator for elafibranor and object to a change made in the health economic model:

[redacted]

Medicinrådets vurdering af transitionssandsynligheder anvendt i modellen

Medicinrådet vurderer, at ansøgers antagelse om, at ***patienter, der modtager UDCA alene ikke er i stand til at forbedre deres helbredstilstand efter 12 måneder afkobler modellens transitionssandsynligheder fra det kliniske data, hvilket resulterer i en markant skævvridning af effekten.*** [redacted]

Response: The DMC are incorrect in their assessment that patients receiving treatment with UDCA can improve in their health state and that assuming that patients treated with UDCA can only worsen is not aligned with clinical data. In our response shared February 21st we explained the rationale and the relevance to clinical data:

[redacted]

In the aforementioned response, Ipsen referred to clinical trial data from ELATIVE. The trial results demonstrated stable ALP (Figure 1) and increase in TB (Figure 2) for patients treated with placebo over the first 52 weeks (i.e., approximately until Cycle 4), which were used to build the transition probabilities in the model. [redacted]

[redacted]

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04.08.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Ipsen Pharma
Lægemiddel	Iqirvo (elafibranor)
Ansøgt indikation	Primær biliær cholangitis i kombination med ursodeoxycholsyre (UDCA) for patienter, som ikke har tilstrækkeligt respons ved UDCA alene, eller som monoterapi for patienter, der ikke kan tåle UDCA
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Iqirvo (elafibranor):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Iqirvo	80 mg (30 stk. tabletter)	35.556,93	[redacted]	[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på Iqirvo samt bezafibrat.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Iqirvo	80 mg (30 stk. tabletter)	80 mg dagligt	[redacted]	[redacted]
Bezafibrat	200 mg (100 stk.)	400 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

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

Opsummering

[redacted]

Application for the assessment of elafibranor for primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Abbreviations

Abbreviation	Definition
5-NT	5'-nucleotidase
AASLD	American Association for the Study of Liver Diseases
AB	Antibody
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AESI	Adverse event of special interest
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali
AIC	Akaike Information Criterion
AIH	Autoimmune hepatitis
ALB	Albumin
ALD	Adrenoleukodystrophy
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibodies
AP1	Activator protein 1
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATMP	Advanced therapy medicinal product
AWMSG	All Wales Medicines Strategy Group
BCL6	B-cell lymphoma 6
BIC	Bayesian Information Criterion
BSEP	Bile salt export pump
BSEP	Bile salt export pump
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-Effectiveness Analysis
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK-18	Cytokeratin-18
CLD	Chronic liver disease
CLDQ	Chronic Liver Disease Questionnaire
CMH	Cochran-Mantel-Haenszel
CRU	Cost and healthcare resource use
CS	Clinically significant (itch)
CTCAE	Common Terminology Criteria for Adverse Events
Cyp27A1	Cytochrome P450 Family 27 Subfamily A Member 1
Cyp3A4	Cytochrome P450 Family 3 Subfamily A Member 4
Cyp7A1	Cytochrome P450 Family 7 Subfamily A Member 1
DB	Double-blind
DCC	Decompensated cirrhosis
DEXA	Dual-energy X-ray absorptiometry
DK	Denmark
DKK	Danish Kroner
DMC	Danish Medicines Council (Medicinrådet)
DRG	Diagnosis-related group
DSGH	Danish Society for Gastroenterology and Hepatology (Dansk Selskab for Gastroenterologi og Hepatologi)
DSU	Decision support unit

Abbreviation	Definition
EASL	European Association for the Study of the Liver
EC	European Comission
ECG	Electrocardiogram
ELF	Enhanced liver fibrosis
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-dimension 5-level Questionnaire
ESS	Epworth Sleepiness Scale
EU	European Union
FDA	US Food and Drugs Administration
FGF-19	Fibroblast growth factor 19
FI	Finland
FPG	Fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss
GGT	Gamma- glutamyl transferase
GLOBE	Global-PBC Study Group
GP	General practitioner
HA	Hyaluronic acid
HAS	Haute Autorité de Santé
hATTR	Hereditary teransthyretin-mediated amyloidosis
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource use
HDL	High-density lipoprotein
HDU	High dependency unit
HSUV	Health state utility value
HTA	Health technology assessment
HTAD	Health Technology Assessment Database
HUI	Health Utilities Index
ICE	Intercurrent events
ICER	Incremental cost effectiveness ratio
ICHLD	International Conference on Hepatology and Liver Disease
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
INR	International normalised ratio
IQR	Interquartile range
IS	Iceland
ITT	Intention-to-treat
JNHB	Joint Nordic HTA Bodies
LDL	Low-density lipoprotein
LLN	Lower limit of normal
LOCF	Last observation carried forward
LS	Least squares
LT	Liver transplant
LTE	Long-term extension
LYG	Life-years gained
MAH	Marketing Authorisation Holder
MAR	Missing at random
MCAR	Missing completely at random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCID	Minimal clinically important difference
MCV	Mean Corpuscular Volume

Abbreviation	Definition
Mdr2/3	Multidrug resistance P-glycoproteins 2/3
MELD	Model for End Stage Liver Disease
MMRM	Mixed models for repeated measures
MSCBS	Ministerio de Sanidad, Consumo Y Bienestar Social
N/A	Not applicable
NA	Not available
NCPE	National Centre for Pharmacoeconomics
NF-kB	nuclear factor kappa B
NF-κB	Nuclear factor kappa-light-chain-enhancer of B cells
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIPH	Norwegian Institute of Public Health
NO	Norway
NR	Not reported
OCA	Obeticholic acid
OLE	Open-label extension
OR	Odds ratio
OS	Overall survival
PAI-1	Plasminogen activator inhibitor-1
PBAC	Pharmaceutical Benefits Advisory Committee
PBC	Primary biliary cholangitis
PDC-E2	Pyruvate dehydrogenase complex 2
PFS	Progression-free survival
PHQ-2	Patient Health Questionnaire-2
PICOS	Population, Intervention, Comparison, Outcomes and Study design
PIINP	Type iii procollagen peptide
PK	Pharmacokinetics
PP	Per-protocol
PPAR	Peroxisome proliferator-activated receptor
PROMIS	Patient Reported Outcome Measurement Information System
PSA	Probabilistic sensitivity analysis
PSC	Primary sclerosing cholangitis
PT	Preferred term
QALY	Quality-adjusted life-years
RCT	Randomised controlled trial
SAE	Serious adverse event
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
ScHARRHUD	University of Sheffield Health Utilities Database
SD	Standard deviation
SE	Standard error
SEK	Swedish Kronor
SEM	Standard error of mean
SF	Short form
SF-36	Medical Outcomes Study Short Form 36
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SST	Danish Health Authority
SULT2A1	Sulfotransferase Family 2A Member.
TA	Technology appraisal
TB	Total bilirubin

Abbreviation	Definition
TC	Total cholesterol
TE	Transient elastography
TEAE	Treatment emergent adverse event
TG	Triglycerides
TGF-β	Transforming growth factor β
TIMP-1	Tissue inhibitor of metalloproteinase 1
TIPPS	Trans jugular intrahepatic portosystemic shunt
TNF-α	Tumour necrosis factor α
TRAE	Treatment-related adverse event
TTD	Time to discontinuation
UDCA	Ursodeoxycholic acid
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
UTI	Urinary Tract Infection
VAS	Visual analogue scale
VLDL	Very low-density lipoprotein
WI-NRS	Worst Itch Numeric Rating Scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Iqirvo®
Generic name	Elafibranor
Therapeutic indication as defined by EMA	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.
Marketing authorization holder in Denmark	Ipsen Pharma
ATC code	A05AX06
Combination therapy and/or co-medication	In combination with UDCA in adults with an inadequate response to UDCA.
(Expected) Date of EC approval	19 September 2024 (1)
Has the medicine received a conditional marketing authorization?	Yes. In order to confirm the efficacy and safety of elafibranor in the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA, the marketing authorisation holder (MAH) shall conduct and submit the final results of the phase III randomised, parallel-group, double-blind, placebo-controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with PBC. Due date: May 2030 (2).
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, 25 July 2019 (3)
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No

Overview of the medicine	
	As there are variations in clinical practice for the treatment of patients with PBC with inadequate response or intolerance to UDCA across the Nordic countries, a joint assessment is not considered relevant.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	30 units of 80 mg film-coated tablets

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Therapeutic indication relevant for the assessment	Treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA
Dosage regiment and administration	80 mg administered orally, once daily
Choice of comparator	As described in the PBC guidelines published by the Danish Society for Gastroenterology and Hepatology (DSGH), UDCA is the only available first-line treatment for PBC, and the backbone of later lines of treatment (4). Apart from Iqirvo® (elafibranor), the only other second-line therapy for PBC currently licensed for use in Denmark is Ocaliva (obeticholic acid). However, the DSGH guidelines do not recommend use of Ocaliva outside of protocol studies, and it is contraindicated for patients with decompensated cirrhosis. In addition, there are uncertainties regarding the continuity of Ocaliva's marketing authorisation. In June 2024, upon review of new study findings, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended that Ocaliva's marketing authorisation be revoked, as its benefits are no longer considered to outweigh its risks (5). This decision has since been suspended, and Ocaliva currently still holds a marketing authorisation (5, 6). However, according to the DSGH guidelines, off-label combination therapy with UDCA+bezafibrate may instead be offered to patients with an inadequate response to UDCA monotherapy within 6-12 months after initiation (4). [redacted] Nevertheless, the DSGH guidelines acknowledge that bezafibrate is not routinely used for PBC in clinical practice in Denmark (4). In addition, there are no products with bezafibrate as the active ingredient with a marketing authorisation for any indication in Denmark, meaning that

	prescription of a bezafibrate product requires a dispensing permit from the Danish Medicines Agency (8). In conclusion, healthcare practitioners (HCPs) and PBC patients in Denmark currently do not have access to any marketing authorised second-line treatments in routine clinical practice. [redacted] a comparison between elafibranor and UDCA monotherapy is deemed appropriate.
Prognosis with current treatment (comparator)	Based on a Swedish registry study and clinical expert input, about 30-40% of PBC patients in Denmark would be assessed to have an inadequate response to first-line UDCA (depending on the response definition used), leaving them at increased risk of disease progression and further complications (11, 12). Studies have shown that UDCA does not improve outcomes such as all-cause mortality, liver transplantation, or serious complications or comorbidities (11). For patients who do not adequately respond to currently available treatments and progress to cirrhosis and severe disease, or suffer with severe medically-resistant pruritus, liver transplant is required (13). The outcome of liver transplant is usually favourable, [redacted], symptoms of PBC, including fatigue, often persist after transplant. Recurrence of PBC has also been reported in patients receiving a liver transplant; following orthotopic liver transplant, recurrent PBC is estimated to occur [redacted] As PBC advances, patients may also develop complications such as hepatocellular carcinoma (HCC), for which there are very limited effective treatments to improve survival (15). [redacted]
Type of evidence for the clinical evaluation	The head-to-head study ELATIVE will be used as evidence for the clinical evaluation (10). In the ELATIVE trial, patients were randomly assigned to receive elafibranor or placebo; patients who were receiving a stable dose of UDCA at baseline (94% of patients in the elafibranor group and 96% in the placebo group) were permitted to continue this treatment throughout the trial (10). Therefore, the placebo group of the ELATIVE trial will represent patients receiving UDCA monotherapy.
Most important efficacy endpoints (Difference/gain compared to comparator)	• Biochemical cholestasis response at week 52 observed in 51% of the patients (55 of 108) who received elafibranor and in 4% (2 of 53) who received placebo (difference: 47 percentage points; 95% confidence interval (CI): 32; 57; p<0.001; odds ratio (OR): 37.6; 95% CI: 7.6; 302.2; p<0.0001) (10). • ALP normalisation at week 52 observed in 15% of the patients in the elafibranor group and in none of the patients in the placebo group (difference: 15 percentage points; 95% CI: 6; 23; p<0.002; OR: infinity; 95% CI: 2.8; infinity; p=0.0019) (10).

	[redacted]
Most important serious adverse events for the intervention and comparator	No serious treatment-emergent adverse events (TEAEs) with frequency of ≥5% were recorded in the ELATIVE study.
Impact on health-related quality of life	[redacted]
Type of economic analysis that is submitted	Type of analysis: cost-utility Type of model: Markov model
Data sources used to model the clinical effects	ELATIVE trial, NICE TA 443 (18, 19)
Data sources used to model the health-related quality of life	ELATIVE trial, NICE TA 443, NICE TA 330, NICE TA 779, Wright et al. 2006, Younossi et al. 2001, Abrahamian et al. 2011 (18-24)
Life years gained	[redacted]

Summary	
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Elafibranor compliance, health states costs (high risk PBC, DCC), and transition probability for liver disease component (high risk PBC -> DCC)
Number of eligible patients in Denmark	[redacted]
Budget impact (in year 5)	[redacted]

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

3.1 The medical condition

3.1.1 Pathophysiology of primary biliary cholangitis

Primary biliary cholangitis (PBC) is a rare, progressive, chronic autoimmune disease of the liver, characterised by the cholestasis-mediated destruction of small intrahepatic bile ducts (13, 25, 26). This prevents the flow of bile and other toxins to the intestine, causing them to build up in the liver in a process known as cholestasis, which leads to scarring of the liver (fibrosis) and eventually can progress to cirrhosis, liver failure and death (13).

One of the most important liver functions is the production of bile acids from cholesterol (27). Bile acids are detergent molecules that are required to break down ingested fats and fat-soluble vitamins for absorption and metabolism in the liver (28, 29). In a healthy liver, bile is produced from cholesterol in the pericentral hepatocytes and flows through the intrahepatic bile ducts to the intestine after a meal, where it serves both digestive and excretory functions.(27-29).

PBC pathogenesis involves both the innate and adaptive immune systems, as well as the biliary epithelium, and leads to the slow destruction of bile ducts (30). Anti-mitochondrial antibodies (AMA) play a key role in this process by interacting with pyruvate dehydrogenase complex 2 (PDC-E2) in the inner mitochondrial membranes of biliary epithelial cells, resulting in T-cell stimulation (31, 32). T cells attack the biliary epithelium in response, preventing the flow of bile and causing it to build up in the liver (cholestasis) (26). As bile is highly acidic and therefore toxic to cells in high concentrations, cholestasis induces hepatocellular apoptosis and necrosis, leading to the loss of biliary duct structure and, eventually, the disappearance of intralobular biliary ducts (26, 33). Damaged bile ducts lead to impaired liver function and fibrosis, which is further exacerbated by innate immune responses such as chronic granulomatous inflammation and pathways regulated by NF-κB (nuclear factor kappa-light-chain-enhancer of B cells), which are activated by necrosis-related biochemical markers released by the hepatocytes and pro-inflammatory cytokines being released by T cells (34-36).

Progression of PBC is driven by the cyclical relationship between immune responses and cholestasis (13). As more bile ducts are blocked and destroyed, more cholestasis-mediated necrosis occurs, causing the release of pro-inflammatory cytokines, leading to further blockage of remaining biliary ducts by granulomatous masses (13). If this cycle continues without therapeutic intervention, scarring of the liver can become severe (cirrhosis), and

can progress to liver failure and the need for transplant, or in some cases, premature death (37).

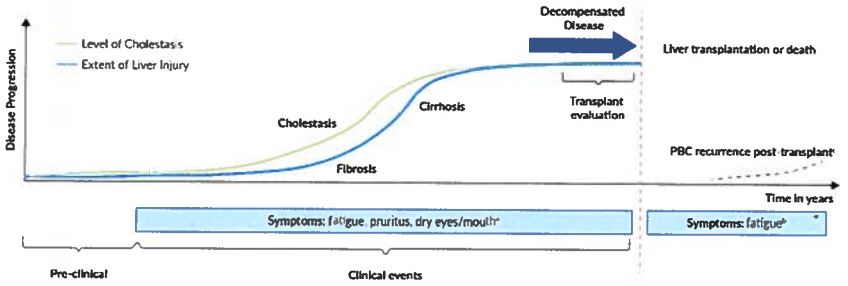
3.1.2 Clinical presentation and prognosis of PBC

More than 50% of patients with PBC are asymptomatic at diagnosis, and the diagnosis of PBC is therefore based primarily on histological or biochemical indicators of disease (25, 26). A diagnosis of PBC can be confirmed when two of the following three criteria are met (13, 25, 38):

- Biochemical evidence of cholestasis based on alkaline phosphatase (ALP) elevation (≥2x upper limit of normal [ULN])
- Presence of AMA at a titre of >1:40. In the absence of AMA, presence of other PBC-specific autoantibodies, such as sp100 or gp210, may also be used to confirm diagnosis
- Histologic evidence of nonsuppurative cholangitis and destruction of interlobular bile ducts

Although often asymptomatic in early stages, patients usually accumulate a range of symptoms and comorbidities as PBC progresses (Figure 1) (13, 39, 40). These include pruritus, fatigue, bone ache, depression and cognitive dysfunction, with pruritus and fatigue being the most common symptoms and affecting up to 70% and 80% of patients, respectively (26, 41-43). End-stage PBC is associated with progressive jaundice, malnutrition, portal hypertension and liver failure, which can lead to premature death in the absence of a liver transplant (37). Patients with PBC experience a significant humanistic burden from diagnosis through to end-stage disease, and the high symptom burden can significantly impact both patients' health-related quality of life (HRQoL) as well as their ability to perform activities of daily living (44, 45).

Figure 1 Natural progression of clinical events in PBC



Footnotes: [a] Symptoms do not correlate with the disease stage and can occur at any point. [b] Fatigue may persist after liver transplant. [c] The frequency of post-transplant PBC is highly variable among studies (9%–61%).
Source: Trivella *et al.* 2023 (46)

The prognosis of PBC is negatively impacted by delayed diagnosis, which occurs in approximately 25% of cases. Patients with a delayed diagnosis are likely to have later-stage PBC than those with an earlier diagnosis, and may therefore be more difficult to treat (47).

An increased risk of disease progression is observed in patients who have an inadequate response to or are intolerant to first-line treatment with ursodeoxycholic acid (UDCA). The impact of current treatments in the prognosis of PBC is further discussed in section 3.3.

3.1.3 Impact of PBC on quality of life

The impact of PBC on HRQoL has been assessed in a cohort of 69 Danish patients (48). Compared to the general population, Danish patients with PBC had significantly lower HRQoL scores in the domains bodily pain, general health, vitality, social functioning, mental health and mental component (48).

Furthermore, as described in section 3.1.2, patients with PBC experience a range of symptoms, which can significantly impact patient HRQoL. Among these symptoms, pruritus has a substantial negative impact on HRQoL of patients with PBC during their disease course. Prior to specific treatment for pruritus, patients with mild or moderate pruritus have reported similar EuroQoL 5-dimension (EQ-5D) scores (0.75 and 0.76 respectively) to the general population (0.80), whereas patients with severe pruritus report notably worse utility scores (0.49), similar to that of Parkinson's Disease, compared to the general population (49). This is because pruritus is detrimental to patients' sleep, social life, housework, and work.

Significantly worse scores has been shown in patients with clinically significant (CS) itch (defined as a PBC-40 Itch domain score ≥ 7 from a maximum of 15) compared to those with no or mild itch (defined as a PBC-40 Itch domain score of 0 or ≥ 1 and < 7 out of 15, respectively) across all patient reported outcomes domains evaluated (50).

3.2 Patient population

Adult PBC patients who have an inadequate response to or do not tolerate UDCA will be eligible for treatment with elafibranor in Denmark. According to a Danish clinical expert, the patient population in the ELATIVE trial (further presented in section 6.1.2.1) is reflective of the Danish setting for patients with PBC eligible for second-line (2L) treatment (7).

[redacted]

Considering a population of approximately 5.985 million people, there are [redacted] patients with PBC in Denmark (52). Out of these prevalent patients, it is estimated that [redacted] have initiated first-line treatment with UDCA, with [redacted] being non-responders at 12 months (53). A similar proportion of non-responders is estimated for the number of incident patients. Therefore, there are approximately [redacted] new patients every year being diagnosed with PBC who do not respond to UDCA.The incidence and prevalence

of patients with PBC who do not respond to UDCA in Denmark for the past 5 years are presented in Table 1.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalence in Denmark[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global prevalence[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] Based on a total population of approx. 5.985 million people in Denmark. [b] [redacted]

Source: Clinical expert (7); Ly *et al.*2021 (51); World Bank Group (54)

The population included in this application consists of adult PBC patients in Denmark who have an inadequate response to or do not tolerate UDCA. The expected number of patients in the coming 5 years are provided in Table 2. Further details on how the number of eligible patients was estimated are presented in section 13.

Table 2 Estimated number of patients eligible for treatment

Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

Currently available therapeutic options, which aim to slow disease progression, are limited (39). As described in the PBC guidelines published by the Danish Society for Gastroenterology and Hepatology (DSGH), UDCA is the only available first-line treatment for PBC, and the backbone of later lines of treatment (4). The DSGH guidelines recommends UDCA 13-15 mg/kg per day as the first choice of treatment for PBC [redacted] Patients who have an inadequate response to or are intolerant to first-line UDCA are at increased risk of disease progression. Studies have shown that UDCA does not improve outcomes such as all-cause mortality, liver transplantation, or serious complications or comorbidities (39, 55, 56). In Denmark, the response to treatment should be assessed after 6 to 12 months (4).

The only second-line treatment option for PBC that has ever been regulatory approved for use in Denmark is obeticholic acid, with the brand name Ocaliva (hereafter referred to as OCA) (57). However, OCA has similar response rates to UDCA (with less than 50% of patients receiving OCA responding to treatment in the POISE Phase III trial) and it is associated with severe side effects, including worsening of pruritus and fatigue, with exacerbated pruritus leading to discontinuation in 10% of OCA-treated patients in the

POISE trial (9, 13, 25). Furthermore, the DSGH guidelines do not recommend use of OCA outside of protocol studies, and it is contraindicated for patients with decompensated cirrhosis [redacted] In June 2024, upon review of new study findings, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended Ocaliva's marketing authorisation to be revoked, as its benefits are no longer considered to outweigh its risks (5). The decision has since been suspended, meaning that OCA currently still holds an active market authorisation in the European Union (EU) (6).

However, according to the DSGH guidelines, off-label combination therapy with UDCA+bezafibrate may instead be offered to patients with an inadequate response to UDCA monotherapy within 6-12 months (4). [redacted] Nevertheless, the DSGH guidelines acknowledge that bezafibrate is not routinely used for PBC in clinical practice in Denmark (4). In addition, there are no products with bezafibrate as the active ingredient with a marketing authorisation for any indication in Denmark, meaning that prescription of a bezafibrate product requires a dispensing permit from the Danish Medicines Agency (8).

For patients who do not adequately respond to currently available treatments and progress to cirrhosis and severe disease, or suffer with severe medically-resistant pruritus, liver transplant is required (13). The outcome of liver transplant is usually favourable, with 5-year patient survival rates of 80–85%. However, symptoms of PBC, including fatigue, often persist after transplant. Recurrence of PBC has also been reported in patients receiving a liver transplant (14). As PBC advances, patients may also develop complications such as hepatocellular carcinoma (HCC), for which there are very limited effective treatments to improve survival [redacted]

In conclusion, healthcare practitioners (HCPs) and PBC patients in Denmark currently do not have access to any marketing authorised second-line treatments in routine clinical practice.

3.4 The intervention

Elafibranor is a novel, first-in-class peroxisome proliferator-activated receptor (PPAR) α/δ co-agonist. Elafibranor targets PBC pathogenesis by combining the effects of PPARα and PPARδ activation on bile acid metabolism, bile production, and inflammation.

While other PPAR agonists are either being used off-label (e.g. bezafibrate) or in development for PBC, elafibranor is the only treatment that selectively targets both PPARα and PPARδ (59). By activating PPAR α and δ selectively, elafibranor is expected to confer

additional therapeutic benefits compared with treatments which agonise only a single PPAR, while avoiding the side effects associated with PPARγ activation (including weight gain, fluid retention, and heart failure) (60, 61). Elafibranor is associated with few use restrictions, contraindications and drug-drug interactions, particularly compared to OCA and off-label bezafibrate (62).

Elafibranor was granted a marketing authorisation by the EMA based on a conditional approval (1). In order to confirm the efficacy and safety of elafibranor in the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA, the marketing authorisation holder (MAH) shall conduct and submit the final results of the phase III randomised, parallel-group, double-blind, placebo-controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with PBC. The due date for submitting the results is May 2030 (2).

Table 3 Overview of intervention

Overview of intervention	
Indication relevant for the assessment	Treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA
ATMP	Not applicable
Method of administration	Oral
Dosing	80 mg once daily
Dosing in the health economic model (including relative dose intensity)	80 mg once daily [redacted]
Should the medicine be administered with other medicines?	In combination with UDCA in adults with an inadequate response to UDCA
Treatment duration / criteria for end of treatment	Lifelong
Necessary monitoring, both during administration and during the treatment period	No additional monitoring is needed for treatment with elafibranor
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No additional tests are needed for treatment with elafibranor
Package size(s)	30 units of 80 mg film-coated tablets

Abbreviations: ATMP: Advanced therapy medicinal product; mg: Milligram; PBC: Primary biliary cholangitis; SmPC: Summary of product characteristics; UDCA: Ursodeoxycholic acid.
Source: Iqirvo SmPC (62); Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18)

3.4.1 The intervention in relation to Danish clinical practice

Iqirvo® (elafibranor) is indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA (1). Thus, elafibranor is positioned as a second-line treatment for PBC. Given that OCA is approved for the same indication [redacted] elafibranor will be the only second-line treatment with a valid marketing authorisation to be used in clinical practice (7). The approved indication for elafibranor is in line with the patient eligibility criteria for the ELATIVE trial (further details presented in section 6.1.2) (10).

3.5 Choice of comparator(s)

As presented in section 3.3, OCA is the only second-line treatment with a currently valid marketing authorisation in Denmark apart from elafibranor, [redacted] Therefore, HCPs and PBC patients in Denmark currently do not have access to any marketing authorised second-line treatments in routine clinical practice.

As there are no other approved treatments as an alternative for adult patients with PBC with an inadequate response or intolerance to UDCA, and given that only approximately 5% of patients are unable to tolerate UDCA (9, 10), a comparison between elafibranor and standard of care UDCA monotherapy (Table 4) is deemed appropriate.

Table 4 Overview of comparator

[redacted]	
Generic name	Ursodeoxycholic acid
ATC code	A05AA02
Mechanism of action	UDCA acts on the liver through various complex and complementary mechanisms, including alterations in the bile acid pool, serving as a cytoprotectant, immunomodulating substance, and choleretic. Furthermore, UDCA markedly decreases biliary cholesterol saturation by inhibiting the absorption of cholesterol in the intestine and its secretion into bile, demonstrated by reduced cholesterol fraction of biliary lipids
Method of administration	Oral
Dosing	Recommended dose in SmPC: 12-16 mg/kg/day
Dosing in the health economic model (including relative dose intensity)	[redacted]

Overview of comparator	
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Lifelong
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	100 hard capsules of 250 mg; or 100 hard capsules of 500 mg

Abbreviations: SmPC: Summary of product characteristics; UDCA: Ursodeoxycholic acid.
Sources: Ursochol SmPC (63); StatPearls 2024 (64); Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18)

3.6 Cost-effectiveness of the comparator(s)

Based on a decision made by the Danish Health and Medicines Authority in 2014, UDCA (Ursochol) has general reimbursement for the treatment of PBC stages I-III (65).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In the ELATIVE trial, the primary outcome of biochemical cholestasis response is a composite of ALP <1.67x ULN, decrease of ALP >15% and total bilirubin (TB) <ULN. ALP is the only disease marker used throughout the disease course from suspicion of PBC through to assessing a patient's treatment response and risk of disease progression (13). ALP is an enzyme mostly found in the liver and bones. High levels of ALP in the blood may indicate a liver damage, with concentration of ALP correlating with the extent of damage (39, 66). Bilirubin is a yellow pigment produced during the breakdown of red blood cells. Bilirubin levels increase as PBC progresses, with high levels of bilirubin indicating cholestatic liver damage, cirrhosis, jaundice and decreased survival in PBC patients, making bilirubin a key marker of disease severity (25, 42). Other secondary endpoints measuring ALP and bilirubin levels were included to provide additional supportive evidence of the treatment effect, including the assessment of treatment response according to the Paris II criteria, which is used in clinical practice in Denmark (4, 7). The Paris II criteria is defined by ALP ≤1.5 x ULN, aspartate aminotransferase (AST) ≤1.5 x ULN and TB ≤ULN.

Additional secondary outcomes assessed the level and impact of pruritus. Pruritus affects up to 70% of patients with PBC and negatively impacts quality of life. Given its high prevalence and significant burden, change from baseline in pruritus utilising the PBC WI-NRS through Week 52 and Week 24 was evaluated in participants with clinically relevant, i.e. moderate-to-severe, pruritus at baseline (PBC WI-NRS score ≥4). Two other patient reported outcome measures assessed pruritus: first, change from baseline in the itch

domain of the PBC-40, an instrument specifically designed and validated for the PBC patient population; and second, change from baseline in the 5-D Itch total score.

Because pruritus fluctuates with the circadian rhythm and is often worse at night, patients with PBC may also suffer from diminished sleep quality, leading to increased fatigue and a further impacted quality of life (67). Two patient reported outcome measures were used to assess fatigue: change from baseline in the fatigue domain of the PBC-40 and change from baseline in Patient Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a score.

The relevant efficacy outcomes from the ELATIVE trial relevant from this application are presented in Table 5. The outcomes are based on two different data cuts: 01 June 2023 (for the variable double-blind [DB] period) and [redacted]

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
Biochemical cholestasis response ELATIVE	Variable DB period: Weeks 52 and 78 [redacted]	ALP <1.67x ULN and TB ≤ULN and ALP decrease ≥15%	[redacted]
ALP normalisation ELATIVE	Variable DB period: Weeks 52 and 78 [redacted]	ALP ≤1.0x ULN (for males ULN was 129 U/L, for females ULN was 104 U/L).	[redacted]
Change in pruritus: PBC WI-NRS score ELATIVE	Variable DB period: Weeks 52 and 24 [redacted]	Change from baseline in PBC WI-NRS score; primary analyses based on Pruritus ITT analysis set (including participants with baseline PBC WI-NRS score ≥4); supplemental analyses based on ITT analysis set	[redacted]

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
			[redacted]
Change in ALP level ELATIVE	Variable DB period: Weeks 52 and 78	Change from baseline in the ALP level	[redacted]
Change in TB level ELATIVE	Variable DB period: Weeks 52 and 78	Change from baseline in the TB level	[redacted]
Treatment response based on Paris II criteria ELATIVE	Variable DB period: Weeks 52 and 78	Response to treatment based on the Paris II criteria, defined as ALP <1.5 x ULN, AST ≤1.5 x ULN, and TB ≤1 mg/dL	[redacted]
Change in pruritus: PBC–40 Itch domain score ELATIVE	Variable DB period: Week 52 [redacted]	Change from baseline in PBC–40 Itch domain score; primary analysis based on Pruritus ITT analysis set (including participants with baseline PBC WI-NRS score ≥4); supplemental analysis based on ITT analysis set	[redacted]
Change in pruritus: 5D-Itch total score ELATIVE	Variable DB period: Week 52 [redacted]	Change from baseline in 5D-Itch total score; primary analysis based on Pruritus ITT analysis set (including participants with baseline PBC WI-NRS score ≥4); supplemental analysis based on ITT analysis set	[redacted]
Change in fatigue: PROMIS Fatigue Short Form 7a score ELATIVE	Variable DB period Week 52 [redacted]	Change from baseline in the PROMIS fatigue Short Form 7a score.	[redacted]
Change in fatigue: PBC-	Variable DB period Week 52	Change from baseline in the PBC-40 Fatigue domain score.	[redacted]

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
40 Fatigue domain score	[redacted]		
ELATIVE			

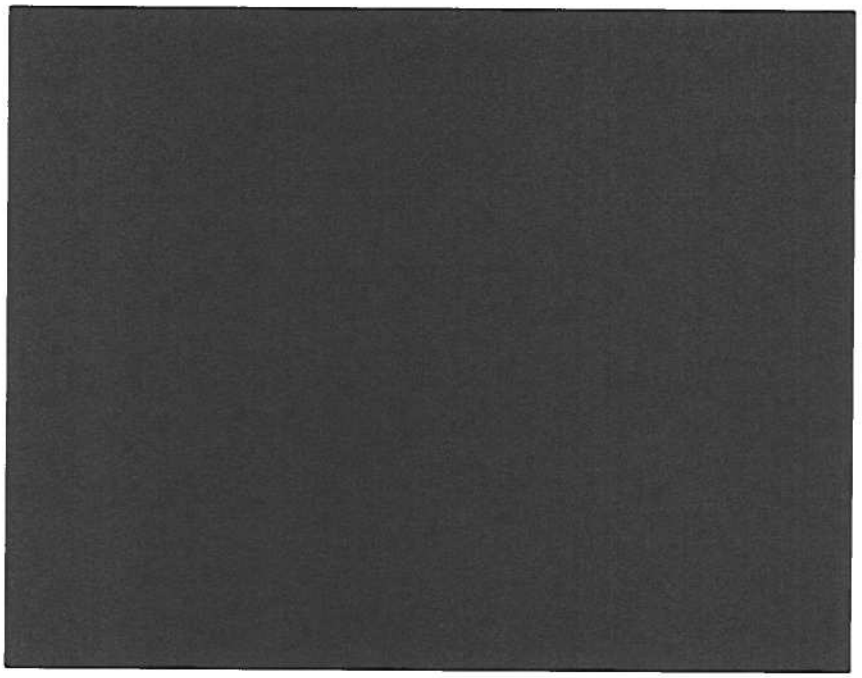
Abbreviations: ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; DB: Double blind; ICE: Intercurrent event; OLE: Open-label extension; PROMIS: Patient Reported Outcome Measurement Information System; WI-NRS: Worst Itch Numeric rating scale; PBC: Primary biliary cholangitis; TB: Total bilirubin; ULN: Upper limit of normal
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18)

Validity of outcomes

Surrogate endpoints as biomarkers of disease progression
Serum levels of ALP and bilirubin are reliable surrogate markers of disease progression in PBC and are powerful predictors of cholestatic injury and liver function, transplant-free survival and the speed of PBC progression when used in combination (66). As a result, these markers can be used to indicate whether a therapy will be efficacious in preventing long-term disease complications such as cirrhosis and liver failure without requiring long-term follow-up to assess endpoints such as transplant-free survival.

The Food and Drug Administration (FDA) has confirmed serum ALP and bilirubin levels as possible surrogate measures of therapeutic efficacy in PBC for use in approvals for novel therapies (68). In 2016, OCA was granted accelerated approval based on a significant reduction in ALP and bilirubin levels demonstrated in the POISE trial (68, 69). Furthermore, in 2019, the FDA granted elafibranor a Breakthrough Therapy Designation based on surrogate endpoint data from the Phase II Elafibranor Trial in PBC, with Orphan Drug Designation granted by the FDA and EMA soon after (3, 70, 71). The EMA conditional approval of elafibranor states that the reductions in ALP and bilirubin observed with elafibranor is considered indicative of an improvement in the condition of the liver.

A 2014 meta-analysis investigated ALP and bilirubin as surrogate endpoints in PBC, using data from 4,845 patients primarily treated with UDCA across North America and Europe, with a median follow-up of 7.3 years (15% were not treated with UDCA or did not have treatment information available) (66). Levels of both ALP and bilirubin, measured at study enrolment and each year for five years, were strongly associated with risk of death or liver transplantation, with combined assessment of both ALP and bilirubin levels being the strongest predictor of transplant-free survival duration (Figure 2) (66).



ALP and bilirubin were also individually predictive of transplant-free survival: [redacted]

Due to their value as prognostic biomarkers, ALP and bilirubin have been routinely used in composite endpoints to assess patients' biochemical response to treatment for PBC (66). Slow progression of PBC has been observed in patients with normal bilirubin and ALP <1.67 x ULN, whereas fast progression of PBC has been observed in patients with abnormal bilirubin and ALP ≥1.67 x ULN (72). Studies have also shown ALP ≥1.67 x ULN and an ALP threshold of <1.67 x ULN combined with TB ≤1 ULN predict lower likelihood of adverse outcomes (66, 73, 74). In alignment with these findings, biochemical cholestasis response, defined as ALP <1.67 x ULN, TB ≤ULN and ALP decrease from baseline of ≥15%, has been recognised as a relevant surrogate marker in PBC clinical trials. The addition of a minimum ALP reduction of ≥15% from baseline was included as part of the composite endpoint in both the POISE and ELATIVE trials as a conservative threshold so that patients who only had a small change in ALP from 1.67 x ULN were excluded. This ensured that only subjects with a relevant clinical effect were judged to have a successful response.

Patient reported outcome measures used in assessment of pruritus and fatigue

- **PBC Worst Itch NRS (WI-NRS)**: A psychometric evaluation of the instrument 'PBC Worst Itch NRS' was undertaken to provide quantitative evidence supporting its use as a longitudinal assessment tool capturing pruritus intensity as reported by the participant (18). Patients were asked to rate their worst itch over the past 24 hours on a scale ranging from zero (no itch) to 10 (worst itch imaginable) (75).

- **5-dimensions pruritus scale (5-D) Itch questionnaire**. The 5-D Itch questionnaire comprises five domains, each accounting for five points, which measure the impact of pruritus from different angles: duration, degree, direction (improvement or worsening), disability (effect on daily activities) and distribution (76). Patients are asked to rate their symptoms in terms of the five domains over the preceding 2-week period on a 1 to 5 scale. Total scores range from 5 (no pruritus) to 25 (most severe pruritus), with higher scores indicating worse itch-related quality of life) (76).

- **PBC-40**: The PBC-40 questionnaire includes 40 questions that evaluate patients' experience across six domains: fatigue, emotional impact, social impact, cognitive function, general symptoms and itch (77). Each question is scored from 1 to 5, then summed to give a total domain score. High scores represent high impact, and low scores low impact of PBC on quality of life (77). PBC-40 is the only questionnaire validated for PBC. It was developed using patient interviews and has undergone extensive validation and psychometric testing in a large PBC population, offering real value in measuring QoL in patient-relevant terms (77).

- **Patient Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form (SF)-7a score**. The PROMIS Fatigue SF consists of seven items measuring the experience of fatigue and its interference with daily activities over the past week (78). A 5-point Likert scale is used for individual items; scores can range from 7 to 35, with higher scores indicating greater fatigue (78).

4. Health economic analysis

4.1 Model structure

A Markov cohort structure was developed to describe the progression of PBC over the lifetime time horizon of the cost-effectiveness model (CEM). This model structure is consistent with other approaches for liver disease-related modelling, for example, for hepatitis C (TA330), and was previously used for OCA submission to National Institute of Health and Care Excellence (NICE) (TA443). (21, 79) The main events and changes in the health of a PBC patient and costs are captured by the health states. The model structure consists of 10 health states divided into two components: the PBC biomarker component and the liver disease component. The PBC biomarker component stratifies patients according to their risk of progression to liver disease. The liver disease component contains patients who have progressed to liver disease. The death health state is absorbing.

The PBC biomarker component uses the following definitions of mild, moderate, and high risk of disease progression, respectively:

- Mild risk: ALP <1.5 x ULN, AST <1.5 x ULN and TB ≤1 mg/dl;
- Moderate risk: ALP >1.5 x ULN or AST >1.5 x ULN and TB ≤1 mg/dl;
- High risk: TB >1mg/dl or liver stiffness score >15 kPa.

As suggested in the Danish PBC guidelines, the Paris II scoring system was used to assess treatment response and estimate patients' distribution between health states at the beginning of the analysis (4). The liver disease component of the model includes the following health states: decompensated cirrhosis (DCC), HCC, pre-liver transplant (LT), LT, post-LT and PBC re-emergence.

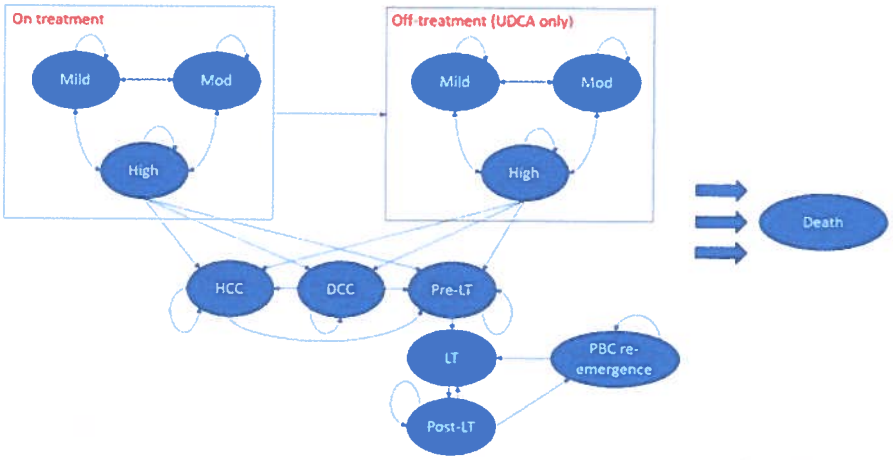
A visual representation of the model structure is presented in Figure 3. Patients enter the CEM on treatment in the PBC biomarker component. Within the PBC biomarker component, patients are categorized into mild, moderate, or high risk of disease progression and they can transition between these three health states. From the PBC biomarker component of the model, patients can transition from the moderate or high risk of disease progression health states to the liver disease component into either the DCC, HCC, or pre-LT health states or discontinuing treatment.

Patients in the DCC health state can remain in the DCC health state or transition to the HCC or pre-LT health states. Patients in the HCC health state can remain in the HCC state or transition into the pre-LT health state. Once in the pre-LT health state, patients can either remain in the pre-LT health state, where they await LT, or they transition to the LT health state. In the LT health state, patients undergo a LT and transition to the post-LT health state in the next cycle. Patients in the post-LT health state may remain in that state, transition back to LT health state for another LT or transition to PBC re-emergence. In the PBC re-emergence health state, patients can either remain or return to the LT health state for another LT.

Patients can transition into the death health state from any other health state, where they remain for the rest of the model time horizon.

If a patient discontinues second-line therapy whilst in one of the PBC biomarker health states, it is assumed that patients remain in the PBC biomarker component of the model 'off-treatment' and follow the UDCA arm transition probabilities from the cycle of discontinuation. Whilst off-treatment, the patients continue to receive treatment with UDCA and accumulate the costs and outcomes associated with UDCA treatment. As for patients on treatment, patients off-treatment can progress to the liver disease health states if they are at moderate or high risk of disease progression.

Figure 3 Model structure schematic



Abbreviations: DCC: Decompensated cirrhosis; HCC: Hepatocellular carcinoma; LT: Liver transplant, PBC: Primary biliary cholangitis; UDCA: Ursodeoxycholic acid

A lifetime time horizon was adopted to estimate the life-long impacts on costs and outcomes of PBC. This was reflected in a 43-year time horizon, based on the mean age of the ELATIVE trial randomised patients' ITT population (57.1 years), with the assumption that no patient can live beyond 100 years.(10)

Over the time horizon, the cohort accrues the costs and outcomes faced when patients transition between the health states. A cycle length of three months is applied with a half-cycle correction applied, assuming patients enter/exit health states mid-way through a cycle.

For each cycle, total costs and quality-adjusted life-years (QALYs) are calculated based on the distribution of patients across all health states. These are accumulated over the model time horizon to calculate total costs and QALYs for the cohorts from which incremental results and the incremental cost-effectiveness ratio (ICER) per QALY are determined. Discount rates for costs and outcomes are in line with Danish guidelines: 3.5% discount rate for the entire time horizon.

The model adopts a limited societal perspective of Denmark. The perspective on outcomes considers all direct health effects for patients.

4.2 Model features

Table 6 Features of the economic model

Patient population	Adult patients with PBC whose disease has an inadequate response to, or who are unable to tolerate, UDCA	-
Perspective	Limited societal perspective	According to DMC guidelines

Model features	Description	Justification
Time horizon	Lifetime (43 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the ELATIVE trial population (57.1 years). Validated by Danish clinical expert.
Cycle length	3 months	The cycle length aligns with the time interval between visits in the ELATIVE trial and sufficiently captures meaningful differences in disease progression over time.
Half-cycle correction	Yes	-
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Elafibranor	-
Comparator(s)	Ursodeoxycholic acid (UDCA)	According to national treatment guideline. Validated by Danish clinical expert that UDCA is standard of care for PBC patients and is the only licensed option used in clinical practice.
Outcomes	Response to treatment at Week 52 according to ALP ≤1.5 x ULN, AST ≤1.5 x ULN and TB ≤ULN, change from baseline in ALP, change from baseline in TB, change from baseline in PBC-40 Itch domain, all-cause discontinuation	-

5. Overview of literature

5.1 Literature used for the clinical assessment

The present application is based on the ELATIVE trial, a head-to-head study comparing elafibranor to placebo in patients with PBC and inadequate response or intolerance to UDCA. Therefore, a literature search for the assessment of efficacy and safety was not conducted. The literature used in the clinical assessment is listed in Table 7.

Table 7 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
Kowdley, KV; Bowlus, CL; Levy, C; et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med. 2024;390(9): p. 795-805 (10)	ELATIVE	NCT04526665	Start: 24/09/20 Completion: 01/12/28 [redacted]	Elafibranor vs. placebo for patients with PBC and inadequate response or intolerance to UDCA
Data on file Unpublished data 2023: ELATIVE Clinical Study Report (18)	ELATIVE	NCT04526665	Start: 24/09/20 Completion: 01/12/28 [redacted]	Elafibranor vs. placebo for patients with PBC and inadequate response or intolerance to UDCA
Bowlus, CL; Kowdley, KV; Levy, C; et al. Efficacy of elafibranor in primary biliary cholangitis: Results from the variable double-blind period of ELATIVE®, a randomised, placebo-controlled phase III trial. Presented at EASL Congress 2024 (80)	ELATIVE	NCT04526665	Start: 24/09/20 Completion: 01/12/28 [redacted]	Elafibranor vs. placebo for patients with PBC and inadequate response or intolerance to UDCA
Kremer, AE; Kowdley, KV;Levy, C; et al. Effect of elafibranor on pruritus in primary biliary cholangitis: Symptom severity and quality of life measurements from the phase III ELATIVE® trial. Presented at EASL Congress 2024 (81)	ELATIVE	NCT04526665	Start: 24/09/20 Completion: 01/12/28 [redacted]	Elafibranor vs. placebo for patients with PBC and inadequate response or intolerance to UDCA
Sonderup, M, Spearman, CW; Calvaruso, V.; et al. Elafibranor efficacy in primary biliary cholangitis according to biochemical response criteria in the phase III ELATIVE®trial. Presented at EASL Congress 2024 (82)	ELATIVE	NCT04526665	Start: 24/09/20 Completion: 01/12/28 [redacted]	Elafibranor vs. placebo for patients with PBC and inadequate response or intolerance to UDCA

Abbreviations: EASL: European Association for the Study of the Liver; PBC: Primary biliary cholangitis; UDCA: ursodeoxycholic acid.

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

A systematic literature review (SLR) was conducted to identify studies reporting on HRQoL associated with PBC. The SLR is described in Appendix I. In total, 12 articles reporting utility data on six unique studies were identified. One of the studies derived EuroQoL 5-dimension 5-level Questionnaire (EQ-5D-5L) utility values for patients with PBC in Denmark (48). However, the data was insufficient to parametrise health-state utility values (HSUVs) in the CEM and therefore alternative data sources were sought. The best identified source for HSUVs in PBC was the NICE submission of OCA (TA443), which were originally sourced from Wright et al. (2006) (23) and published values in the NICE submission for sofosbuvir in chronic hepatitis C (TA330) (21, 23). The literature used for health-related quality of life is listed in Table 8.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
NICE. Obetiholic acid for treating primary biliary cholangitis [TA443]. 2017. (19)	All health states utilities	Section 10.2.3
Younossi Z. M., Michelle M.P.H., et al. Cholestatic Liver Diseases and Health-Related Quality of Life. Am. Coll. Of Gastroenterology. 2000; 95: pp. 497-502. (24)	Mild and moderate risk PBC health states utilities	Section 10.2.3
NICE. Sofosbuvir – Chronic hepatitis C [TA330]. 2014. (21)	High risk PBC, DCC, HCC, pre-LT, LT, post-LT and re-emergence of PBC health states utilities	Section 10.2.3
Abrahamian F. M., Krishnadasan A., et al. The association of antimicrobial resistance with cure and quality of life among women with acute uncomplicated cystitis. Infection. 2011; 39: pp. 507-514. (20)	Urinary tract infection disutility	Section 10.2.3
Wright M., Grieve G., et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomized controlled trial and economic evaluation. Health Technology assessment. 2006; 10 (21). (23)	High risk PBC, HCC and re-emergence of PBC health state utilities	Section 10.2.3
NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA779]. 2021. (22)	Fatigue disutility	Section 10.2.3

5.3 Literature used for inputs for the health economic model

A SLR was conducted to identify studies reporting economic evaluations associated with PBC. As the searches were conducted simultaneously for the SLR of economic evaluations, HRQoL studies and cost and healthcare resource use (CRU) studies, the SLR methodology is described in Appendix I whilst the SLR results related to CRU are presented in Appendix J. In total, 13 articles reporting on 11 unique studies were identified. Supplementary searches were conducted to identify inputs reflecting the Danish context. The literature used for input to the health economic model are presented in Table 9.

Table 9 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
Kowdley K. V., et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med. 2024; 390 (9): pp. 795-805. (10)	Patients baseline characteristics (age, percentage of male)	ELATIVE trial results publication	
NICE. Obetiholic acid for treating primary biliary cholangitis [TA443]. 2017. (19)	Transition probabilities for liver disease component, excess in mortality	SLR	Section 8.1.2, Table 17 Section 8.4.1, Table 19
Wright M., Grieve G., et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomized controlled trial and economic evaluation. Health Technology assessment. 2006; 10 (21). (23)	Health states resource use	SLR	Section 11.4.1
Folkhalsomyndigheten (Swedish) report: Hepatit B-vaccination som ett särskilt vaccinationsprogram. 2016. (83)	Post-LT costs	Desk search	Section 11.4.1, Table 31
Medicinraadet Unit costs catalogue. 2024 (84)	Unit costs	Desk search	Section 11, Table 33, Table 35, Table 37
Rigshospitalets Labportal (2024) (85)	Blood tests	Desk search	Section 11.4.1, Table 33, Table 35, Table 37

Reference (full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Vestergaard A. H. S., et al. Healthcare Costs at the End of Life for Patients with Non-cancer Diseases and Cancer in Denmark. Pharmacoecon Open. 2023; 7 (5): pp. 751-764. (86)	End-of-life costs	Desk search	Section 11.8, Table 40

6. Efficacy

6.1 Efficacy of elafibranor compared to placebo for adults with PBC and an inadequate response or intolerance to UDCA

6.1.1 Relevant studies

An overview of the study design for the ELATIVE trial is presented in Table 10, with the main study characteristics presented in Appendix A.

Table 10 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
ELATIVE, NCT04526665 (10)	Randomised, double-blinded, placebo-controlled, phase III study of	DB period: 52 weeks, followed by a continuation period until all patients had completed their week 52 assessment or for a	Adult patients with PBC and inadequate response or intolerance to UDCA	Elafibranor (oral administration), 80 mg once daily in addition to UDCA	Placebo (oral administration) once daily in addition to UDCA	Data cut-offs: 01 June 2023, [redacted] Pre-defined data cut. For the first data cut, database lock occurred after the last patient completed the week 52 visit. Primary outcome: Biochemical cholestasis response, defined as ALP <1.67 x ULN and TB ≤ULN and ALP decrease of ≥15% from baseline (week 52).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
	elafibranor versus placebo	maximum of 104 weeks, whichever came first. OLE: patients could receive elafibranor for up to 5 additional years.				Key secondary outcomes: ALP normalisation (week 52); change in PBC WI-NRS score among patients with moderate-to-severe pruritus, i.e. baseline PBC WI-NRS score ≥4 (weeks 52 and 24). Other secondary outcomes: ALP change (weeks 4, 13, 26, 39 and 52); ALP response[a] (week 52); response to treatment[b] (week 52); PBC risk scores: UK PBC score and GLOBE score (week 52); bilirubin normalisation (week 52); albumin normalisation (week 52); change in hepatobiliary injury and liver function (week 52); change in biomarkers of inflammation (week 52); change in immune response (week 52); change in biomarkers, and non-invasive measures of hepatic fibrosis and liver stiffness (week 52); change in lipid parameters (week 52); change from baseline in FPG (week 52); change in bile acids and biomarkers of bile acid synthesis (week 52); proportion of responders in PBC WI-NRS according to clinically meaningful change among patients with moderate-to-severe pruritus (weeks 52 and 24); proportion of patients with no worsening of pruritus from baseline as measured by PBC WI-NRS (weeks 52 and 24); change in 5D-Itch (week 52); change in PROMIS Fatigue Short Form 7a (week 52); change in ESS (week 52); change in PBC-40 (week 52); change in EQ-5D-5L (week 52); change in serum markers of bone turnover and in bone mineral density (week 52); onset of clinical outcomes described as a composite endpoint composed of: MELD-Na >14 for patients with baseline MELD-Na <12, liver transplant, uncontrolled ascites requiring treatment, hospitalisation for new onset or recurrence of variceal bleed, hepatic encephalopathy defined as West-Haven/Conn score of 2 or more , spontaneous bacterial peritonitis, or death; safety and tolerability as assessed by SAE, AE, AESI, physical examination, vital signs, medical history, ECG, chemistry and haematology, liver markers, renal biomarkers (including urinalysis), other biochemical safety markers; PK assessments by GFT505 and

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						GFT1007 concentrations measurement in plasma at steady state following daily oral administration at 80 mg.

Note: [a] ALP response defined as 10%, 20% and 40% ALP reduction from baseline at Week 52; [b] Response to treatment according to: ALP <1.5 x ULN, ALP decrease ≥40% and TB ≤ULN; ALP <3 x ULN, AST <1 mg/dL (Paris I); ALP ≤1.5 x ULN, AST ≤1.5 x ULN and TB ≤ULN (Paris II); TB response rate of 15% change; normalisation of abnormal TB and/or albumin (Rotterdam); TB ≤0.6 x ULN; ALP ≤1.67 x ULN and TB ≤1 mg/dL; No worsening of TB defined as level of TB <ULN or no increase from baseline of more than 0.1 x ULN; complete biochemical response defined as normal ALP, TB, AST, ALT, albumin and INR.

Abbreviations: AE: Adverse event; AESI: Adverse event of special interest; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DB: Double-blind; ECG: Electrocardiogram; EQ-5D-5L: EuroQoL 5-dimension 5-level Questionnaire; ESS: Epworth Sleepiness Scale; FPG: fasting plasma glucose; INR: international normalised ratio; MELD-Na: model for end-stage liver disease-sodium; OLE_ Open-label extension; PBC: Primary Biliary Cholangitis; PK: pharmacokinetics; PROMIS: Patient Reported Outcome Measurement Information System; SAE: serious adverse event; TB: total bilirubin; ULN: upper limit of normal; WI-NRS: Worst Itch Numeric Rating Scale.

6.1.2 Comparability of studies

Not applicable, as the comparison is based on the head-to-head study ELATIVE.

6.1.2.1 Comparability of patients across studies

Baseline patient and disease-specific characteristics for the ITT analysis set in the ELATIVE trial are presented in Table 11. Demographics and baseline characteristics were well-balanced across treatment groups, except that the proportion of White patients was numerically higher in the elafibranor group than in the placebo group. The majority of patients were female (95.7%, n=154) with a mean age of 57 years, which is consistent with the characteristics of the PBC population (10, 26).

Generally, disease-specific characteristics were also well-balanced across treatment arms. Mean ALP values at baseline were well-balanced, with both arms reporting values of approximately 320 U/L (10). Additionally, across both treatment arms, 37.7% to 39.8% of patients were reported to have >3 x ULN for baseline ALP and TB of 9.41-9.71 µmol/L, indicating similar disease severity in both the elafibranor and placebo groups (10, 18).

Concomitant use of UDCA at baseline was similar between treatment groups; in total, 102 (94%) patients in the elafibranor group and 51 (96%) patients in the placebo group continued their concurrent UDCA treatment during the study (10). Six (5.6%) patients in the elafibranor group and two (3.8%) patients in the placebo group were not on concurrent UDCA therapy at baseline, consistent with literature describing a small proportion (up to 5%) of the population with PBC being unable to tolerate UDCA (10).

Similar characteristics were observed for the other analysis sets (18).

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ELATIVE		
	Elafibranor (N=108)	Placebo (N=53)	Total (N=161)
Age at randomisation, years, mean (SD)	57.5 (8.4)	56.4 (9.3)	57.1 (8.7)
Female sex, n (%)	102 (94)	52 (98)	154 (96)
White race, n (%)	101 (93.5)	46 (86.8)	147 (91.3)
Time since diagnosis, years, mean (SD)	7.9 (5.9)	8.3 (6.8)	8.0 (6.2)
ALP, U/L, mean (SD)	321.3 (121.9)	323.1 (198.6)	321.9 (150.9)
ALP >3 x ULN[a], n (%)	43 (40)	20 (38)	63 (39)
Total bilirubin[b], µmol/L, mean (SD)	9.7 (5.1)	9.4 (5.0)	9.6 (5.1)

	ELATIVE		
	Elafibranor (N=108)	Placebo (N=53)	Total (N=161)
Mean AST, U/L (SD)	45.0 (24.2)	47.2 (32.8)	45.7 (27.2)
Mean ALT, U/L (SD)	49.3 (29.4)	50.3 (38.7)	49.6 (32.6)
Mean GGT, U/L (SD)	213.3 (186.1)	220.0 (220.3)	215.5 (197.4)
Concurrent UDCA treatment, n (%)	102 (94)	51 (96)	153 (95)
PBC WI-NRS Score, mean (SD)[c]	3.3 (2.8)	3.2 (2.9)	3.3 (2.8)
PBC WI-NRS Score, moderate-to-severe pruritus (≥4), n (%)	44 (41)	22 (42)	66 (41)
Liver stiffness[d], kPa, mean (SD)	9.9 (7.8)	10.7 (8.9)	10.1 (8.2)
Liver stiffness[d] >10.0 kPa, n/total n (%)	31/104 (30)	17/50 (34)	48/154 (31)
Bridging fibrosis or cirrhosis[e], n/total n (%)	12/31 (39)	8/16 (50)	20/47 (43)
Liver stiffness >10.0 kPa and/or bridging fibrosis or cirrhosis on histology[d,e], n/total n (%)	35/104 (34)	19/50 (38)	54/154 (35)

Footnotes: [a] Alkaline phosphatase ULN values were 104 U/L in females and 129 U/L in males; [b] Total bilirubin ULN value was 20.5 µmol/L in females and males; [c] Mean baseline PBC Worst Itch NRS score over the 14 days preceding randomisation; [d] Liver stiffness was assessed by means of vibration-controlled transient elastography; scores range from 2 to 75 kPa, with higher values indicating greater liver stiffness; [e] The presence or absence of bridging fibrosis or cirrhosis was determined by histologic findings in the patients who underwent a liver biopsy.
Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; SD: Standard deviation; PBC: Primary biliary cholangitis; UDCA: Ursodeoxycholic acid; WI-NRS: Worst Itch Numeric Rating Scale.
Source: Kowdley *et al.* 2024 (10)

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

The characteristics of patients used in the health economic model (Table 12) were based on the patient population of the ELATIVE trial (10, 87). [redacted]

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age (years), mean (SD)	57.1 (8.7) (10)	57.1 (8.7) (10)
Male, n (%)	7 (4.3) (10)	7 (4.3) (10)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CS: Clinically significant; SD: Standard deviation.
Source: As presented in the table.

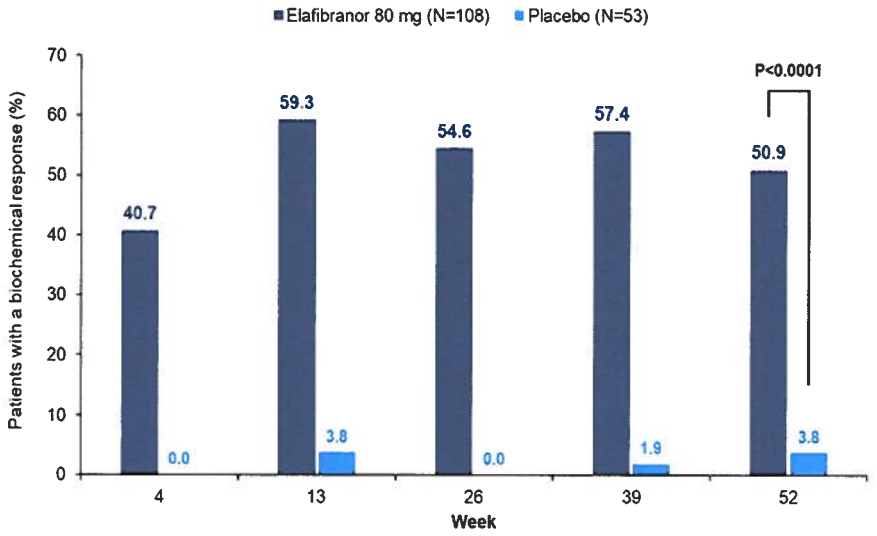
6.1.4 Efficacy – results per the ELATIVE trial

This section describes 52-week results from the ELATIVE trial (Table 5). Long-term follow results from 78 weeks and from the OLE phase are presented in Appendix K.

6.1.4.1 Biochemical response at Week 52

At Week 52, the primary endpoint of biochemical response was met; 50.9% of patients in the elafibranor group had a biochemical cholestasis response (55/108), compared with 3.8% (2/53) in the placebo group, resulting in a difference of 47.2% (95% CI: 32.0; 56.9; p<0.0001) favouring the elafibranor group. The odds ratio (OR) for a cholestasis response with elafibranor versus placebo was statistically significant in favour of elafibranor (OR: 37.6; 95% CI: 7.6; 302.2; p<0.0001). Patients responded to elafibranor treatment as early as Week 4, and this was maintained through to Week 52 (Figure 4). [redacted]

Figure 4 Percentage of patients with biochemical (cholestasis) response[a] to Week 52 (ITT analysis set)

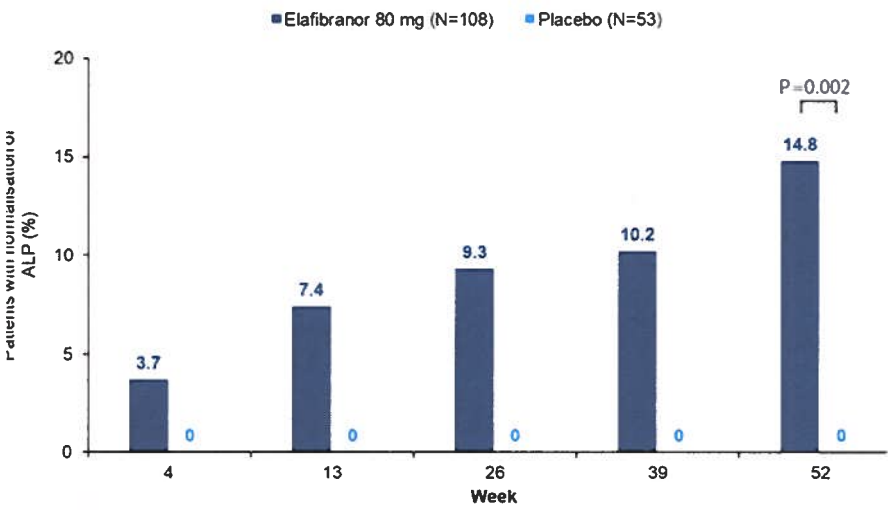


Footnotes: [a] Cholestasis response was defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%.
Abbreviations: ALP: Alkaline phosphatase; ITT: intent-to-treat; mg: Milligram; TB: total bilirubin.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18), Kowdley *et al.* 2024 (10).

6.1.4.2 ALP normalisation at Week 52

The first key secondary efficacy endpoint was the response to treatment based on ALP normalisation at Week 52, defined as ALP ≤1.0x ULN. ULN was 129 U/L and 104 U/L for males and females, respectively. Participants who prematurely discontinued the study treatment or used rescue therapy for PBC prior to the Week 52 assessment were considered as non-responders. The proportion of responders was greater in the elafibranor group (16/108 [14.8%] patients) than in the placebo group (0/53 [0.0%] patients), with a difference of 14.8% (95% CI: 6.1; 22.7; <0.002) favouring the elafibranor group. The OR was statistically significant in favour of elafibranor (OR: infinity; 95% CI: 2.8; infinity; p=0.0019). Some patients receiving elafibranor treatment achieved ALP normalisation as early as Week 4, and the number of patients with normalised ALP increased through to Week 52 (Figure 5) (10, 18). ALP normalisation in patients treated with elafibranor was sustained with a longer follow-up, as presented in Appendix K.

Figure 5 Percentage of patients achieving ALP normalisation to Week 52 (ITT analysis set)



Abbreviations: ALP: Alkaline phosphatase; ITT: Intent-to-treat; mg: Milligram.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18), Kowdley *et al.* 2024 (10)

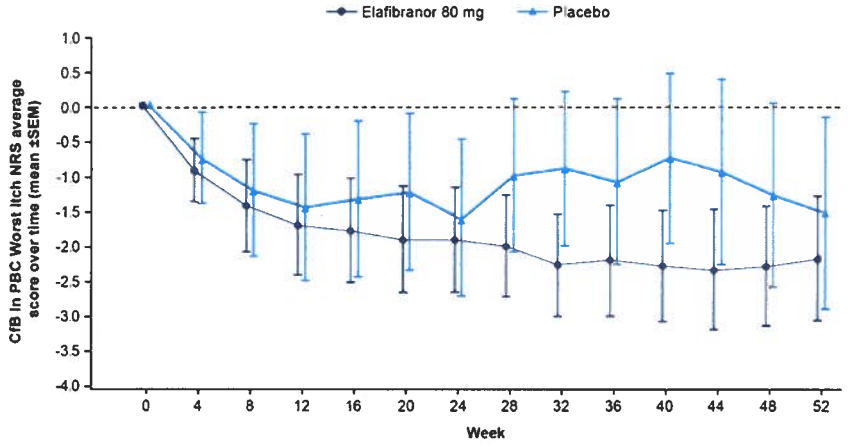
6.1.4.3Change in pruritus from baseline through Weeks 52 and 24 (PBC WI-NRS)

Patients with baseline PBC WI-NRS score ≥4 (Pruritus ITT analysis set, as described in Table 48) were asked to rate their worst itch over the past 24 hours on a scale ranging from zero (no itch) to 10 (worst itch imaginable) (75). The results are summarised in Figure 6. Within this analysis, the outcome value for patients who prematurely discontinued the study treatment or used rescue therapy for pruritus was set to missing after such intercurrent events (10, 18).

The mean baseline PBC WI-NRS score in the Pruritus ITT population was 6.2 (SD: 1.5) for the elafibranor group and 6.3 (SD: 1.2) for the placebo group. In patients with moderate-to-severe pruritus, the LS mean change in the PBC WI-NRS score demonstrated a trend towards greater reduction in pruritus with elafibranor treatment compared with placebo but did not differ significantly from baseline through Week 52 (-1.93 vs. -1.15; difference: -0.78; 95% CI: -1.99; 0.42; p=0. 1970) and from baseline through week 24 (-1.60 vs. -1.26; difference: -0.34; 95% CI: -1.49; 0.80; p=0.5522) .

Although the difference between treatments was not statistically significant, there was a clear trend for a greater improvement in pruritus for patients treated with elafibranor compared with placebo, seen as early as Week 1 and increasingly apparent from Week 24 onwards.

Figure 6 Change in PBC WI-NRS score from baseline to Week 52 in patients with moderate-to-severe pruritus (Pruritus ITT analysis set)



No. of Patients														
Elafibranor 80 mg	44	41	40	39	40	38	37	34	35	34	32	34	35	32
Placebo	22	21	19	18	18	17	16	15	15	16	15	14	13	12

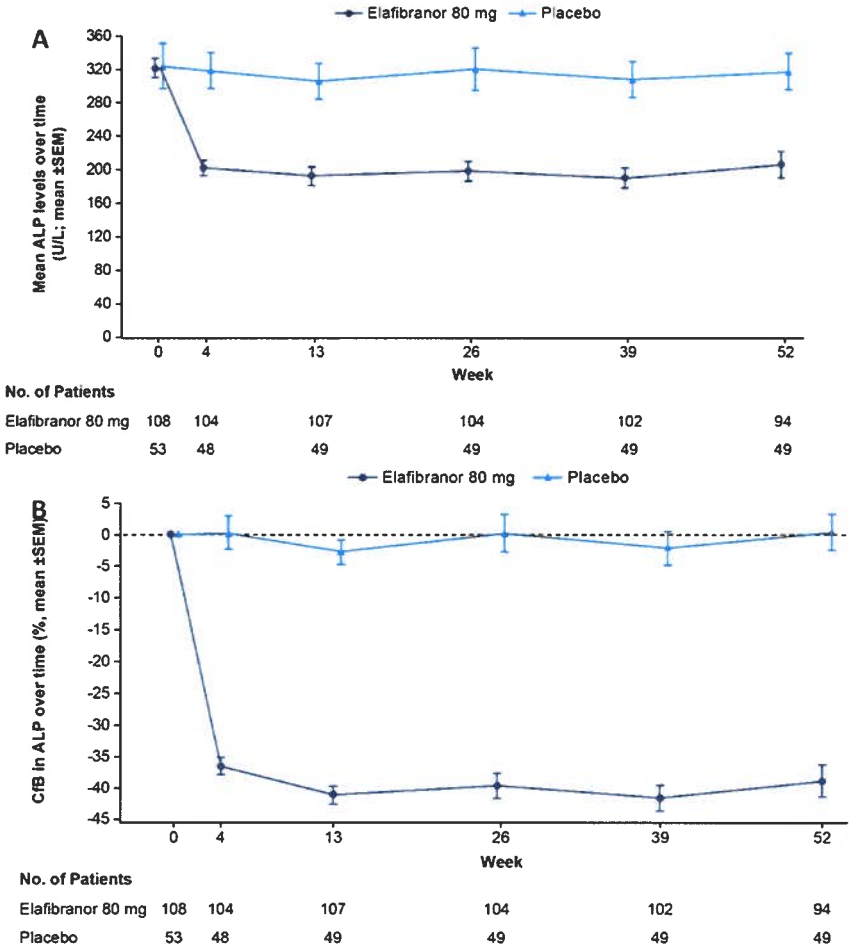
Abbreviations: CfB: Change from baseline; ITT: Intent-to-treat; LS: Least squares; mg: Milligram; SEM: Standard error of mean; PBC: Primary biliary cholangitis. WI-NRS: Worst itch numeric rating scale
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18); Kowdley *et al.* 2024 (10)

6.1.4.4 Change from baseline in ALP at Week 52

Patients treated with elafibranor demonstrated a rapid reduction in ALP as early as Week 4 that was sustained over 52 weeks of treatment compared with patients who received placebo, as shown in Figure 7. At Week 4, the LS mean change from baseline in ALP was -115.8 U/L (95% CI: -126.7; -105.0) in the elafibranor group, which further decreased to -117.0 U/L (95% CI: -134.4; -99.6) by Week 52. In contrast, the LS mean change in the placebo group was -10.4 U/L (95% CI: -26.0; 5.2) and -5.3 U/L (95% CI: -30.4; 19.7) at Weeks 4 and 52, respectively. This translated to a statistically significant reduction in ALP compared with placebo at both time points, with a LS means difference between groups of -105.4 U/L ([95% CI: -124.2; -86.7]; p<0.001) at Week 4 and -111.7 U/L ([95% CI: -142.0; -81.3]; p<0.001) at Week 52 (10, 18). Further improvement in mean change from baseline in ALP was also observed at Week 78, as described in Appendix K (80, 88).

At Week 4, the mean percent change from baseline in ALP was -36.5% (SD: 13.2) in the elafibranor group, which further decreased to -38.9% (SD: 24.8) by Week 52 (Figure 7B) (10, 18). In contrast, the mean percentage change in the placebo group was 0.2% (SD: 18.2) by Week 4, and 1.7% (SD: 18.5) by Week 52. Elafibranor treatment resulted in a statistically significant reduction in ALP compared with placebo, with a treatment estimate of -40.6% (95% CI: -47.8; -33.5) between groups in favour of elafibranor of (p<0.0001) by Week 52 (10, 18).

Figure 7 (A) Mean and (B) percentage change from baseline in ALP levels (U/L) over time to Week 52 (ITT Analysis Set)



Footnotes: Data are presented as collected and do not account for ICE.
Abbreviations: ALP: Alkaline phosphatase; CfB: Change from baseline; ICE: Intercurrent event; ITT: Intent-to-treat; SEM: Standard error of mean.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18), Kowdley *et al.* 2024 (10)

6.1.4.5 Change from baseline in TB at Week 52

In alignment with the ALP levels, participants on elafibranor 80 mg compared to placebo had greater decreases in TB levels from baseline at Week 52 (LS means difference from placebo: -1.3 µmol/L; 95% CI: -2.8; 0.2[redacted] (10). Reduction in TB in the elafibranor 80 mg group was evident from Week 4 onwards and was sustained at subsequent timepoints and up to Week 52. At Week 52, LS mean change from baseline in TB for patients receiving elafibranor was −0.1 µmol/L (n=93). Further improvement in mean change from baseline in TB was also observed at Week 78, as described in Appendix K.

6.1.4.6 Treatment response according to Paris II criteria

When assessing treatment response according to the Paris II criteria (defined as ALP <1.5 x ULN, AST ≤1.5 x ULN, and TB ≤1 mg/dL), a significantly greater proportion of patients treated with elafibranor demonstrated a response to treatment at Week 52 compared with patients who received placebo (82). The proportion of patients demonstrating a response was 43% in the elafibranor group compared with 6% in the placebo group, resulting in a difference of 37.5% (95% CI: 22.3; 47.7; p<0.0001). The OR was 16.7 (95% CI: 4.6; 91.8; [redacted] (82). [redacted]

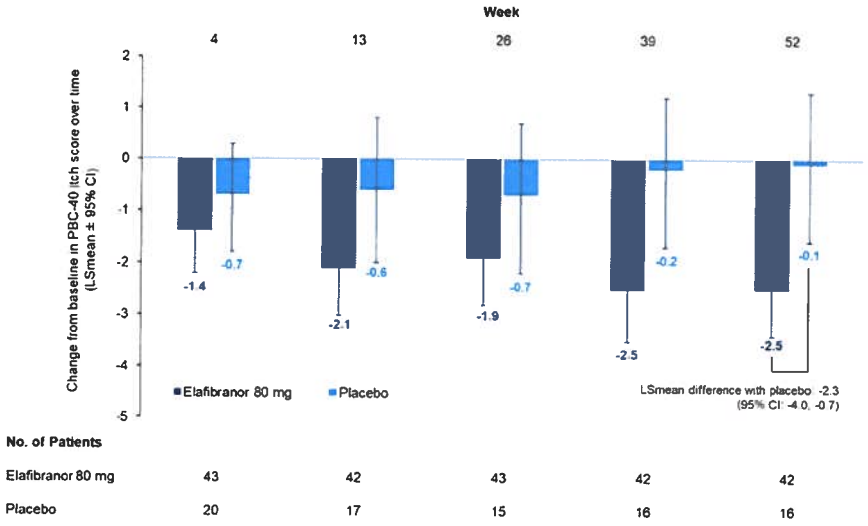
6.1.4.7 Change from baseline in PBC-40 Itch domain

Treatment with elafibranor led to an improvement in symptom burden in the itch domain of the PBC-40 questionnaire compared with treatment with placebo. Improvement in pruritus was seen in the Pruritus ITT analysis set, with an LS mean change from baseline to Week 52 of -2.5 in the elafibranor group and -0.1 in the placebo group (Figure 8) (18). The LS means difference from placebo was -2.3 (95% CI: -4.0; -0.7; nominal p=0.0070) (10, 81). This improvement was also observed in the ITT analysis set (LS mean difference [95% CI]: −1.2 [−2.0; −0.3]; p=0.0065) (81).

For the Pruritus ITT analysis set, the proportion of patients who improved, showed no change or worsened from baseline to Week 52, for individual PBC-40 Itch domains, is presented in Table 13 (81). More patients in the elafibranor group compared to the placebo group showed an improvement in PBC-40 Itch individual items.

Previous studies in PBC have indicated that a 0.5-point reduction from baseline in PBC-40 items represents a clinically meaningful difference, suggesting that the improvement in pruritus observed with elafibranor treatment versus placebo in ELATIVE is clinically meaningful. This emphasises the potential of elafibranor to alleviate the pruritus burden and impact on QoL associated with PBC, addressing an important unmet need (81).

Figure 8 Change from baseline in the PBC-40 itch score over time in patients with moderate-to-severe pruritus (Pruritus ITT analysis set)



No. of Patients					
Elafibranor 80 mg	43	42	43	42	42
Placebo	20	17	15	16	16

Abbreviations: CI: confidence interval; LS: least squares; mg: milligram; PBC: primary biliary cholangitis.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18); Kowdley *et al.* 2024 (10)

Table 13 Patients who improved, showed no change or worsened between baseline and Week 52 for individual PBC-40 Itch items (Pruritus ITT analysis set)

	Improved		No change		Worsened	
Treatment group	Elafibranor	Placebo	Elafibranor	Placebo	Elafibranor	Placebo
Itching disturbed my sleep	50.0%	33.3%	33.3%	38.9%	16.7%	27.8%
I scratched so much I made my skin raw	61.9%	22.2%	31.0%	55.6%	7.1%	22.2%
I felt embarrassed because of the itching	35.7%	27.8%	61.9%	38.9%	2.4%	33.3%

Some patients had missing data at baseline and Week 52 and only patients with a valid baseline and Week 52 assessment are included (elafibranor: n=42; placebo: n=18).
Source: Kremer *et al.* 2024 (81).

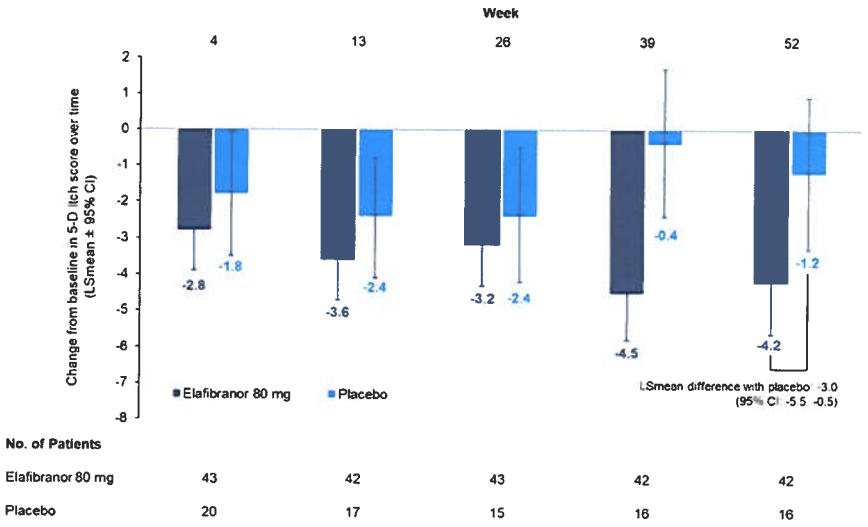
6.1.4.8 Change from baseline in 5-D Itch score

Treatment with elafibranor led to a significant improvement in pruritus as measured by the 5-D Itch scale in the Pruritus ITT analysis set (Figure 9). At Week 52, there was an LS mean change from baseline of -4.2 in the elafibranor group and -1.2 in the placebo group; resulting in an LS means treatment difference of -3.0 (95% CI: -5.5; -0.5; nominal p=0.0199), favouring elafibranor (10, 18). This trend was also supported by similar results in the ITT analysis set (LS mean difference [95% CI]: −1.3 [−2.4; −0.2]; p=0.0238) (81).

For the Pruritus ITT analysis set, the proportion of patients who improved, showed no change or worsened from baseline to Week 52, for individual 5-D Itch domains, is presented in Table 14 (81). Generally, more patients in the elafibranor group compared to

the placebo group showed an improvement in 5-D Itch individual domains. Considering the Duration domain specifically, 14/24 (58%) patients treated with elafibranor reported a reduction in itching duration from ≥6 hours/day to <6 hours/day between baseline and Week 52, compared with 3/11 (27%) patients treated with placebo. In addition, responses to the sleep question of the Disability domain also suggested a benefit of elafibranor: among 25 patients receiving elafibranor with at least frequently delayed sleep (score ≥3, 20 (80%) improved to occasionally delayed sleep or no disturbance (score <3) from baseline to Week 52, compared with 3/10 (30%) patients receiving placebo (81).

Figure 9 Change from baseline in the 5-D Itch score over time in patients with moderate-to-severe pruritus (Pruritus ITT analysis set)



Abbreviations: CI: confidence interval; LS: least squares; mg: milligram; PBC: primary biliary cholangitis.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18); Kowdley *et al.* 2024 (10)

Table 14 Patients who improved, showed no change or worsened between baseline and Week 52 for individual 5-D Itch domains (Pruritus ITT analysis set)

	Improved		No change		Worsened	
Treatment group	Elafibranor	Placebo	Elafibranor	Placebo	Elafibranor	Placebo
Duration	42.90%	27.80%	50.00%	61.10%	7.10%	11.10%
Degree	66.70%	38.90%	21.40%	55.60%	11.90%	5.60%
Direction	64.30%	33.30%	21.40%	55.60%	14.30%	11.10%
Disability	66.70%	44.40%	23.80%	27.80%	9.50%	27.80%
Distribution	45.20%	55.60%	40.50%	22.20%	14.30%	22.20%

Some patients had missing data at baseline and Week 52 and only patients with a valid baseline and Week 52 assessment are included (elafibranor: n=42; placebo: n=18).
Source: Kremer *et al.* 2024 (81).

6.1.4.9 Change from baseline in PROMIS Fatigue Short Form 7a score

In the ELATIVE trial, change from baseline in fatigue outcomes were assessed in ITT Analysis and Pruritus ITT Analysis (including patients with a baseline WI-NRS score of ≥4) sets as pre-specified analyses. [redacted]

6.1.4.10 Change from baseline in PBC-40 Fatigue domain score

[redacted]

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Not applicable, as the application is based on a head-to-head study.

7.1.2 Method of synthesis

Not applicable, as the application is based on a head-to-head study.

7.1.3 Results from the comparative analysis

Table 15 Results from the comparative analysis of elafibranor vs. placebo for adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA

[redacted]

Biochemical cholestasis response, Week 52	**55/108, 51%** (95% CI: 42; 60)	**2/53, 4%** (95% CI: 1; 13)	**Absolute risk difference: 47%** (95% CI: 32; 57; p<0.001)

Outcome measure	Elafibranor (N=108)	Placebo (N=53)	Result
			OR: 37.6 (95% CI: 7.6; 302.3; p<0.001)
Biochemical cholestasis response, Week 78	**19/27, 70%** (95% CI: NA)	**0/13, 0%** (95% CI: NA)	**Absolute risk difference: 70%** (95% CI: NA) **OR: NA**
ALP normalisation, Week 52	**16/108, 15%** (95% CI: 9; 23)	**0/53, 0%** (95% CI: 0; 7)	**Absolute risk difference: 15%** (95% CI: 6; 23; p<0.002) **OR: Infinity** (95% CI: 2.8; infinity; p=0.0019)
ALP normalisation, Week 78	**5/27, 19%** (95% CI: NA)	**0/13, 0%** (95% CI: NA)	**Absolute risk difference: 19%** (95% CI: NA) **OR: NA**
Change in PBC WI-NRS score from baseline (Pruritus ITT Analysis Set) Week 52	n=44 LS mean: -1.93 (95% CI: -2.60; -1.26)	N=22 LS mean: -1.15 (95% CI: -2.14; -0.15)	**LS means difference: -0.78** (95% CI: −1.99; 0.42; p=0.1970)
Change in PBC WI-NRS score from baseline (Pruritus ITT Analysis Set), Week 24	n=44 LS mean: -1.60 (95% CI: -2.25; -0.95)	n=22 LS mean: -1.26 (95% CI: -2.20; -0.31)	**LS means difference: -0.34** (95% CI: −1.49; 0.80; p=0.5522)
Change in ALP level from baseline, Week 52	LS mean: -117.0 U/L (95% CI: -134.4; -99.6)	LS mean: -5.3 U/L (95% CI: -30.4; 19.7)	**LS means difference: -111.7 U/L** (95% CI: -142.0; -81.3; [redacted]
Change in ALP level from baseline, Week 78	n=26 Mean: −135.3 U/L (95% CI: NR)	N=12 Mean: 31.0 U/L (95% CI: NR)	**Difference: -166.3 U/L** (95% CI: NA)
Change in TB level from baseline, Week 52	LS mean: −0.1 (95% CI: −1.0; 0.7)	LS mean: 1.1 (95% CI: −0.1; 2.4)	**LS means difference: -1.3 µmol/L** (95% CI: -2.8; 0.2; [redacted]
Change in TB level from baseline, Week 78	N=25 Mean: -1.21 µmol/L (95% CI: NA)	N=12 Mean: 3.08 µmol/L (95% CI: NA)	**Difference: -4.39 µmol/L** (95% CI: NA)
Treatment response based on Paris II criteria, Week 52	[redacted]	[redacted]	**Absolute risk difference:** [redacted]

Treatment response based on Paris II criteria, Week 78			
Change in PBC–40 itch domain score from baseline (Pruritus ITT Analysis Set), Week 52	n=44 LS mean: -2.5	n=22 LS mean: -0.1	**LS means difference:** **-2.3** (95% CI: −4.0; −0.7; p=0.0070)
Change in 5D-Itch total score from baseline (Pruritus ITT Analysis Set), Week 52	n=44 LS mean: -4.2	n=22 LS mean: -1.2	**LS means difference:** **-3.0** (95% CI: −5.5; −0.5; p=0.0199)
Change in PROMIS Fatigue Short Form 7a score from baseline, Week 52 (ITT Analysis Set)			
Change in PROMIS Fatigue Short Form 7a score from baseline, Week 52			
Change in PBC-40 Fatigue domain score from baseline, Week 52 (ITT Analysis Set)			
Change in PBC-40 Fatigue domain score from baseline, Week 52			

Abbreviations: 5D: 5-dimensions pruritus scale; ALP: Alkaline phosphatase; CI: Confidence interval; ITT: Intention to treat; LS: Least squares; NA: Not available; OR: Odds ratio; PROMIS: Patient Reported Outcome Measurement Information System; SE: standard error; TB: Total bilirubin; UDCA: Ursodeoxycholic acid; WI-NRS: Worst Itch Numeric rating scale.
Sources: Ipsen Data on File 2023 (ELATIVE Clinical Study Report) (18); Kowdley *et al.* 2024 (10); Bowlus *et al.* 2024 (80); Sonderup *et al.* 2024 (82)

7.1.4 Efficacy – results per [outcome measure]

Not applicable, as results from the head-to-head study ELATIVE are presented in 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 Extrapolation of efficacy data

Data from the ELATIVE trial (12 months) were directly used in the analysis for transition probabilities calculations (section 8.1.2). Transition probabilities for the remaining modelled time horizon were based on the following assumptions: patients on elafibranor were assumed to remain in the same health state, and patients on UDCA were assumed to transit between health states using transition probabilities from ELATIVE trial (between cycle 3 and 4), to capture worsening condition. For more details, please refer to section 8.1.2.

Parametric distributions were used to extrapolate the all-cause time to discontinuation (TTD) of elafibranor treatment during and beyond the ELATIVE study duration. Estimates from the extrapolations beyond the ELATIVE study period were used to model the movement of patients between the on and off-treatment PBC biomarker health states. More details can be found in section 8.1.1.1.

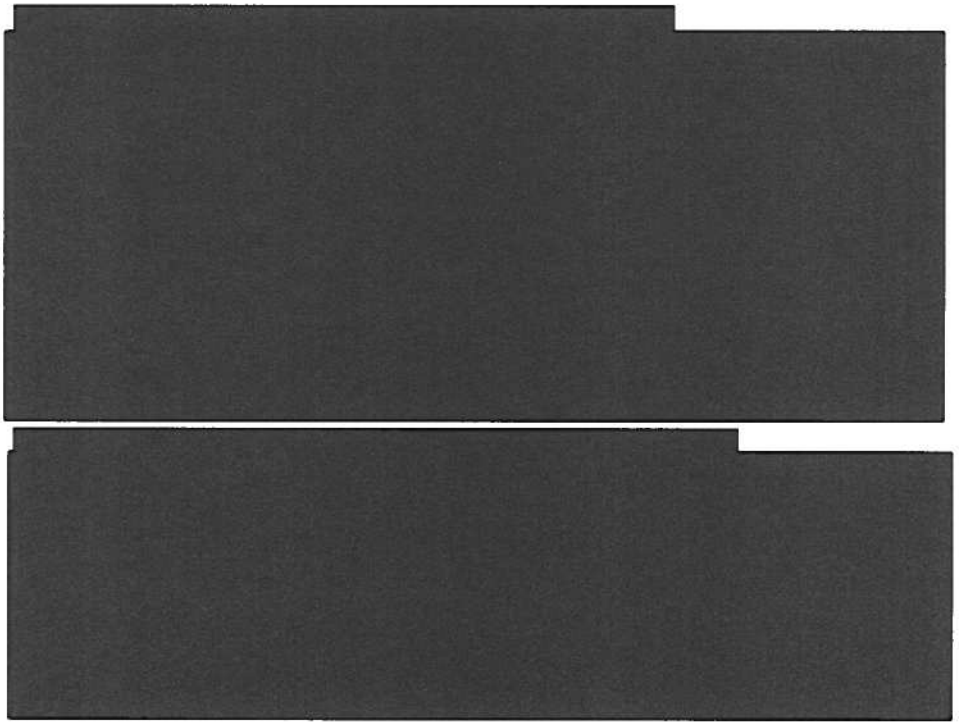
8.1.1.1 Extrapolation of treatment discontinuation

All-cause discontinuation is assumed in the base-case and applied across the entire time horizon for elafibranor in the model. For patients receiving elafibranor, parametric distributions were fitted to the Kaplan Meier all-cause TTD data. More details about TTD extrapolation analysis are provided in the Appendix D.

Table 16 Summary of assumptions associated with extrapolation of treatment discontinuation

Method/approach	Description/assumption
Data input	ELATIVE trial
Model	Standard parametric models
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Elafibranor: Exponential
Function with best BIC fit	Elafibranor: Exponential
Function with best visual fit	Elafibranor: Exponential

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	ELATIVE trial, clinical expert's opinion
Function with the best fit according to external evidence	Elafibranor: Exponential, Gompertz
Selected parametric function in base case analysis	Elafibranor: Gompertz
Adjustment of background mortality with data from Statistics Denmark	No; adjustment by background mortality is not relevant for non-survival data
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No



According to the clinical expert's opinion, the most clinically plausible parametric distribution to reflect treatment duration of elafibranor in practice is the flattest curve

compared to other distributions (7, 12). The rationale underlying is that occurrence of adverse events and lack of response should be assessed at the beginning of the treatment period.

Additionally, a recent evaluation by NICE of elafibranor underscores the importance of considering treatment discontinuation curves that reflect real-world clinical practice and trends. The Evidence Assessment Group (EAG) also identified the Gompertz function to be the model closest aligned with expert opinion and highlighted in their evaluation that, after the initial years, discontinuation predominantly occurs due to disease progression or lack of efficacy. (89) Therefore, Gompertz was selected as the base case distribution.

8.1.2 Calculation of transition probabilities

PBC biomarker health states: elafibranor and UDCA

The transition probabilities for health states in the PBC biomarker component of the model of the elafibranor and UDCA treatment arms were calculated using the proportion of patients in the mild, moderate, and severe risk health states (according to ALP, AST, TB, and liver stiffness) in the ELATIVE trial for patients treated with elafibranor and placebo, respectively. In line with the model cycle length, movement between the health states was captured at five time points:

- Baseline (Visit 1), the beginning of cycle 1
- Visit 3, the end of cycle 1
- Visit 4, the end of cycle 2
- Visit 5, the end of cycle 3
- Visit 6, the end of cycle 4

At each timepoint, patients' ALP, TB, AST and kPa (liver stiffness) levels were recorded. Patient level data was used to assign patients to the mild, moderate, or severe health state at each time point. As kPa was measured at baseline, Visit 4, and Visit 6 only, missing kPa observations were imputed using the last observation carried forward (LOCF) approach for Visits 3 and 5. For each cycle and health state, transition probabilities were then calculated as the proportion of patients remaining within the same health state or moving into either of the alternative PBC biomarker health states. For transitions after cycle 4 in the PBC biomarker component, patients receiving elafibranor were assumed to remain in their health state for the remainder of the lifetime time horizon. Patients who discontinue elafibranor were assumed to return to their health state at baseline. To capture the worsening condition of patients who are treated with UDCA only, the LOCF assumption was implemented by continuing to apply to transition probabilities from cycle 3 to cycle 4 for the remainder of the time horizon. Interim data from Week 78 and from the OLE phase of the ELATIVE trial support the assumptions for the trajectory of disease for patients treated with elafibranor and UDCA (Figure 28, Figure 30 and OLE results in Appendix F). Notably, both ALP and TB were demonstrated to increase for patients treated with placebo compared to stabilization or further reduction in patients treated with elafibranor.

Transition probabilities matrices used in the base case analysis for elafibranor and UDCA are presented in Appendix L.

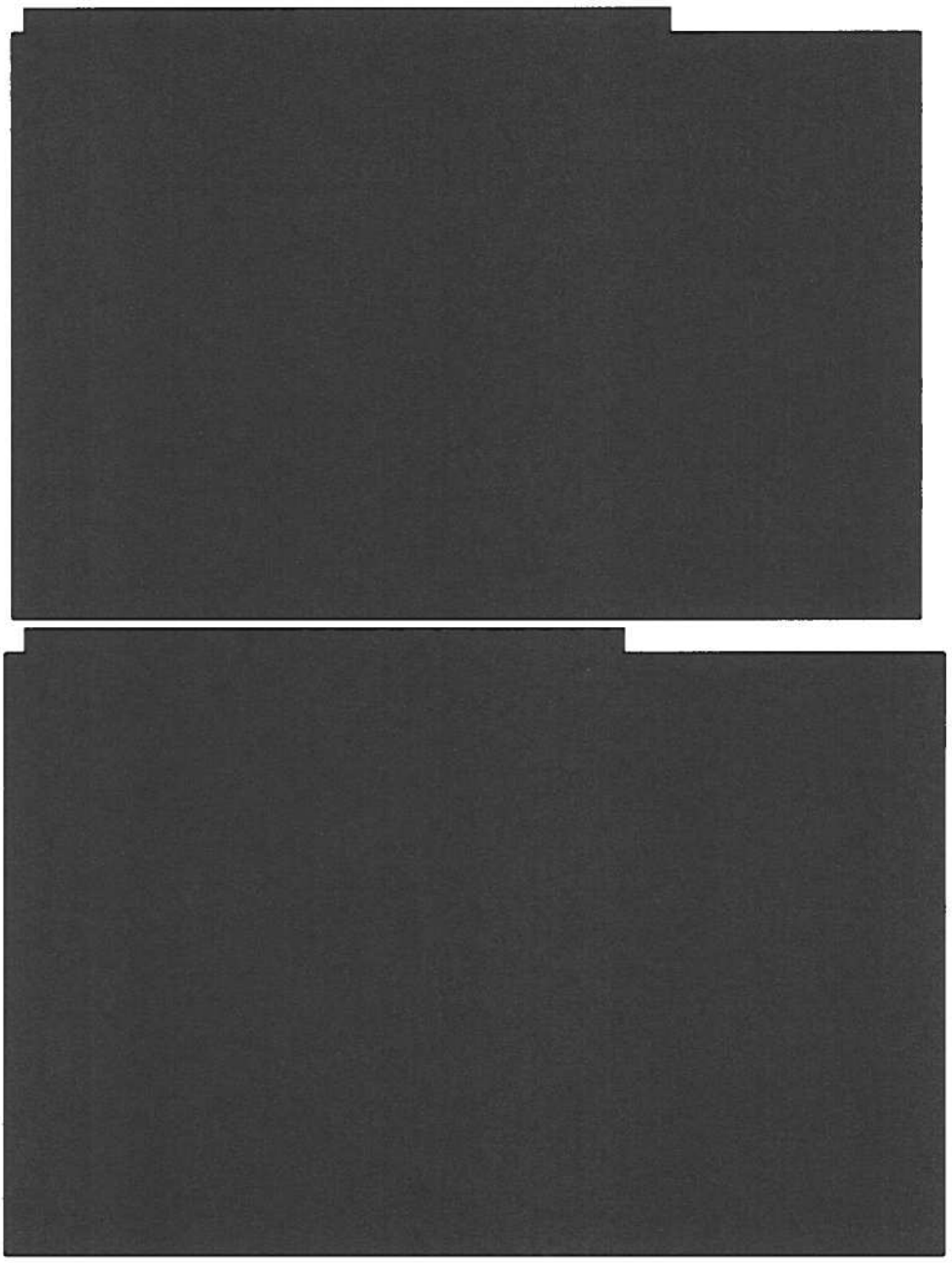
Liver disease health states

To inform the transition probabilities in the liver disease component of the CEM, the transition probabilities reported in the NICE submission of OCA were used (Table 41) (74). These transition probabilities were originally sourced from published literature. The chosen transition probabilities were presented to international health economics and outcomes research and both international and Danish clinical experts, who agreed that the probabilities were appropriate to use in the elafibranor CEM. In validation of the transition probabilities, clinical experts also advised of the probabilities of moving from the moderate risk health state to the liver disease component.

Table 17 Transitions in the health economic model (liver disease component)

Health state (from)	Health state (to)	Transition probability per cycle	Reference
Moderate risk of PBC disease progression	DCC	0.16%	Clinical expert opinion, 2024 (12). Validated by Danish clinical expert (7).
	HCC	0.02%	
	Pre-LT	0.06%	
High risk of PBC disease progression	DCC	2.60%	NICE TA443, 2017 (79)
	HCC	0.25%	
	Pre-LT	1.02%	
DCC	HCC	0.25%	
	Pre-LT	1.53%	
HCC	Pre-LT	1.02%	NICE TA443, 2017 (79)
Pre-LT	LT	10.21%	
Post-LT	LT	0.02%	
	Re-emergence of PBC	0.58%	
Re-emergence of PBC	LT	0.02%	

Abbreviations: DCC: Decompensated cirrhosis; DK: Denmark; HCC: Hepatocellular carcinoma; LT: Liver transplant; NICE: National Institute for Health and Care Excellence; PBC: Primary biliary cholangitis; TA: Technology appraisal



8.1.3 Pruritus

Pruritus is a common symptom in PBC, with 41% and 59% of patients reporting pruritus at baseline in the ELATIVE and POISE trials, respectively (9, 10). Therefore, it is considered an outcome of interest in the CEM. The CEM considers the impact of pruritus by modelling the severity of pruritus over time. The patient population is stratified into three itch severity categories: no itch, moderate itch, and clinically significant itch. The thresholds of itch severity were developed by creators of the PBC-40 Itch instrument (range: 0 to 15), as presented in Mayo et al. (2023) (50):

- No itch: PBC-40 Itch domain score = 0
- Mild itch: PBC-40 Itch domain score ≥1 to <7
- Clinically significant itch: PBC-40 Itch domain score ≥7

For elafibranor and UDCA, the change in the distribution of pruritus severity over time is informed by patient level data of PBC-40 Itch scores from the ELATIVE trial (90). The distribution of itch severity was parameterised using recorded PBC-40 Itch scores from baseline, Visit 1, and Visits 3 to 6 of the ELATIVE trial. From Month 12 onwards, the distribution of itch severity was assumed to remain constant as a conservative extrapolation assumption (Table 18).

[redacted]

Timepoint	Elafibranor			UDCA		
	No itch	Mild itch	CS itch	No itch	Mild itch	CS itch
Month 3	[redacted]					
Month 6	[redacted]					
Month 9	[redacted]					
Month 12+	[redacted]					

Abbreviations: CS: Clinically significant; UDCA: Ursodexycholic acid

8.2 Presentation of efficacy data from additional documentation

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable. Elafibranor is indicated for second-line treatment. No recommendations for third-line and later lines of treatment of PBC in Denmark were identified, and subsequent treatments were not assessed in the ELATIVE trial.

8.4 Other assumptions regarding efficacy in the model

8.4.1 Mortality

Age- and sex-specific general population mortality rates sourced from the Statistics Denmark were applied to all patients in the model (91). With exception of the high-risk health state (upon advice from international clinical experts), the biomarker component health states had mortality rates equal to the general population. Excess mortality for health states in the liver disease component of the model were sourced from the NICE submission for OCA and applied throughout the liver disease component of the model

(79). Increases in mortality were verified by the Danish clinical expert (7). The excess mortality rates applied in the CEM are shown in Table 19.

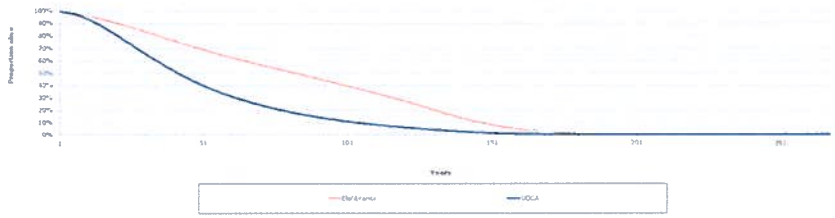
Table 19 Excess mortality applied in the CEM

Health state	Annual excess mortality	Reference
Mild	0.0%	NICE TA443 (79) Clinical expert (12)
Moderate	0.0%	NICE TA443 (79); Clinical expert (12)
High	1.2%	DK expert opinion (7)
DCC	4.2%	NICE TA443 (79)
HCC	10.2%	NICE TA443 (79)
Pre-LT	2.2%	NICE TA443 (79)
LT	18.9%	NICE TA443 (79)
Post-LT	1.5%	NICE TA443 (79)
Re-emergence of PBC	2.2%	NICE TA443 (79)

Abbreviations: CEM: Cost-effectiveness model; DCC: Decompensated cirrhosis; DK: Denmark; HCC: Hepatocellular carcinoma; LT: Liver transplant; NICE: National Institute of Health and Care Excellence; PBC: Primary biliary cholangitis; TA: Technology appraisal

The resulting survival curves applied in the model are illustrated in Figure 14.

Figure 14 Proportion of patients alive over lifetime time horizon



Abbreviations: UDCA: Ursodexycholic acid

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

Table 20 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Mild [months]	Moderate [months]	High [months]	DCC [months]	HCC [months]	Pre-LT [months]	LT [months]	Post-LT [months]	PBC re-emergence [months]	Dead [months]
Elafibranor											
UDCA											

Abbreviations: DCC: Decompensated cirrhosis; HCC: Hepatocellular carcinoma; LT: Liver transplant; N/A: Not applicable; PBC: Primary biliary cholangitis; UDCA: Ursodexycholic acid

9. Safety

9.1 Safety data from the clinical documentation

In the ELATIVE trial, safety analyses were performed using the Safety Analysis Set (18). The Safety Analysis Set consisted of all participants who were administered at least one dose of DB study drug irrespective of the treatment received. Participants who received any amount of active treatment, even by mistake and for one intake, were assigned to the active treatment group. All 161 patients from the ITT Analysis Set were included in the Safety Analysis Set, being 108 patients from the elafibranor ITT Analysis Set and 53 patients from the placebo ITT Analysis Set (18).

Due to the temporal relationship between treatment and event onset, the results presented in Table 21 refer to TEAEs.

The mean duration of exposure during the DB period was 66.2 weeks (SD: ±22.4) in the elafibranor group and 62.2 weeks (SD: ±26.2) in the placebo group (10).

Table 21 Overview of safety events in the ELATIVE trial in the DB period (minimum 52 weeks)

	Elafibranor (N=108) (10, 18)	Placebo (N=93) (10, 18)	Difference (95 % CI)
Number of adverse events, n	626	259	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	104 (96.3) EAIR: 4.080	48 (90.6) EAIR: 3.123	EAIR difference: [redacted]
Number of serious adverse events*, n	30	10	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	11 (10.2) EAIR: 0.083	7 (13.2) EAIR: 0.113	EAIR difference: [redacted]
Number of CTCAE grade ≥ 3 events, n	NA	NA	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	NA	NA	NA
Number of severe† adverse events, n	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥1 severe adverse events†, n (%)	[redacted]	[redacted]	EAIR difference: [redacted]
Number of adverse reactions, n	89	30	N/A
Number and proportion of patients with ≥ 1 adverse reaction, n (%)	42 (38.9) EAIR: 0.420	21 (39.6) EAIR: 0.440	EAIR difference: [redacted]
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 (%)	12 (11.1)	6 (11.3)	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	11 (10.2) EAIR: 0.080	5 (9.4) EAIR: 0.078	EAIR difference: [redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.
† Severe AEs were defined as AEs that caused an interruption in normal activities of daily living and generally required systemic drug therapy or other treatment; these adverse events were usually incapacitating.
Abbreviations: AE: Adverse event; DB: Double-blind; CI: Confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; N/A: Not applicable; NA: Not available

No serious TEAEs with frequency of ≥5% were recorded in the ELATIVE study. A list of all serious TEAEs observed in the ELATIVE study is reported in Appendix E.

Table 22 Serious adverse events (DB period)

Adverse events	Elafibranor (N=108)		Placebo (N=53)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	N/A	N/A	N/A	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Abbreviations: DB: Double blind; N/A: Not applicable

Standard practice for cost-effectiveness analyses is to include any grade 3+ AE reported in ≥5% of one arm of the study population. However, as no grade 3+ AEs occurred in ≥5% of one arm of the study population in ELATIVE, the threshold was reduced such that any grade 2+ AEs reported in ≥5% of one arm of the study population were considered (18). The resulting AEs considered in the CEM are presented below in Table 23. Despite grade 2+ COVID-19 being an AE that occurred in ≥5% of one arm of the study population, it was excluded, given the timing of the trial coinciding with the COVID-19 pandemic and that it is not expected to occur at this frequency in clinical practice on an ongoing basis.

Table 23 Adverse events used in the health economic model (per cycle)

Adverse events	Elafibranor	UDCA	Source	Justification
	Frequency used in economic model for intervention	Frequency used in economic model for comparator		
Pruritus	12.8%	14.2%	ELATIVE trial (18)	Considered as relevant AEs for patients with PBC. Validated by DK clinical expert (7).
Urinary tract infection	5.8%	1.9%		
Fatigue	4.7%	5.9%		

Abbreviations: AE: Adverse event; DK: Denmark; PBC: Primary biliary cholangitis; UDCA: Ursodexycholic acid

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

Not applicable.

Table 24 AEs that appear in more than X % of patients

AEs	Elafibranor (N=108)			Placebo (N=53)			Difference, % (95 % CI)	
	Number of patients with AEs	Number of AEs	Frequency used in economic model for intervention	Number of patients with AEs	Number of AEs	Frequency used in economic model for comparator	Number of patients with AEs	Number of AEs
AE, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: AE: Adverse event; N/A: Not applicable

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

Table 25 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	ELATIVE trial	Utilities, disutilities

Abbreviations: EQ-5D-5L: EuroQoL 5-dimension 5-level Questionnaire

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

During the ELATIVE study, patients completed the EQ-5D-5L and EQ-5D-5L-VAS at multiple time points across the study. In the study protocol, it was specified for EQ-5D-VAS and EQ-5D-5L domain scores to be summarised according to study arm. (18)

The EQ-5D-5L descriptive system of health states comprises five dimensions ('5D'): (1) mobility; (2) self-care; (3) usual activities; (4) pain/discomfort and (5) anxiety/depression. Those are rated by a verbal 5-point rating scale allowing for distinction of five levels ('5L') of severity in each dimension: Level 1: no problems; Level 2: slight problems; Level 3: moderate problems; Level 4: severe problems; Level 5: extreme problems. Each level provides a 1-digit number for each dimension (1-5, where 1 is Level 1, and 5 is Level 5). The digits for the five dimensions can be combined in a 5-digit code describing the patient's health state according to the five dimensions. A total of 3,125 combinations of different health states are possible (92).

Quality of life analysis was run using the overall ITT population of the ELATIVE individual patient-level data.

10.1.2 Data collection

During the ELATIVE study, patients completed the EQ-5D-5L questionnaire at the study site on Days 1, 29, 92, 183, 274, 365, 547 and 729 (occurring in weeks 0, 4, 13, 26, 39, 52, 78 and 104) during the DB period; at a maximum of 13 weeks after last visit 5 (day 274) for the last participant; and during the LTE starting 91 days after the first long-term visit and every 182 days up to 26 weeks. (18)

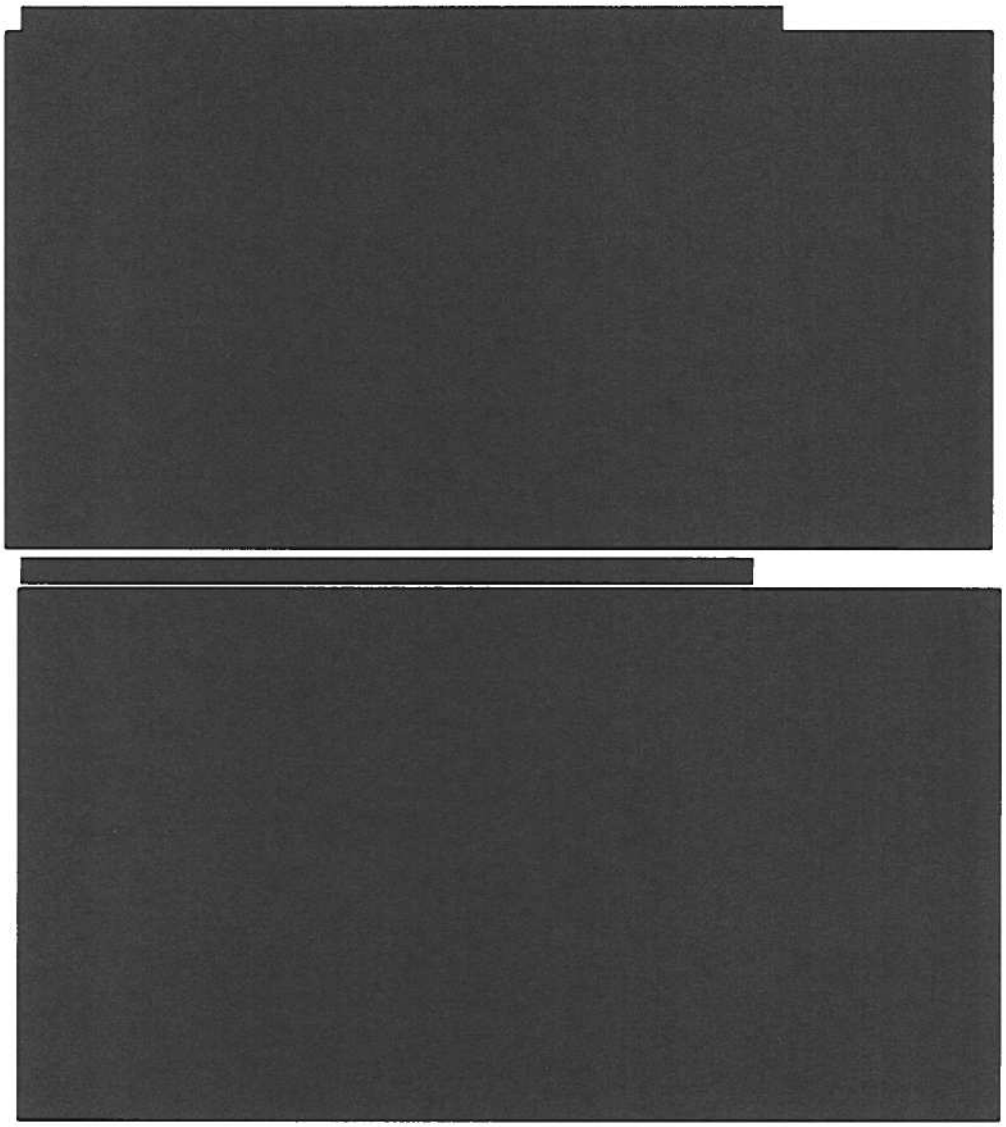
Validity of results relies heavily on the level and handling of missing data within the dataset. Not allowing for missing data i.e., where patients do not respond to a dimension/question of the EQ-5D-5L questionnaire can introduce bias and misleading results. Literature suggested calculating response rates for each of the five dimensions (93). Completion rates for each of the EQ-5D-5L components in the data entries were calculated and results demonstrated that there were no missing data across each treatment arm and progression status at the domain level. Therefore, no additional tests were required to investigate if data was missing completely at random (MCAR) (94, 95).

Pattern of missing data and completion is presented in Table 52 and Table 53 in Appendix F.

HRQoL results

Overall, HRQoL as measured by EQ-5D-5L remained high and stable throughout the study period, with no meaningful differences observed between groups. Baseline EQ-5D-5L scores were [redacted] (SD: [redacted]) for the elafibranor group and [redacted] (SD: [redacted] for the placebo group. The LS means change from baseline to Week 52 was [redacted] in the elafibranor group and [redacted] in the placebo groups; the LS means difference from placebo was [redacted]

EQ-5D-5L domain scores at baseline (on the lefthand side) and after Week 52 (on the righthand side) of the ELATIVE study for elafibranor and placebo are presented in Figure 15 and Figure 16, respectively. Patients treated with elafibranor and placebo had a large proportion of patients with no problems at baseline in the mobility and self-care domains. The most impacted domains were the pain/discomfort and anxiety/depression domains. For patients treated with elafibranor, there was a small increase in the proportion of patients reporting no or slight problems in the usual activities and anxiety/depression domains at Week 52 compared to baseline. For patients treated with placebo, there were limited improvements observed.



A regression analysis was performed on the ELATIVE trial data to identify differences in utility values according to risk of progression to liver disease and the severity of pruritus. To conduct the analysis, EQ-5D-5L domain responses, ALP levels, bilirubin levels and kPa levels were collected at Visit 1, Visit 3, Visit 4, Visit 5, and Visit 6, of patients treated with both elafibranor and placebo in the ELATIVE study. Pruritus was included as a covariate in the utility analyses to determine whether severity of pruritus also predicts HRQoL in combination with the risk of disease progression. Categorical variables were assigned according to the level of itch severity, classified according to PBC-40 Itch domain score.

More details on estimated HRQoL based on the ELATIVE trial data can be found in Appendix F.

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

10.2.1 HSUV calculation

In the base case analysis literature-based UK-specific health states utilities have been used. As reported in Appendix F, for EQ-5D-5L HSUVs with Danish weights, the p-value for the risk variables is greater than 0.05 and therefore demonstrates a non-statistically significant difference between the utility of patients in the mild risk health state compared to patients in the moderate and high risk health states, respectively, at a 5% significance level. However, HSUVs identified from published literature showed differences in HRQoL between mild risk and high risk, and between moderate risk and high risk, respectively (23, 96). Thus, the results of the regression analysis are not consistent with the published literature, indicating the same difference in utility estimate for the moderate and high-risk health states, compared to the mild risk health state.

Additionally, ELATIVE trial population data were not sufficient to generate HSUVs for all the health states included in the CEM. Therefore, to not include utilities not reflecting previous publications, and to avoid mixing HSUVs generated using different preference weights (UK vs. Denmark), it was considered most appropriate to use UK-specific, literature-based utilities in the base case analysis.

Utilities are adjusted to age using the multiplicative method, as recommended by the DMC guidelines.

10.2.1.1 Mapping

Not applicable. Appendix F describes HSUVs generated from the ELATIVE trial.

10.2.2 Disutility calculation

Disutilities associated with adverse events and pruritus are applied in the base case CEM.

Adverse events disutilities

AE disutilities for pruritus, urinary tract infection (UTI) and fatigue were sourced from clinical expert opinion, the literature and previous NICE submissions identified by SLR. Table 27 summarizes AE disutilities applied in the analysis.

Pruritus disutilities

Pruritus was considered as an outcome of interest in the CEM. For this reason, the disutility associated with pruritus was considered separate to pruritus as a TEAE and the HSUVs. As described in section 0 and Appendix F, pruritus was included in a regression analysis of EQ-5D data collected during the ELATIVE study. The disutility of pruritus according to its severity was sourced from this regression and applied in the CEM. Patients with no pruritus have no disutility applied. As the distribution of severity of pruritus is considered throughout all time in the CEM, the disutility is applied throughout time and is considered distinct to the disutility of pruritus as a TRAE, which occurs only in the first cycle of treatment. As such, any double counting of the disutility associated with pruritus as an

outcome and as a TRAE is minimised. The disutilities applied for pruritus over the model time horizon are reported in Table 26. Pruritus disutilities were based on the EQ-5D-5L data from ELATIVE trial using Jensen et al. 2021 value set. (97) [redacted]

Table 26 Disutility of pruritus applied in the model

Severity of pruritus	Disutility value
Mild itch	[redacted]
CS itch	[redacted]

Abbreviations: CS: Clinically significant

10.2.3 HSUV results

Due to the lack of statistically significant differences in HSUVs based on the ELATIVE trial (see section 10.1) and lack of Danish-specific utilities from literature, HSUVs used in the CEM were primarily identified from the NICE submission of OCA, which were originally sourced from Wright et al., (2006) and published values in TA330, as shown in Table 27 below. (19, 21, 23) These utility values were used in the OCA NICE submission (TA443) and were also validated by a clinical expert. (7, 19)

Table 27 Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Mild	0.84 [0.39; 1.00]	HUI	UK	Cholestatic disease utility reported in Younossi 2001 (96)
Moderate	0.84 [0.39; 1.00]	HUI	UK	Cholestatic disease utility reported in Younossi 2001 (96)
High	0.55 [0.33; 0.76]	EQ-5D-5L	UK	Previously reported value for compensated cirrhosis (NICE TA330) (21)
DCC	0.38 [0.24; 0.53]	EQ-5D-5L	UK	Previously reported value for DCC (NICE TA330); redacted utility decrement not applied (21)
HCC	0.45 [0.28; 0.63]	EQ-5D-5L	UK	Previously reported value for HCC (NICE TA330) (21)

	Results (95% CI)	Instrument	Tariff (value set) used	Comments
Pre-LT	0.38 [0.24-0.53]	EQ-5D-5L	UK	Previously reported value for pre-LT (NICE TA330); redacted utility decrement not applied (21)
LT	0.57 [0.34-0.78]	EQ-5D-5L	UK	Previously reported value for LT (NICE TA330); redacted utility decrement not applied (21)
Post-LT	0.67 [0.39-0.90]	EQ-5D-5L	UK	Previously reported value for post-LT (NICE TA330) (21)
Re-emergence of PBC	0.67 [0.39-0.90]	EQ-5D-5L	UK	Assumed equivalent to post-LT, without utility decrement (NICE TA330) (21)
Disutilities				
Pruritus – Mild itch	[redacted]	EQ-5D-5L	DK	ELATIVE trial
Pruritus – CS itch	[redacted]	EQ-5D-5L	DK	ELATIVE trial
AE – pruritus	-0.11	-	UK	Validated by DK clinical expert opinion (7)
AE – UTI	-0.06	SF-36	UK	Abrahamian et al. 2011 (20)
AE - fatigue	-0.07	EQ-5D	UK	NICE TA779 (22)

Abbreviations: AE: Adverse event; CI: Confidence interval; CS: Clinically significant; DCC: Decompensated cirrhosis; DK: Denmark; EQ-5D-5L: EuroQoL 5-dimension 5-level Questionnaire; HCC: Hepatocellular carcinoma; HUI: Health utility index; HSUVs: Health state utilities values; LT: Liver transplantation; NICE: National Institute for Health and Care Excellence; PBC: Primary biliary cholangitis; SF-36: Medical Outcomes Study Short Form 36; TA: Technology appraisal; UK: United Kingdom; UTI: Urinary tract infection

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

More details for the utilities used in the CEM is provided in the section 10.2.

Wright et al. 2006 (23) estimates QoL based on the two clinical trials data. For completeness both studies were described below. Additionally, for patients with cholestatic liver disease data reported in Younossi et al. 2001 were used. (97)

10.3.1 Study design

Mild hepatitis C clinical trial (23)

The mild hepatitis C study is a multicentre National Health Service (NHS) setting based clinical trial. Adult patients with mild chronic hepatitis C (Ishak necroinflammatory score

<4, fibrosis score <3) not previously treated with interferon- or another antiviral regimen were identified. A histological diagnosis consistent with mild chronic hepatitis C was confirmed by the trial histopathologist at the coordinating centre and a report of the pretreatment liver biopsy performed within 1 year of the screening visit was available before screening.

During the Mild hepatitis C study, patients completed the EQ-5D-5L and Medical Outcomes Study Short Form 36 (SF-36) at multiple time points across the study.

Ratcliffe et al., 2002 (98)

A prospective multicentre study to assess pre-transplantation and post-transplantation HRQoL of liver transplant recipients was performed. The study was undertaken using a postal questionnaire. The population of interest was all individuals eligible to receive treatment from the UK NHS who were selected to receive treatment as part of the liver trans-plantation program at each of the six Department of Health–designated liver transplantation centres in England and Wales during the period January 1996 to December 1998 (n=542).

During the study, patients completed the EQ-5D-5L and SF-36 at multiple time points across the study.

Younossi et al., 2001 (96)

Between November 1997 and April 1998, patients with the diagnosis of PBC (antimitochondrial antibody, elevated liver enzymes with or without liver biopsy) or PSC (by typical cholangiogram, elevated liver enzymes with or without liver biopsy) were enrolled. Patients were excluded if they had other major chronic active medical or psychiatric conditions requiring treatment; malignancy; had undergone orthotopic liver transplantation; or were unable to consent.

During the study, patients completed the Medical Outcomes Study Short Form 36 (SF-36), Chronic Liver Disease Questionnaire (CLDQ) and HUI questionnaires.

10.3.2 Data collection

Mild hepatitis C clinical trial (23)

During the mild hepatitis C study, patients completed the EQ-5D-5L questionnaire at the study site at baseline, and weeks 12, 24 and 48. Following the completion of treatment (week 48), patients were evaluated by the study staff at the end of post-treatment weeks 12 and 24. Patients completed the questionnaires in the clinic before seeing the healthcare professional and without knowing their current disease status. The questionnaires were self-administered and reviewed for completeness by a local investigator. The data from all cases attending the baseline visit were used to estimate the HRQoL associated with mild disease. This was the most appropriate data point as it used the maximum amount of data and was applied before patients had suffered any detrimental effects to their HRQoL from being in the trial. The data at weeks 24 and 48 post-treatment were used to estimate the effect of having a sustained virological response on HRQoL. For the treatment group, the

effect of antiviral treatment on HRQoL was estimated using the data from weeks 12 and 24, when most cases were still taking antiviral treatment.

Ratcliffe et al., 2002 (98)

The questionnaire was administered to individual patients at regular intervals during the course of their treatment. The questionnaire was administered initially to all eligible patients whose first language was English at the point of listing, then to patients still waiting to receive a transplant at 3, 6, and 12months post listing (no patient in the sample waited longer than 14 months to receive a transplant). The questionnaire was readministered to all eligible patients 3-, 6-, 12-, and 24-months post-transplantation. One reminder was sent to all nonrespondents at each timepoint, approximately 3 weeks after the administration of the initial questionnaire.

Younossi et al., 2001 (96)

Two HRQoL questionnaires were administered. The SF-36 is a widely used and validated generic HRQoL questionnaire, which includes 36 items divided into eight scales. The CLDQ is a validated liver-disease specific HRQoL questionnaire, which includes 29 items divided into six domains (Abdominal Symptoms, Activity, Emotional Function, Fatigue, Systemic Symptoms, and Worry).

10.3.3 HRQoL Results

Mild hepatitis C clinical trial (23)

The mean HRQoL scores were calculated for all cases with mild hepatitis C who completed the EQ-5D at the baseline visit. To estimate the effect of treatment on HRQoL, EQ-5D data had to be available at 24 or 48 weeks post-treatment (or control), otherwise the follow-up HRQoL was defined as missing, and the case was excluded from the main analysis.

Of the 196 cases (98 treatment, 98 controls) included in the mild hepatitis C RCT, 14 patients did not complete a baseline EQ-5D questionnaire (three treatment, 11 controls) and were excluded from the analysis.

Ratcliffe et al., 2002 (98)

Four hundred fifty-five individuals (84%) returned at least one completed questionnaire at any stage of the survey. The majority of respondents had received one transplant during the study period (79%). Eighteen percent of respondents died during the study period. Classification by primary liver disease at the time of referral for transplantation showed that the largest group of respondents had alcoholic liver disease, with primary biliary cirrhosis and sclerosing cholangitis forming the second and third largest groups, respectively. The largest group of non-responders included patients with post-hepatic C cirrhosis, followed by patients with alcoholic liver disease.

Of the 302 patients included, the overall response rate in the observational study was 56%, 60% for patients with moderate disease, 54% for those with cirrhosis and 28% for patients with decompensated cirrhosis. The low response rate for the group with decompensated

cirrhosis meant that there were insufficient data to provide a robust estimate of HRQoL for this group, who were therefore excluded from the analysis.

Younossi et al., 2001 (96)

One hundred and four patients with chronic cholestatic liver disease (75 PBC and 29 PSC) were enrolled into the study. Using both the SF-36 and CLDQ, patients with PBC had greater HRQoL impairment than the so-called "healthy" population ($p < 0.001$). As clinical severity worsened (measured by Child-Pugh class), HRQoL as measured by CLDQ and the physical component summary of the SF-36 deteriorated.

Given that the symptom of pruritus is an important outcome for patients with cholestatic liver disease, the impact of pruritus on patients' HRQoL was assessed. Patients with moderate to severe pruritus had more HRQoL impairment than those without pruritus.

10.3.4 HSUV and disutility results

Summary of utilities sourced from studies described in the sections above is presented in Table 28 below.

Table 28 Overview of health state utility values [and disutilities]

	Results (95% CI)	Instrument	Tariff (value set) used	Comments
HSUVs				
Cirrhotic	0.55 (SD: 0.34)	EQ-5D-5L	UK	Wright et al., 2006 (99)
HCC	0.45	EQ-5D-5L	UK	Wright et al., 2006 (99)
DCC	0.45	EQ-5D-5L	UK	Wright et al., 2006 (99)
Post-liver transplantation	0.67	EQ-5D-5L	UK	Wright et al., 2006 (99)
Cholestatic liver disease	0.84 (SE: 0.15)	HUI	UK	Younossi et al., 2001 (96)

Abbreviations: CI: confidence interval; DCC: decompensated cirrhosis; EQ-5D-5L: EuroQoL 5-dimension 5-level Questionnaire; HCC: Hepatocellular carcinoma; HRQoL: Health-related quality of life; HSUV: Health states utilities value; HUI: health utility index; SD: Standard deviation; SE: Standard error; UK: United Kingdom

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

The dosing schedule for concomitant UDCA was based on the total daily dose received at baseline for patients enrolled in the ELATIVE trial. (18) Throughout the time horizon of the model, the dosing schedule for UDCA (whether received concomitantly or as

monotherapy) was assumed equal across both treatments. To derive the treatment cost per cycle, the number of tablets administered per cycle was calculated by dividing the pack price by the number of tablets per pack. The number of tablets per cycle was then multiplied by price per tablet to derive the treatment acquisition cost per cycle.

Wastage costs were not applied in the economic analysis as it was assumed patients would receive their medication in full tablets. A compliance rate of [redacted] (based on the mean cumulative dose sourced from the ELATIVE study) was applied to the treatment acquisition cost of elafibranor (18). As the average dose per day of UDCA was obtained from patients at baseline in the ELATIVE study, it was not necessary to consider compliance in addition to this. Dose adjustments are not included in the model.

It is assumed that 95% of patients receive concomitant UDCA or UDCA monotherapy, as informed by the ELATIVE trial (10).

Table 29 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Price (DKK)
Elafibranor	80 mg	-	Once daily	No	[redacted]
UDCA	[redacted]	-	Once daily	No	141.48

Abbreviations: DKK: Danish Kroner; mg: Milligram; UDCA: Ursodeoxycholic acid

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

As all treatments are orally administered, no administration costs were applied in the model.

11.4 Disease management costs

11.4.1 Health states costs

Costs associated with the management and monitoring of patients with PBC were captured over the lifetime time horizon of the CEM. Health care resource use (HCRU) for the mild, moderate and high-risk health states in the PBC biomarker component were based on estimates from the Danish clinical expert or sourced from the NICE TA443 submission for OCA (79). Similarly, HCRU for the liver disease component health states (except pre-LT, LT and post-LT) was sourced from the Wright et al. study. (23) Clinical opinion in the TA443 submission suggested that the health state costs for patients in the high-risk health state would be 50% of the health state costs accrued per cycle in the DCC health state. Thus, HCRU for patients in the high-risk health state was assumed to be 50%

of the HCRU associated with DCC. All resource used and frequencies were confirmed with the Danish clinical expert. All costs were inflated to 2024 values.

The cost of liver transplant is assumed equivalent to the cost reported in the 2024 Danish diagnosis-related group (DRG) tariffs (26MP06 Levertransplantation). The cost is applied to patients in the year of transplant (Table 30).

Table 30 Costs incurred in year of liver transplant

Type of cost	Cost (2024 DKK)	Reference
Transplant	837,199.00	Danish DRG tariffs 2024, 26MP06 Levertransplantation (100)

Abbreviations: DKK: Danish Kroner; DRG: Diagnosis-related group

No direct Danish evidence for post-liver transplant follow-up costs was found. Therefore, Swedish evidence of the two years post-liver transplant costs was adapted to the Danish context by applying an exchange rate (Table 31) (83). This Swedish source of post-liver transplant follow-up costs was previously accepted by the DMC in the assessments of patisiran for hereditary teransthyretin-mediated amyloidosis (hATTR) and progressive familial intrahepatic cholestasis (101, 102). [redacted]

Table 31 Costs incurred in years following liver transplant

Type of cost	Cost (2024 DKK) – first 2 years	Cost (2024 DKK) – years 2+	Reference
Post-liver transplant cost	122,375.00	44,500.00	2016 Folkhalsomyndigheten (Swedish) report: Hepatit B-vaccination som ett särskilt vaccinationsprogram. 70,000 1st year + 40,000 2nd year (83). Cost estimates converted from SEK to DKK and inflated.

Abbreviations: DKK: Danish Kroner; SEK: Swedish Kronor

Additionally, costs of immunosuppression were included in the analysis. Immunosuppression treatment was validated with Danish clinical expert, and is in line with Medicinrådet guideline for immunosuppression after liver transplantation (12, 103).

Table 32 Costs of immunosuppression

Therapy	Dose per day	Mg/unit	Units/pack	Cost/pack (DKK)	Reference
Mycophenolate Mofetil	3,000 mg	180	120	1,050.00	Medicinrådet Unit costs catalogue. 2024 (104)
Tacrolimus	Month 0-3: 0.12 Month 3-6: 0.09 Month 6-9: 0.08	1	50	595.48	Medicinrådet Unit costs catalogue. 2024 (105)

	Month 9-12+: 0.07				
Prednisolone	Month 0-3: 15 Month 3-6: 7.5	5	300	99.00	Medicinrådet Unit costs catalogue. 2024 (106)

Abbreviations: DKK: Danish Kroner; mg: Milligram

Due to limited data for the costs associated with re-emergence of PBC, the resource use per cycle in the re-emergence of PBC is assumed to be the same as patients in the high-risk health state.

A list of health states and associated costs in the economic model are presented in Table 33.

Table 33 Disease management costs used in the model

Health state	Resource	Frequency per cycle	Unit cost (DKK)	Reference
Mild	Blood tests	0.25	126.00	Rigshospitalets Labportal (2024). Test code for complete blood count tests included (codes): NPU01961 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU02319 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC) (85).
	Total cost per cycle (DKK)			**31.50**
Moderate	Blood tests	0.25	126.00	Rigshospitalets Labportal (2024). Test code for complete blood count tests included (codes): NPU01961 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU02319 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC) (85).
	Total cost per cycle (DKK)			**31.50**
High	Inpatient days - ICU	0.03	31,847.00	Assumed the same as liver unit
	Inpatient days - HDU	0.03	31,847.00	Assumed the same as liver unit
	Inpatient days - Liver unit	1.68	31,847.00	DRG 2024: 07MA14 (Observation for sygdom i lever, galdeveje eller bugspytkirtel u. endoskopi) (100)
	Inpatient days - General ward	0.39	31,847.00	Assumed the same as liver unit

Health state	Resource	Frequency per cycle	Unit cost (DKK)	Reference
	TIPPS	0.02	96,530.00	DRG-takster 2024: 07MP08 (Andre operationer på lever, galdeveje og bugspytkirtel) (100)
	Hepatic angiographies (pre-and post-contrast)	0.02	17,173.00	DRG-takster 2024: 30PR12 (Angiografi) (100)
	Endoscopies	0.28	18,593.00	DRG-takster 2024: 08MP55 (Endoskopi/artroskopi, øvrige) (100)
	Liver biopsies	0.01	5,242.00	DRG-takster 2024: 05PR02 (Nålebiopsi på kar el. Lymfesystem) (100)
	Outpatient visits - Doctor (consultant-led)	0.67	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
	Outpatient visits - Nurse (non-consultant led)	0.00	-	Not used in DK (7)
	Blood tests	0.67	126.00	Rigshospitalets Labportal (2024). Test code for complete blood count tests included (codes): NPU01961 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU02319 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC) (85).
	Total cost per cycle (DKK)			**75,937.74**
DCC	Inpatient days - ICU	0.06	31,847.00	Assumed the same as liver unit

Health state	Resource	Frequency per cycle	Unit cost (DKK)	Reference
	Inpatient days - HDU	0.06	31,847.00	Assumed the same as liver unit
	Inpatient days - Liver unit	3.35	31,847.00	DRG 2024: 07MA14 (Observation for sygdom i lever, galdeveje eller bugspytkirtel u. endoskopi) (100)
	Inpatient days - General ward	0.78	31,847.00	Assumed the same as liver unit
	TIPPS	0.04	96,530.00	DRG-takster 2024: 07MP08 (Andre operationer på lever, galdeveje og bugspytkirtel) (100)
	Hepatic angiographies (pre-and post-contrast)	0.05	17,173.00	DRG-takster 2024: 30PR12 (Angiografi) (100)
	Endoscopies	0.57	18,593.00	DRG-takster 2024: 08MP55 (Endoskopi/artroskopi, øvrige) (100)
	Liver biopsies	0.02	5,242.00	DRG-takster 2024: 05PR02 (Nålebiopsi på kar el. Lymfesystem) (100)
	Outpatient visits - Doctor (consultant-led)	1.34	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costscatalogue (84)
	Outpatient visits - Nurse (non-consultant led)	0.00	-	Not used in DK (7)
	Total cost per cycle (DKK)			**151,707.49**

Health state	Resource	Frequency per cycle	Unit cost (DKK)	Reference
HCC	Inpatient days - Liver unit	2.72	31,847.00	DRG 2024: 07MA14 (Observation for sygdom i lever, galdeveje eller bugspytkirtel u. endoskopi) (100)
	Inpatient days - General ward	0.93	31,847.00	Assumed the same as liver unit
	Hepatic angiographies (pre-and post-contrast)	0.16	17,173.00	DRG-takster 2024: 30PR12 (Angiografi) (100)
	Endoscopies	0.12	18,593.00	DRG-takster 2024: 08MP55 (Endoskopi/artroskopi, øvrige) (100)
	Liver biopsies	0.08	5,242.00	DRG-takster 2024: 05PR02 (Nålebiopsi på kar el. Lymfesystem) (100)
	Outpatient visits - Doctor (consultant-led)	1.34	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
	Outpatient visits - Nurse (non-consultant led)	0.00	-	Not used in DK (7)
	Total cost per cycle (DKK)			**122,882.85**
LT	LT cost	1.00	837,199.00	Danish DRG tariffs 2024, 26MP06 Levertransplantation (100)

Health state	Resource	Frequency per cycle	Unit cost (DKK)	Reference
	Post-LT (first 2 years)	1.00	122,375.00	2016 Folkhalsomyndigheten (Swedish) report: Hepatit B-vaccination som ett särskilt vaccinationsprogram. 70000 1st year + 40000 2nd year (83). Cost estimates converted from SEK to DKK and inflated.
	LT immunosuppression cost (first year)	1.00	53,792.72	Table 39
	Total cost per cycle (DKK)			**1,013,286.72**
Post-LT	LT immunosuppression cost (subsequent years)	0.25	53,570.12	Table 39
	Post-LT (annual cost)	0.25	44,500.00	2016 Folkhälsomyndigheten (Swedish) report: Hepatit B-vaccination som ett särskilt vaccinationsprogram. 40000 2nd year (83). Cost estimates converted from SEK to DKK and inflated.
	Total cost per cycle (DKK)			**24,517.53**
Re-emergence of PBC	Assumed equal to healthcare resource use of high-risk health state			
	Total cost per cycle (DKK)			**75,937.74**

Abbreviations: DCC: Decompensated cirrhosis; DKK: Danisk Kroner; DRG: Diagnosis-related group; HCC: Hepatocellular carcinoma; HDU: High dependency unit; ICU: Intensive care unit; LT: Liver transplant; PBC: Primary biliary cholangitis; TA: Technology appraisal; TIPPS: Trans jugular intrahepatic portosystemic shunt

11.4.2 Pruritus costs

The percentage of patients who are prescribed medicines for pruritus when treated with UDCA was based on clinical expert opinion and is presented in Table 34 (7).

Table 34 Percentage of patients who receive medicines for pruritus (based on clinical expert opinion)

Drug	Frequency	Percentage of patients cost applies to for patients treated with elafibranor	Percentage of patients cost applies to for patients treated with UDCA
Rifampicin	Once daily	50%	50%
Cholestyramine	Once daily	50%	50%

Abbreviations: UDCA: Ursodeoxycholic acid

Resources associated with monitoring pruritus were sourced from the OCA NICE appraisal. Resource use for mild and CS itch were estimated by a Danish clinical expert (7). The pruritus monitoring resource use was validated with a Danish clinical expert and are presented in Table 35.

Table 35 Pruritus monitoring resource use

	Resource	Resource use per year	Resource use per cycle: all cycles	Unit costs (DKK)	Reference
Mild itch	Outpatient visits (doctor)	1.0	0.25	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
	Outpatient visits follow-up (doctor)	1.0	0.25	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
	Blood test monitoring	1.0	0.25	126.00	Assumed as B-Haemoglobin (107)
CS itch	Outpatient visits (doctor)	2.0	0.50	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
	Outpatient visits follow-up (doctor)	3.0	0.75	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit

Resource	Resource use per year	Resource use per cycle: all cycles	Unit costs (DKK)	Reference
				costs catalogue (84)
Blood test monitoring	3.0	0.75	126.00	Assumed as B-Haemoglobin (107)

Abbreviations: CS: Clinically significant; DKK: Danish Kroner

For both elafibranor and UDCA, the total mild pruritus cost per cycle was 1,077.18, and the total CS pruritus cost per cycle was 1,923.18 (Table 36).

Table 36 Pruritus cost per cycle for elafibranor and UDCA

Pruritus severity	Cost per cycle for elafibranor (DKK)	Cost per cycle for UDCA (DKK)
Mild itch	1,077.18	1,077.18
CS itch	1,923.18	1,923.18

Abbreviations: CS: Clinically significant; DKK: Danish Kroner; UDCA: Ursodeoxycholic acid

11.5 Costs associated with management of adverse events

It was assumed that each AE is only experienced once per patient, and the cost of each AE will be applied within the first cycle of the CEM for elafibranor and UDCA. Costs were multiplied by the frequency of AEs to evaluate the total costs associated with AEs by treatment, as shown in Table 39.

The cost of pruritus was sourced from the NICE TA443 submission (79). The same resources and proportions of patients requiring it were used to estimate costs related to treatment of pruritus.

Table 37 Pruritus adverse event treatment costs

Resource use	Percentage of patients cost applies to	Costs (DKK)	Source
Staff (GP visit)	100%	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
Cholestyramine / 327.10 days	85%	2,028.02	Medicinrådet Unit costs catalogue. 2024 (108)
Rifampicin cost / 327.10 days	15%	1,723.82	Medicinrådet Unit costs catalogue. 2024 (109)
Naltrexone cost / 327.10 days	5%	15,186.79	Medicinrådet Unit costs catalogue. 2024 (110)

Resource use	Percentage of patients cost applies to	Costs (DKK)	Source
Total cost (DKK) (weighted average)	N/A	3,785.73	-

Abbreviations: DKK: Danish Kroner; GP: General practitioner, N/A: Not applicable

For treatment of UTI resource use needed were assumed based on the NHS report evaluating treatment of UTIs in women under 65 years old (111).

Table 38 UTI adverse event treatment costs

Resource use	Number of cases	Percentage	Unit cost (DKK)	Source
GP consultations	1,576	83.33%	1,044.00	Hourly wage of a senior physician. Medicinrådet Unit costs catalogue (84)
Walk-in centre	121	6.41%	1,044.00	Assumed the same as GP consultation
Out-of-hours medical services	97	5.13%	1,044.00	Assumed the same as GP consultation
A&E attendances	97	5.13%	31,847.00	DRG-takster 2024: 07MP10 (100)
Totals	1,891	100%	2,624.19	-

Abbreviations: A&E: Accident and emergency; DKK: Danish Kroner; DRG: Diagnosis-related group; GP: General practitioner; UTI: Urinary tract infection

The model assumes costs associated with fatigue equal to the cost of outpatient visit (non-consultant led), as no drug treatment is recommended for fatigue according to PBC guidelines.

Table 39 Cost associated with management of adverse events

Adverse event	Weighted average cost (DKK)
Pruritus	3,785.73
Urinary tract infection	2,624.19
Fatigue	1,044.00

Abbreviations: DKK: Danish Kroner

11.6 Subsequent treatment costs

Not applicable.

11.7 Patient costs

Not applicable. Both elafibranor and UDCA are administered orally, thus no additional patient costs are anticipated. This should be regarded as a conservative assumption, as any variations in patient costs would likely favor elafibranor.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

The economic model includes end of life costs for patients who die in health states where there is expected to be palliative care. End of life costs are included for patients who die in the DCC and HCC health states and were sourced from published literature (Vestergaards 2023 (86)) and converted to DKK; the details are presented in Table 40.

Table 40 End of life costs considered in the CEM

Health state	End of life cost (DKK)	Source
DCC	84,433.47	Vestergaard *et al.* 2023 (86). Cost per month converted to DKK.
HCC	84,433.47	

Abbreviations: CEM: Cost-effectiveness model; DCC: Decompensated cirrhosis; DKK: Danish Kroner; HCC: Hepatocellular carcinoma

12. Results

12.1 Base case overview

An overview of the base case is presented in Table 41.

Table 41 Base case overview

Feature	Description
Comparator	UDCA
Type of model	Markov model
Time horizon	43 years (lifetime)
Treatment line	Second-line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in ELATIVE trial. Danish population weights were used to estimate disutilities related to pruritus. AE disutilities and health-state utility values were literature-based.
Costs included	• Medicine costs • Health states costs

Feature	Description
	• Costs of adverse events • End-of-life costs
Dosage of medicine	Fixed dose
Average time on treatment	Intervention: [redacted] Comparator: [redacted]
Parametric function for PFS	Intervention: Not applicable Comparator: Not applicable
Parametric function for OS	Intervention: Not applicable Comparator: Not applicable
Inclusion of waste	No
Average time in model health state	
Mild	[redacted]
Moderate	[redacted]
High	[redacted]
DCC	[redacted]
HCC	[redacted]
Pre-LT	[redacted]
LT	[redacted]
Post-LT	[redacted]
Re-emergence of PBC	[redacted]
Death	[redacted]

Abbreviations: DCC: Decompensated cirrhosis; EQ-5D-5L: EuroQoL 5-dimension 5-level Questionnaire; HCC: Hepatocellular carcinoma; LT: Liver transplant; PBC; Primary biliary cholangitis; UDCA: Ursodeoxycholic acid

12.1.1 Base case results

Table 42 Base case results, discounted estimates

	Elafibranor (DKK)	UDCA (DKK)	Difference (DKK)
Medicine costs (treatment costs)	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	N/A	N/A	N/A
Administration	N/A	N/A	N/A
Disease management costs (health state costs, pruritus costs)	1,069,577	2,243,419	-1,190,665
Costs associated with management of adverse events	684	648	37
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	17,957	33,577	-15,620
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (Mild)	[redacted]	[redacted]	[redacted]
Life years gained (Moderate)	[redacted]	[redacted]	[redacted]
Life years gained (High)	[redacted]	[redacted]	[redacted]
Life years gained (DCC)	[redacted]	[redacted]	[redacted]
Life years gained (HCC)	[redacted]	[redacted]	[redacted]
Life years gained (Pre-LT)	[redacted]	[redacted]	[redacted]
Life years gained (LT)	[redacted]	[redacted]	[redacted]
Life years gained (Post-LT)	[redacted]	[redacted]	[redacted]
Life years gained (Re-emergence of PBC)	[redacted]	[redacted]	[redacted]
Life years gained (Dead)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (Mild)	[redacted]	[redacted]	[redacted]

	Elafibranor (DKK)	UDCA (DKK)	Difference (DKK)
QALYs (Moderate)	[redacted]	[redacted]	[redacted]
QALYs (High)	[redacted]	[redacted]	[redacted]
QALYs (DCC)	[redacted]	[redacted]	[redacted]
QALYs (HCC)	[redacted]	[redacted]	[redacted]
QALYs (Pre-LT)	[redacted]	[redacted]	[redacted]
QALYs (LT)	[redacted]	[redacted]	[redacted]
QALYs (Post-LT)	[redacted]	[redacted]	[redacted]
QALYs (Re-emergence of PBC)	[redacted]	[redacted]	[redacted]
QALYs (Dead)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

Abbreviations: DCC: Decompensated cirrhosis; DKK: Danisk Kroner; HCC: Hepatocellular carcinoma: ICER: Incremental cost-effectiveness ratio; N/A: Not applicable; PBC:Primary biliary cholangitis; UDCA: Ursodeoxycholic acid

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The CEM one-way sensitivity analysis includes all model parameters.

Table 43 below summarizes results for 10 most impactful parameters in the model.

Table 43 One-way sensitivity analyses results

	Distribution	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Elafibranor compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Distribution	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Health state cost – High						
Health state cost – DCC						
Liver disease transition: High to DCC						
Elafibranor clinically significant itch at Month 12+						
Liver disease transition: DCC to Pre-LT						
Per-cycle excess mortality probability: DCC						
Liver disease transition: High to Pre-LT						

	Distribution	Change	Reason / Rationale / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Health state cost – LT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinically significant itch disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCC: Decompensated cirrhosis; DKK: Danish Kroner; ICER: Incremental cost effectiveness ratio; LT: Liver transplant; QALY: Quality-adjusted life-years

[redacted]

[redacted]

12.2.2 Probabilistic sensitivity analyses

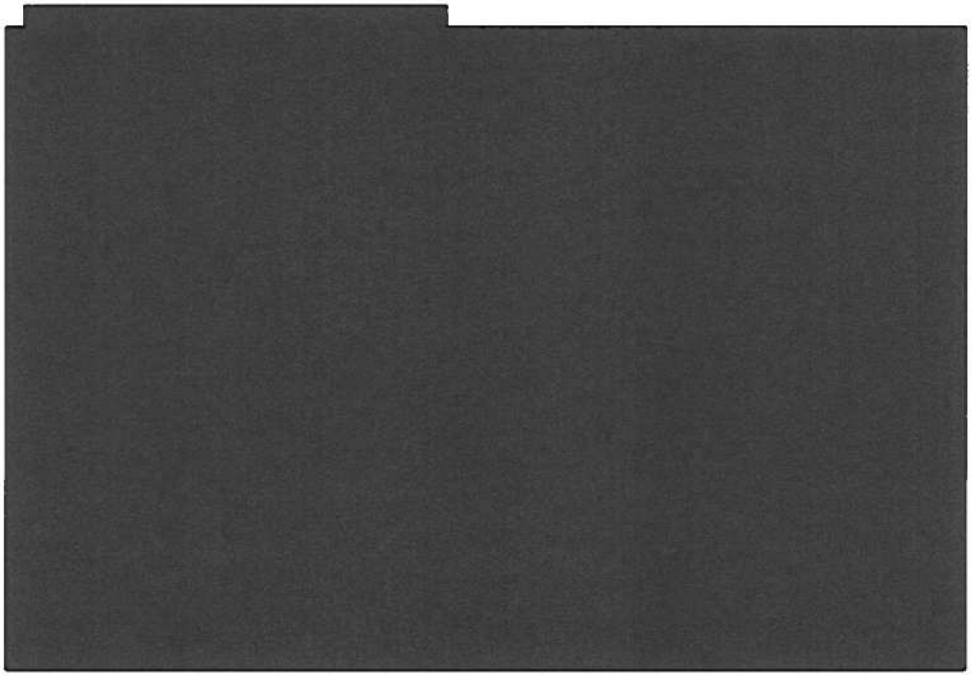
The results of the PSA (for 1,000 iterations) are presented in Table 44, which also presents results from the deterministic analysis for comparison of elafibranor and UDCA. This analysis supports the conclusions from the deterministic analysis.

Table 44 Probabilistic sensitivity analysis results

	Analysis	Incr. costs, DKK	Incr. QALYs	Incremental cost per QALY (DKK)
Elafibranor vs UDCA	Deterministic	[redacted]	[redacted]	[redacted]
	Probabilistic	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Kroner; QALY: Quality-adjusted life years; UDCA: Ursodeoxycholic acid

The result of the cost-effectiveness analyses is presented in a cost-effectiveness plane in Figure 18. The cost-effectiveness acceptability curve is shown in Figure 19.



[redacted]

13. Budget impact analysis

The incidence and prevalence of patients with PBC who do not respond to UDCA in Denmark over the past five years are detailed in section 3.2. For the budget impact model, an additional assumption was incorporated: [redacted] of patients who do not respond to UDCA in Denmark will receive second-line treatment. Consequently, the total number of prevalent patients receiving second-line treatment is [redacted]), and the annual number of incident patients is [redacted]

For the budget impact analysis calculations, it was assumed that in the first year, the total population included [redacted] For subsequent years, it was assumed that the total number of patients receiving second-line treatment would increase by [redacted]

Market shares were allocated in a [redacted] with the assumption that only [redacted] of patients would be treated with elafibranor.

Number of patients (including assumptions of market share)

[redacted]

Year 1 Year 2 Year 3 Year 4 Year 5

Recommendation

Elafibranor	0	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
UDCA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Elafibranor	0	0	0	0	0
UDCA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: UDCA: Ursodeoxycholic acid

Budget impact

Table 46 Expected budget impact of recommending the medicine for the indication

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

Abbreviations: DKK: Danish Kroner

14. List of experts

Table 47 Clinicians consulted for the development of this application

Name	Job function	Workplace
[redacted]	[redacted]	[redacted]

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Appendix A. Main characteristics of studies included

Table 48 Main characteristic of studies included

Trial name: ELATIVE	NCT number: NCT04526665
Objective	Evaluate the efficacy and safety of elafibranor in patients with PBC
Publications – title, author, journal, year	Kowdley, KV; Bowlus, CL; Levy, C; et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med. 2024;390(9): p. 795-805 (10)
Study type and design	Phase III, randomised, double-blind, placebo-controlled, parallel group study, followed by open-label long-term extension. Enrolled patients were randomly assigned 2:1 using an interactive voice- or web-response system. Patients were stratified at baseline according to two factors: ALP >3 x ULN or TB > ULN, and WI-NRS score ≥4. The investigators, participants, and study personnel were blinded to the treatment. The ELATIVE trial is ongoing.
Sample size (n)	161 patients with PBC and inadequate response or intolerance to UDCA randomised to elafibranor (n=108) or placebo (n=53)
Main inclusion criteria	• Informed consent • Males or females age of 18 to 75 years inclusive • PBC diagnosis as demonstrated by at least 2 of 3 diagnostic factors: o ALP elevated for ≥6 months prior to randomization o Positive AMA titre or presence of PBC-specific ANA o Liver biopsy consistent with PBC • UDCA for at least 12 months prior and at stable dose for ≥3 months, or unable to tolerate UDCA treatment • ALP ≥1.67 x ULN[a] • TB ≤2 x ULN[b] • Females must be of non-childbearing potential or must be using highly effective contraception for the full duration of the study and for 1 month after the last drug intake
Main exclusion criteria	• History or presence of other concomitant liver disease, including: HAV, HBV, HCV, AIH, PSC, ALD, NASH, Gilbert's syndrome, or alpha-1-antitrypsin deficiency • History of: o Liver transplant, or current placement on liver transplant list o MELD-Na score ≥12

	○ Signs and symptoms of cirrhosis/portal hypertension ○ Hepatorenal syndrome • Markers of liver damage, such as: ○ ALT and/or AST >5 x ULN ○ Platelet count <150 x 103/µL ○ Albumin <3.0 g/dL ○ Known pregnancy or lactating (female patients) ○ Severely advanced patients according to Rotterdam criteria (TB >ULN and albumin <LLN) • Prohibited medications: ○ Fibrates and glitazones (2 months prior to screening) ○ OCA, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, budesonide and other systemic corticosteroids (3 months prior to screening) ○ Immunotherapy directed against interleukins or other cytokines or chemokines (12 months prior to screening)
Intervention	108 patients received elafibranor 80 mg once daily, in addition to SoC (UDCA) (if applicable)
Comparator(s)	53 patients received placebo once daily, in addition to SoC (UDCA) (if applicable)
Follow-up time	• Double blind phase: maximum of 104 weeks, or until the last completed Week 52 visit • Long term extension: up to 5 years, or until the patient's total treatment duration is 6 years Primary analyses were done at week 24/52 (depending on the endpoint) and are reported in the main part of the dossier. Additional long-term data are reported in Appendix K.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • Primary endpoint: biochemical cholestasis response at week 52, defined as ALP <1.67 x ULN and TB ≤ULN and ALP decrease of ≥15% from baseline. • Key secondary endpoints: ALP normalisation at week 52; and change in pruritus intensity (WI-NRS) from baseline through week 52 and through week 24 among patients with moderate-to-severe pruritus (defined as a WI-NRS score of ≥4 at baseline)

- Other relevant endpoints: Change from baseline in ALP and TB levels; change from baseline in HRQoL measures at week 52, including the PBC–40, 5D-Itch, PROMIS and EQ-5D-5L; response to treatment at Week 52 according to Paris II criteria (ALP ≤1.5 x ULN, AST ≤1.5 x ULN and TB ≤ULN); safety

Other endpoints (results not included in this application):

Secondary:

- ALP response defined as 10%, 20% and 40% ALP reduction from baseline at Week 52
- Response to treatment at Week 52 according to:
  - ALP <1.5 x ULN, ALP decrease ≥40% and TB ≤ULN
  - ALP <3 x ULN, AST <1 mg/dL (Paris I)
  - TB response rate of 15% change
  - Normalisation of abnormal TB and/or albumin (Rotterdam)
  - TB ≤0.6 x ULN
  - ALP ≤1.67 x ULN and TB ≤1 mg/dL
  - No worsening of TB defined as level of TB at Week 52 <ULN or no increase from baseline of more than 0.1 x ULN at Week 52
  - Complete biochemical response defined as normal ALP; TB; AST; ALT; albumin; and INR
- PBC risk scores at Week 52: UK PBC score and GLOBE score
- Response based on the normalisation of bilirubin at Week 52
- Response based on the normalisation of albumin at Week 52
- Change from baseline to Week 52 in hepatobiliary injury and liver function as measured by AST, ALT, GGT, 5-NT, total and conjugated bilirubin, albumin, INR, and ALP fractionated (hepatic)
- Change from baseline to Week 52 in biomarkers of inflammation as measured by hsCRP, fibrinogen, haptoglobin and TNF-a
- Change from baseline to Week 52 in immune response as measured by IgG and IgM
- Change from baseline to Week 52 in biomarkers, and non-invasive measures of hepatic fibrosis as measured by ELF (HA, PIINP, TIMP-1), PAI-1, TGF-β, CK-18 (M65 and M30), Pro-C3 and liver stiffness measured by TE (continuous)
- Change from baseline to Week 52 in lipid parameters as measured by TC, LDL-C, HDL-C, calculated VLDL-C and TG
- Change from baseline to Week 52 in FPG
- Change from baseline to Week 52 in bile acids and biomarkers of bile acid synthesis as measured by bile acids, C4 and FGF-19
- Proportion of responders in PBC WI-NRS according to clinically meaningful change; at least 30% reduction; and one point, two points or three points decrease in score from baseline through Week 52 and through Week 24 in patients with a baseline NRS score ≥4
- Proportion of patients with no worsening of pruritus from baseline through Week 52 and through Week 24 as measured by the PBC WI-NRS
- Change from baseline in ESS
- Change from baseline to Week 52 in serum markers of bone turnover and in bone mineral density (hip and lumbar) assessed by DEXA scanning
- Onset of clinical outcomes described as a composite endpoint composed of:
  - MELD-Na >14 for patients with baseline MELD-Na <12
  - Liver transplant

- Uncontrolled ascites requiring treatment
- Hospitalisation for new onset or recurrence of any of the following:
  - Variceal bleed
  - Hepatic encephalopathy defined as West-Haven/Conn score of 2 or more
  - Spontaneous bacterial peritonitis
- Death

- Safety and tolerability as assessed by:
  - Physical examination, vital signs, medical history, ECG
  - Chemistry and haematology
  - Liver markers
  - Renal biomarkers (including urinalysis)
  - Other biochemical safety markers
- PK assessments by GFT505 and GFT1007 concentrations measurement in plasma at steady state following daily oral administration at 80 mg

Exploratory:

- Change from baseline in the histological scores:
  - Fibrosis stage according to Nakanuma scoring
  - Bile duct loss scores
  - Cholangitis activity
  - Interface Hepatitis activity
  - Stage of disease (Sum of Fibrosis stage by Nakanuma and Bile duct loss score)
  - Other exploratory scores (fibrosis according to Ishak scoring, portal inflammation, ductular reaction, cholestasis, concentric periductal fibrosis)

Correlation of Fibrosis scores with non-invasive markers of fibrosis (liver stiffness, ELF test and ProC3)

Additionally, apart from histology (if applicable) and PK assessments, the same endpoints as for the DB period will be collected over the LTE period to assess the maintenance of efficacy and safety of the treatment.

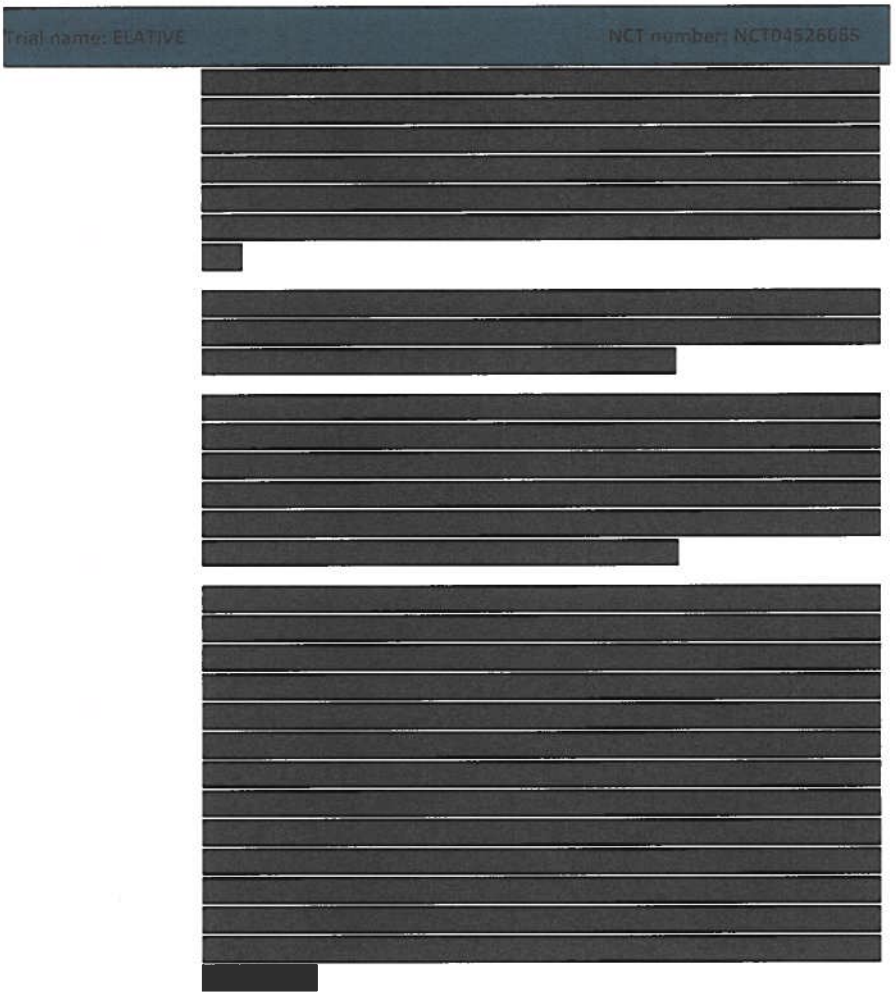
Method of analysis

Analyses of the primary endpoint and the key secondary endpoint of ALP level normalisation at week 52 were performed in the ITT population with the use of the exact CMH test, stratified according to the randomization factors. For these two binary endpoints, a composite strategy of imputation of nonresponse among patients who had intercurrent events (discontinuation of the trial regimen or use of rescue therapy for primary biliary cholangitis) before week 52 was applied. Response data for patients who did not have intercurrent events and had missing data at week 52 were imputed with data from the closest non-missing assessment from the double-blind period before or after the date of the theoretical week 52 visit.

Change from baseline in the WI-NRS score through week 52 and through week 24 in patients with moderate-to-severe pruritus was compared with the use of a mixed model for repeated measures (MMRM).

Subgroup analyses

[redacted]



Other relevant information	Analysis sets: • **ITT set:** All randomised patients • **Pruritus ITT set:** All patients from the ITT Analysis Set with baseline PBC Worst Itch NRS score ≥4 • **PP set:** All patients from the ITT set without any major protocol deviation affecting the primary efficacy endpoint • **Pruritus PP set:** All patients from the Pruritus ITT Analysis Set without any major protocol deviation or event affecting the primary efficacy endpoint and/or the second and third key secondary endpoints • **Safety set:** All patients who were administered at least one dose of study drug

Footnotes: [a] ULN = 104 U/L for females, 129 U/L for males; [b] To ensure inclusion of a relevant ratio of patients with substantial risk of long-term clinical outcomes or moderate disease stage, it was planned that ~10% of randomised patients would be moderately advanced per Rotterdam Criteria (TB >ULN or ALB <LLN) and ~20% would have a TB >0.6x ULN (patients at risk of progression).
Abbreviations: 5D-Itch: 5-dimensions pruritus scale; AE: Adverse event; AESI: Adverse event of special interest; AIH: autoimmune hepatitis; ALB: Albumin; ALD: alcohol-related liver disease; ALP: Alkaline phosphatase; CI: Confidence interval; CMH: Cochran-Mantel-Haenszel; ECG: Electrocardiogram; ELF: Enhanced Liver Fibrosis; EQ-

5D-5L: European Quality of Life 5 Dimensions 5 Level Version; ESS: Epworth Sleepiness Scale; FPG: Fasting plasma glucose; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; ICE: Intercurrent event; ITT: Intent-to-treat; LLN: Lower limit of normal; MELD-Na: Model for End Stage Liver Disease-Sodium; NASH: non-alcoholic steatohepatitis; OCA: Obeticholic acid; PBC: Primary biliary cholangitis; PSC: primary sclerosing cholangitis; PP: Per protocol; PROMIS: Patient Reported Outcome Measurement Information System; SAE: Serious adverse event; SoC: Standard of care; TB: Total bilirubin; TE: Transient elastography; UDCA: Ursodeoxycholic acid; UK: United Kingdom; ULN: Upper limit of normal; WI-NRS: Worst itch Numeric rating scale
Sources: (10, 18)

Appendix B. Efficacy results per study

Results per study

Table 49 Results per study

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Biochemical cholestasis response at week 52 (ITT)	Elafibranor	108	50.9% (41.6; 60.2) Events: 55	47.2%	32.0; 56.9	<0.0001	OR: 37.6	7.6; 302.2	<0.0001	The response rates at Week 52 were compared between the treatment groups using the exact CMH test stratified by the randomization strata. The estimate of the OR and the corresponding 95% exact CI and exact p-value were provided. In addition, the difference between the treatment groups and 95% CI were calculated using the Newcombe method stratified by randomization strata. For consistency, the Wilson score 95% CI for single proportion was provided for within group description. In case of missing data at Week 52 (visit 6) for participants without intercurrent event, the closest non-missing assessment from the DB treatment period before or after the	(2, 10)
	Placebo	53	3.8% (1.0; 12.8) Events: 2								

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
										theoretical visit 6 date was taken into account.	
Biochemical cholestasis response at week 78 (ITT)	Elafibranor	27	70% (NR) Events: 19	70%	NA	NA	NA	NA	NA	Biochemical cholestasis response at Week 78 are presented descriptively.	(80)
	Placebo	13	0% (NR) Events: 0								
Patients with ALP normalisation at week 52 (ITT)	Elafibranor	108	14.8% (9.3; 22.7) Events: 16	14.8%	6.1; 22.7	<0.002	OR: infinity	2.8; infinity	0.0019	The ALP normalisation rates at Week 52 were compared between the treatment groups using the exact CMH test stratified by the randomization strata. The estimate of the OR and the corresponding 95% exact CI and exact p-value were provided. In addition, the difference between the treatment groups and 95% CI were calculated using the Newcombe method stratified by randomization strata. For consistency, the Wilson score 95% CI for single proportion was provided for within group description.	(2, 10)
	Placebo	53	0.0% (0.0; 6.8) Events: 0								

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
										In case of missing data at Week 52 (Visit 6) for participants without intercurrent event, the closest non-missing assessment from the DB treatment period before or after the theoretical V6 date was taken into account.	
Patients with ALP normalisation at week 78 (ITT)	Elafibranor	27	19% (NR) Events: 5	19%	NA	NA	NA	NA	NA	ALP normalisation at Week 78 are presented descriptively.	(80)
	Placebo	13	0% (NR) Events: 0								
Change in PBC WI-NRS score from baseline at week 52 (Pruritus ITT)	Elafibranor	44	LS mean: -1.93 (-2.60; -1.26)	LS means difference: -0.78	-1.99; 0.42	0.1970	NA	NA	NA	[redacted] All 4-week periods until Week 52 were included as fixed effects along with treatment, treatment by 4-week period	(2, 10, 18)
	Placebo	22	LS mean: -1.15 (-2.14; -0.15)								

Results of ELATIVE (NCT04526665)

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										interaction, baseline PBCWI-NRS values and the stratification factor of ALP >3x ULN or TB >ULN). An unstructured variance-covariance structure was used. The estimated LS means, treatment differences, together with the 95% CIs and p-value were presented separately for the overall period (i.e. through Week 52) and for each 4-week period until Week 52. Missing values were handled within the analysis itself with the assumption that the model specification is correct, and that the data will be MAR. [redacted]	
Change in WI-NRS score from	Elafibranor	44	LS mean: −1.60 (-2.25; -0.95)	-1.49; 0.80		0.5522	NA	NA	NA	The analysis was conducted by modelling the change from baseline	(2, 10, 18)

Results of ELATIVE (NCT04526665)										
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
baseline at week 24 (Pruritus ITT)	Placebo	22	LS mean: −1.26 (-2.20; -0.31)	LS means difference: -0.34						values over the entire duration between baseline and Week 24 (the average of NRS changes from baseline for the 6 four-week periods) via a MMRM. The 4-week periods were considered as a repeated variable within a participant. All 4-week periods until Week 24 were included as fixed effects along with treatment, treatment by 4-week period interaction, baseline PBC WI-NRS values and the stratification factor of ALP >3x ULN or TB >ULN. An unstructured variance-covariance structure was used. The estimated LS means, treatment differences, together with the 95% CIs and p-value were presented separately for the overall period (i.e. through Week 24) and for each 4-week period until Week 24. See above for handling of missing values.	

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Change in ALP level from baseline at week 52 (ITT)	Elafibranor	108	LS mean: -117.0 U/L (-134.4; -99.6)	LS means difference: -111.7 U/L	[redacted]	[redacted]	NA	NA	NA	Analysis used the MMRM with treatment, visits (until week 52) and treatment by visit interaction as fixed factor and adjusting for baseline values and stratification factors..	(10, 18)
	Placebo	53	LS mean: -5.3 U/L (-30.4; 19.7)								
Change in ALP level from baseline at week 78 (ITT)	Elafibranor	26	Mean: -135.3 U/L (NR)	Difference: -166.3 U/L	NA	NA	NA	NA	NA	Change from baseline in biochemical parameters to Week 78 are presented descriptively.	(80, 88)
	Placebo	12	Mean: 31.0 U/L (NR)								
Change in TB level from baseline at week 52 (ITT)	Elafibranor	108	LS mean: −0.1 µmol/L (−1.0; 0.7)	LS means difference: -1.3 µmol/L	[redacted]	[redacted]	NA	NA	NA	Analysis used the MMRM with treatment, visits (until week 52) and treatment by visit interaction as fixed factor and adjusting for baseline values and stratification factors.	(10, 18)
	Placebo	53	LS mean: 1.1 µmol/L (−0.1; 2.4)								
Change in TB level from	Elafibranor	25	Mean: -1.21 µmol/L (NR)	Difference: -4.29	NA	NA	NA	NA	NA		(80, 88)

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
baseline at week 78 (ITT)	Placebo									Change from baseline in biochemical parameters to Week 78 are presented descriptively.	
Treatment response based on Paris II criteria at week 52 (ITT)	Elafibranor				22.3; 47.7	p<0.0001	OR: 16.65			Same as for biochemical cholestasis response.	(18, 82)
	Placebo										
Treatment response based on Paris II criteria at week 78 (ITT)	Elafibranor				NA	NA	NA	NA	NA		(18)
	Placebo										
Change in PBC–40 itch domain from baseline at week 52 (Pruritus ITT)	Elafibranor			LS means difference: -2.3	-4.0; -0.7	0.0070	NA	NA	NA	Analysis used the MMRM with treatment, visits (until week 52) and treatment by visit interaction as fixed factor and adjusting for baseline values and the stratification factor of ALP > 3x ULN or TB > ULN.	(10, 18, 81)
	Placebo										

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change in 5D-Itch total score at week 52 (Pruritus ITT)	Elafibranor			LS means difference: −3.0	-5.5; -0.5	0.0199	NA	NA	NA		(10, 18)
	Placebo										
Change in PROMIS Fatigue Short Form 7a score from baseline at week 52 (ITT)	Elafibranor						NA	NA	NA		(18)
	Placebo										
Change in PROMIS Fatigue Short Form 7a score from baseline at week 52	Elafibranor						NA	NA	NA		
	Placebo										

[redacted]

Results of ELATIVE (NCT04526665)											
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Change in PBC-40 Fatigue domain from baseline at week 52 (ITT)	Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	(18)
	Placebo	[redacted]	[redacted]								
Change in PBC-40 Fatigue domain from baseline at week 52 [redacted]	Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	
	Placebo	[redacted]	[redacted]								

Abbreviations: 5-D: 5-dimensions pruritus scale; ALP: Alkaline phosphatase; CI: Confidence interval; CMH: Cochran-Mantel-Haenszel; DB: Double-blind; EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level Version; ESS: Epworth Sleepiness Scale; LS: Least squares; MAR Missing at random; MMRM: Mixed model for repeated measures; NA: Not available; OR: Odds ratio; PROMIS: Patient Reported Outcome Measurement Information System; TB: Total bilirubin; ULN: Upper limit of normal; VAS: Visual analogue scale; WI-NRS: Worst itch numeric rating scale

Appendix C. Comparative analysis of efficacy

Not applicable

Appendix D. Extrapolation

D.1 Extrapolation of time to discontinuation

D.1.1 Data input

Parametric distributions were used to extrapolate the all-cause time to discontinuation (TTD) of elafibranor treatment during and beyond the ELATIVE study duration. Estimates from the extrapolations beyond the ELATIVE study period were used to model the movement of patients between the on and off-treatment PBC biomarker health states.

For patients receiving elafibranor, parametric distributions were fitted to the Kaplan Meier all-cause TTD data.

D.1.2 Model

Independent parametric distributions were fitted to elafibranor Kaplan-Meier data (exponential, Weibull, Gompertz, log-logistic, lognormal, generalized Gamma).

D.1.3 Proportional hazards

Not applicable.

D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 50 shows all estimated distributions, along with their respective Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for both treatment arms. Lower AIC and BIC values indicate a better statistical fit of the curves to the Kaplan Meier. Thus, the exponential curve is considered the best fit to the data. As the AIC of exponential, Weibull, Gompertz and log-logistic curves are all within 2 points, they may be considered equally good statistical fits.

Table 50 AIC and BIC statistics from all-cause TTD parametric distributions

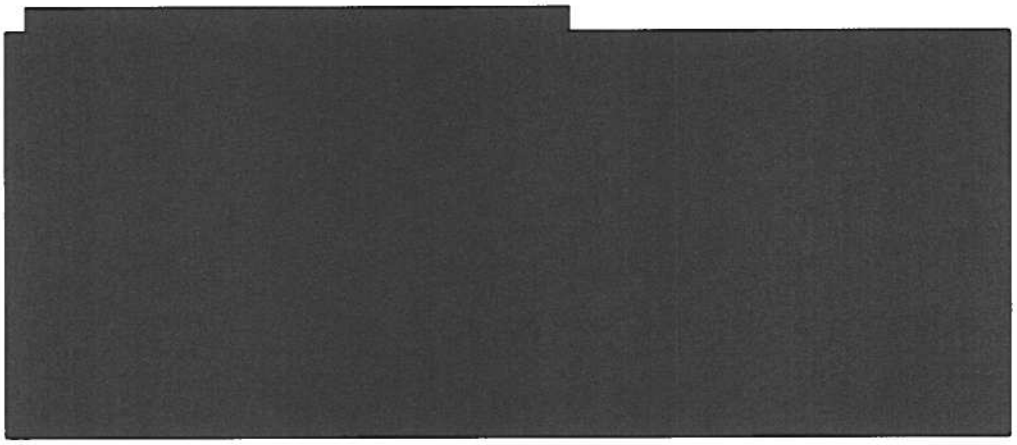
Distribution	AIC	BIC
Exponential	258.84	261.51
Weibull	260.81	266.16
Gompertz	260.56	265.90
Log-logistic	260.69	266.04
Lognormal	260.88	266.23

Generalized Gamma	262.96	270.98

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; TTD: time to discontinuation

D.1.5 Evaluation of visual fit

All considered curves provide good visual fit to the Kaplan-Meier KM data for elafibranor from the ELATIVE trial. However, all distributions underestimate the number of patients on treatment in the initial period slightly.



D.1.6 Evaluation of hazard functions

Not applicable.

D.1.7 Validation and discussion of extrapolated curves

Exponential, Weibull and Gompertz provide good statistical fit to the Kaplan-Meier data from the ELATIVE trial. Based on AIC and BIC values, the exponential distribution would be considered the best fit, however, according to clinical expert opinion, a more suitable parametric distribution to reflect treatment duration of elafibranor in a clinical setting is expected to be flatter compared to other distributions. As such the Gompertz distribution may be considered the most appropriate. (7, 12) Clinical expert validation has indicated that treatment discontinuation is often observed at the onset of therapy, primarily due to the occurrence of adverse events or a lack of treatment efficacy. Patients who do not discontinue treatment during this initial period are likely to remain on therapy for an extended duration. To accurately capture this clinically observed trend, the Gompertz distribution was selected as the most appropriate model for time-to-treatment discontinuation (TTD) extrapolation in the base case analysis.

D.1.8 Adjustment of background mortality

Not applicable.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

Table 51 Serious TEAEs observed in the ELATIVE trial (DB period)

MedDRA PT	Elafibranor (N=103)	Placebo (N=53)
Acute kidney injury	3 (2.8)	1 (1.9)
Hip fracture	2 (1.9)	0 (0)
Abdominal hernia	1 (0.9)	0 (0)
Appendicitis	1 (0.9)	0 (0)
Ascites	1 (0.9)	0 (0)
Asthma	1 (0.9)	0 (0)
Biliary sepsis	1 (0.9)	0 (0)
Blood bilirubin increased	1 (0.9)	0 (0)
Cardiac arrest	1 (0.9)	0 (0)
Cardiac failure	1 (0.9)	0 (0)
Cholecystitis acute	1 (0.9)	0 (0)
Crohn's disease	1 (0.9)	0 (0)
Edema peripheral	1 (0.9)	0 (0)
Hemorrhagic stroke	1 (0.9)	0 (0)
Hypervolemia	1 (0.9)	0 (0)
Multiple fractures	1 (0.9)	0 (0)
Multiple organ dysfunction syndrome	1 (0.9)	0 (0)
Osteonecrosis	1 (0.9)	0 (0)
Parkinsonism	1 (0.9)	0 (0)
Pneumonia	1 (0.9)	0 (0)
Pulmonary embolism	1 (0.9)	0 (0)
Pulseless electrical activity	1 (0.9)	0 (0)

MedDRA PT	Elafibranor (N=108)	Placebo (N=53)
Rhabdomyolysis	1 (0.9)	0 (0)
Retroperitoneal hematoma	1 (0.9)	0 (0)
Sudden hearing loss	1 (0.9)	0 (0)
Tremor	1 (0.9)	0 (0)
Anxiety	0 (0)	1 (1.9)
Cataract	0 (0)	1 (1.9)
COVID-19	0 (0)	1 (1.9)
Invasive ductal breasts carcinoma	0 (0)	1 (1.9)
Pain	0 (0)	1 (1.9)
Papillary thyroid cancer	0 (0)	1 (1.9)
Procedural pain	0 (0)	1 (1.9)
Syncope	0 (0)	1 (1.9)
Urinary tract infection	0 (0)	1 (1.9)

Abbreviations: DB: Double blind; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred term; TEAE: Treatment-emergent adverse event
Source: Kowdley *et al.* 2024 (10)

Appendix F. Health-related quality of life

Table 52 Pattern of missing data and completion (EQ-5D-5L)

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)
Elafibranor				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3 - Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4 - Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5 - Week 39	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 - Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3 - Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4 - Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5 - Week 39	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 - Week 52	[redacted]	[redacted]	[redacted]	[redacted]

Reference: Data on file Unpublished data 2024.

Table 53 Pattern of missing data and completion (EQ-5D-5L VAS)

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)
Elafibranor				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3 - Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4 - Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5 - Week 39	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 - Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3 - Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4 - Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5 - Week 39	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 - Week 52	[redacted]	[redacted]	[redacted]	[redacted]

Reference: Data on file Unpublished data 2024.

Health-related quality of life estimated based on the ELATIVE trial data

UK value set

The UK utility analysis was conducted in two phases. The first phase involved mapping of EQ-5D-5L data collected in the ELATIVE trial to EQ-5D-3L utilities, using the Hernandez-Alava mapping. Subsequently, regression and supplementary descriptive analyses were performed on the EQ-5D-3L utility values. The Hernandez-Alava mapping was performed on the EQ-5D-5L domain responses in R, using the code provided by the NICE decision support unit (DSU). (112, 113)

In the regression analysis, a linear mixed effect model for repeated measures was used to estimate the utility values of each biomarker health state, to account for correlations between repeated measurements within each patient. (119) This model contained both fixed effects and random effects; unique patient identifier was fitted as a random effect component while biomarker health state and itch severity were fixed effect components. Pruritus was included as a covariate in the utility analyses, to determine whether severity of pruritus also predicts HRQoL in combination with the risk of disease progression. [redacted]

Following this, the mean utility within each health state was estimated. The analysis was performed using the lme4 package in R. (114) The results of the linear mixed effects regression analysis of the EQ-5D-3L utilities obtained using the mapping algorithm by Hernandez-Alava et al. 2020 are presented in Table 54. (112)

Table 54 Results of the regression analysis for the overall population: United Kingdom

	Estimate	SE	P-value
(Intercept)	[redacted]	[redacted]	[redacted]
Moderate risk	[redacted]	[redacted]	[redacted]
High risk	[redacted]	[redacted]	[redacted]
Mild itch	[redacted]	[redacted]	[redacted]
Mild itch	[redacted]	[redacted]	[redacted]
CS itch	[redacted]	[redacted]	[redacted]

Abbreviations: CS: Clinically significant; SE: Standard error

As reported in Table 54, the p-value for the risk variables (>0.05) demonstrates a non-statistically significant difference between the utility of patients in the mild risk health state compared to patients in the moderate and high risk health states, respectively, at a 5% significance level. However, there are numerical differences in the utility of patients across risk health states, with utility decreasing as risk increases. This is consistent with HSUVs identified from published literature where differences in HRQoL are observed between mild risk and high risk, and between moderate risk and high risk (23, 96).

The p-value for the mild itch variable (> 0.05) demonstrates a non-statistically significant difference between the utility of patients with no itch compared to patients with moderate itch. The p-value of the CS itch variable (< 0.05) demonstrates a statistically significant difference in utility of patients with no itch compared to patients with CS itch, at a 5% significance level.

From the final mixed effects regression models, described by Table 54, the final HSUVs were be derived. Table 55 presents the HSUVs derived from the regression analysis based on the EQ-5D-5L from ELATIVE using the Hernandez-Alava et al. (2020) algorithm (112). The HSUVs show a trend for decreasing utility as the risk of progression increases. The disutility values for mild and CS itch derived from the regression analyses are also presented in Table 55. The disutility values demonstrate a greater reduction in utility for patients with CS itch compared to mild itch, relative to patients with no itch (112).

Table 55 HSUVs derived from the regression analysis: United Kingdom

HSUV	
Mild risk	
Moderate risk	
High risk	
Disutility value	
No itch	
Mild itch	
CS itch	

Abbreviations: CS: clinically significant; HSUV: health state utility values.

Descriptive analysis: EQ-5D-3L UK tariff utilities

A descriptive, means-based analysis of EQ-5D-3L UK utilities was conducted at baseline and at Weeks 13, 26, 39 and 52, across the elafibranor and placebo arms. Table 56 presents the results of the descriptive analyses for elafibranor and placebo, including the number of observations and the mean and standard error (SE) of the utility estimates. The difference between the utilities of elafibranor versus placebo at each timepoint, 95% CI, and associated p-value are also presented based on the results from the linear regression analysis. The p-value for the treatment variable (> 0.05) demonstrates a non-statistically

significant difference between the utility of patients treated with elafibranor and patients treated with placebo, at a 5% significance level.

Table 56 Descriptive analysis of EQ-5D-3L UK tariff utilities

Timepoint	Elafibranor		Placebo		Difference elafibranor versus placebo (95% CI), p-value
	N	Mean (SE)	N	Mean (SE)	
Baseline	[redacted]				
Week 13	[redacted]				
Week 26	[redacted]				
Week 39	[redacted]				
Week 52	[redacted]				

Abbreviations: CI: confidence interval; SE: standard error.

Figure 21 presents the mean change in EQ-5D-3L UK utilities from baseline across the elafibranor and placebo arms. The figure demonstrates no clear trend in EQ-5D-3L utility score change over time in either group, though numerically the utilities in across both treatment arms tended to be slightly higher at subsequent timepoints than at baseline.

[redacted]

Danish value set

Health states utilities analysis using ELATIVE trial data was repeated using the EQ-5D-5L Danish value set. (115)

The EQ-5D-5L utilities were obtained by applying the Danish EQ-5D-5L value set by Jensen et al. (2021) to convert the EQ-5D-5L observations into a single summary index (utility value). (97) [redacted]

As reported in Table 57, the p-value for the risk variables (> 0.05) demonstrates a non-statistically significant difference between the utility of patients in the mild risk health state compared to patients in the moderate and high-risk health states, respectively, at a 5% significance level. HSUVs identified from published literature showed differences in HRQoL between mild risk and high risk, and between moderate risk and high risk, respectively (23, 96). The results of the regression analysis are not consistent with the published literature, indicating the same difference in utility estimate for the moderate and high-risk health states, compared to the mild risk health state.

The p-value for the mild itch variable (> 0.05) demonstrates a non-statistically significant difference between the utility of patients with no itch compared to patients with moderate itch. The p-value of the CS itch variable (< 0.05) demonstrates a statistically significant difference in utility of patients with no itch compared to patients with CS itch, at a 5% significance level.

Table 57 Results of the regression analysis for the overall population: Denmark

	Estimate	SE	P-value
(Intercept)	[redacted]	[redacted]	[redacted]
Moderate risk	[redacted]	[redacted]	[redacted]
High risk	[redacted]	[redacted]	[redacted]
Mild itch	[redacted]	[redacted]	[redacted]
CS itch	[redacted]	[redacted]	[redacted]

Abbreviations: CS: Clinically significant; SE: Standard error.

From the final mixed effects regression models, described byTable 57, the final HSUVs were derived. Table 58 presents the HSUVs derived from the regression analysis based on the EQ-5D-5L from ELATIVE using the Jensen et al. (2021) value set. (97) The HSUV for the mild risk state is higher than for the moderate and high risk HSUVs which are identical The disutility values for mild and CS itch derived from the regression analyses are also presented in Table 58. The disutility values demonstrate a greater reduction in utility for patients with CS itch compared to mild itch, relative to patients with no itch.

Table 58 HSUVs derived from the regression analysis: Denmark

HSUV	
Mild risk	[redacted]
Moderate risk	[redacted]
High risk	[redacted]
Disutility value	
No itch	[redacted]
Mild itch	[redacted]
CS itch	[redacted]

Abbreviations: CS: Clinically significant; HSUV: Health state utility values.

The incremental difference in utility between the moderate and high-risk health states is lower than expected from the regression analysis. This is thought to be driven by the low sample size in the high-risk health state, which reduces the reliability of the utility estimates. Consequently, HSUVs derived from these analyses are not used in the CEM base case and are sourced from the literature instead. However, the disutility values for mild

and CS itch derived from the regression analyses are deemed appropriate for use in the CEM base case.

Descriptive analysis EQ-5D-3L Danish tariff utilities

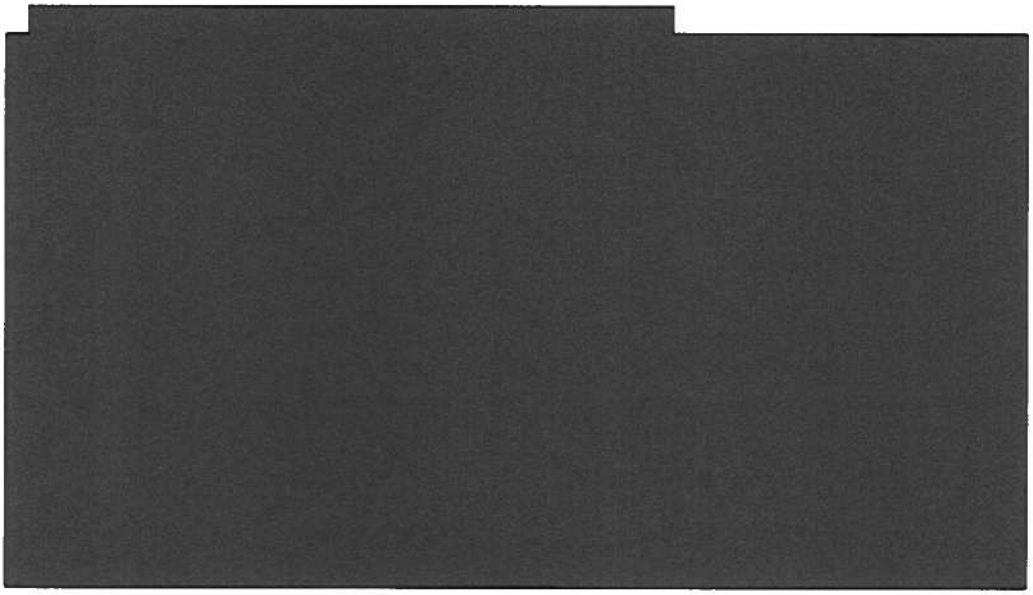
A descriptive, means-based analysis of EQ-5D-5L Danish utilities was conducted at baseline and at Weeks 13, 26, 39 and 52, across the elafibranor and placebo arms. Table **59** presents the results of the descriptive analyses for elafibranor and placebo, including the number of observations and the mean and SE of the utility estimates. The difference between the utilities of elafibranor versus placebo at each timepoint, 95% CI, and associated p-value are also presented based on the results from the linear regression analysis. The p-value for the treatment variable (> 0.05) demonstrates a non-statistically significant difference between the utility of patients treated with elafibranor and patients treated with placebo, at a 5% significance level.

Table 59 Descriptive analysis of EQ-5D-5L Danish tariff utilities

Timepoint	Elafibranor		Placebo		Difference elafibranor versus placebo (95% CI), p-value
	N	Mean (SE)	N	Mean (SE)	
Baseline					
Week 13					
Week 26					
Week 39					
Week 52					

Abbreviations: CS: Clinically significant; SE: Standard error.

Figure 22 presents the mean change in EQ-5D-5L Danish utilities from baseline across the elafibranor and placebo treatment arms. The figure demonstrates no clear trend in EQ-5D-5L utility score over time in either group, though numerically the utilities tended to be higher at subsequent timepoints than at baseline for elafibranor and lower for placebo. Furthermore, the change in utility from baseline was numerically higher for elafibranor than for placebo across all subsequent timepoints.



EQ-VAS analysis

A descriptive, means-based analysis of EQ-VAS scores was conducted at baseline and at weeks 13, 26, 39 and 52, across the elafibranor and placebo arms. Table 60 presents the results of the descriptive analyses for elafibranor and placebo, including the number of observations and the mean and SE of the estimates. The difference between the estimates for elafibranor versus placebo at each timepoint, 95% CI, and associated p-value are also presented based on the results from the linear regression analysis. The p-value for the treatment variable (> 0.05) demonstrates a non-statistically significant difference between the estimates for patients treated with elafibranor and patients treated with placebo, at a 5% significance level.

Table 60 Descriptive analysis of EQ-VAS

Timepoint	Elafibranor		Placebo		Difference elafibranor versus placebo (95% CI), p-value
	n/N (%)	Mean (SE)	n/N (%)	Mean (SE)	
Baseline					
Week 13					
Week 26					

Week 39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS: Clinically significant; SE: Standard error.

Figure 23 presents the mean change in EQ-VAS from baseline across the elafibranor and placebo arms. The figure demonstrates no clear trend in EQ-VAS score over time in either group, though for elafibranor, the utilities tended to be numerically higher at subsequent timepoints than at baseline. Furthermore, the change in utility from baseline was numerically higher for elafibranor than for placebo across all subsequent timepoints.

[redacted]

Appendix G. Probabilistic sensitivity analyses

For all parameters included in the probabilistic sensitivity analysis standard error (SE) was used as a basis for selected distribution parameters. Therefore, in the table below columns with "lower bound" and "upper bound" remains empty. Additionally, for baseline distribution as well as elafibranor and UDCA transition probabilities Dirichlet distribution was used, based on the ELATIVE trial data.

Table 61 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Liver disease transition: Moderate to DCC	0.16%	-	-	Beta
Liver disease transition: Moderate to HCC	0.02%	-	-	Beta
Liver disease transition: Moderate to Pre-LT	0.06%	-	-	Beta
Liver disease transition: High to DCC	2.60%	-	-	Beta
Liver disease transition: High to HCC	0.25%	-	-	Beta
Liver disease transition: High to Pre-LT	1.02%	-	-	Beta
Liver disease transition: DCC to HCC	0.25%	-	-	Beta
Liver disease transition: DCC to Pre-LT	1.53%	-	-	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Liver disease transition: HCC to Pre-LT	1.02%	-	-	Beta
Liver disease transition: Pre-LT to LT	10.21%	-	-	Beta
Liver disease transition: Post-LT to LT	0.02%	-	-	Beta
Liver disease transition: Post-LT to re-emergence of PBC	0.58%	-	-	Beta
Liver disease transition: re-emergence of PBC to LT	0.02%	-	-	Beta
Per-cycle excess mortality probability: Mild	0%	-	-	Beta
Per-cycle excess mortality probability: Moderate	0%	-	-	Beta
Per-cycle excess mortality probability: High	1%	-	-	Beta
Per-cycle excess mortality probability: DCC	4%	-	-	Beta
Per-cycle excess mortality probability: HCC	10%	-	-	Beta
Per-cycle excess mortality probability: Pre-LT	2%	-	-	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Per-cycle excess mortality probability: LT	[redacted]	-	-	Beta
Per-cycle excess mortality probability: Post-LT	[redacted]	-	-	Beta
Per-cycle excess mortality probability: Re-emergence of PBC	[redacted]	-	-	Beta
Elafibranor mild itch at Month 3	[redacted]	-	-	Beta
Elafibranor mild itch at Month 6	[redacted]	-	-	Beta
Elafibranor mild itch at Month 9	[redacted]	-	-	Beta
Elafibranor mild itch at Month 12+	[redacted]	-	-	Beta
Elafibranor clinically significant itch at Month 3	[redacted]	-	-	Beta
Elafibranor clinically significant itch at Month 6	[redacted]	-	-	Beta
Elafibranor clinically significant itch at Month 9	[redacted]	-	-	Beta
Elafibranor clinically significant itch at Month 12+	[redacted]	-	-	Beta
UDCA mild itch at Month 3	[redacted]	-	-	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
UDCA mild itch at Month 6	[redacted]	-	-	Beta
UDCA mild itch at Month 9	[redacted]	-	-	Beta
UDCA mild itch at Month 12+	[redacted]	-	-	Beta
UDCA clinically significant itch at Month 3	[redacted]	-	-	Beta
UDCA clinically significant itch at Month 6	[redacted]	-	-	Beta
UDCA clinically significant itch at Month 9	[redacted]	-	-	Beta
UDCA clinically significant itch at Month 12+	[redacted]	-	-	Beta
Proportion of patients receiving concomitant UDCA per cycle - Elafibranor	[redacted]	-	-	Beta
Proportion of patients receiving UDCA per cycle - UDCA	[redacted]	-	-	Beta
Elafibranor compliance	[redacted]	-	-	Normal
HSUV				
Elafibranor - AE rate pruritus	[redacted]	-	-	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Elafibranor - AE rate urinary tract infection	5.8%	-	-	Beta
Elafibranor - AE rate fatigue	4.7%	-	-	Beta
UDCA - AE rate pruritus	14.2%	-	-	Beta
UDCA - AE rate urinary tract infection	1.9%	-	-	Beta
UDCA - AE rate fatigue	5.9%	-	-	Beta
Utility: Mild	0.84	-	-	Beta
Utility: Moderate	0.84	-	-	Beta
Utility: High	0.55	-	-	Beta
Utility: DCC	0.38	-	-	Beta
Utility: HCC	0.45	-	-	Beta
Utility: Pre-LT	0.38	-	-	Beta
Utility: LT	0.57	-	-	Beta
Utility: Post-LT	0.67	-	-	Beta
Utility: Re-emergence of PBC	0.67	-	-	Beta
Adverse event disutility - pruritus	0.11	-	-	Beta
Adverse event disutility - urinary tract infection	0.06	-	-	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Adverse event disutility - fatigue	[redacted]	-	-	Beta
Mild itch disutility	[redacted]	-	-	Beta
Clinically significant itch disutility	[redacted]	-	-	Beta
Costs				
UDCA cost per cycle (DKK)	512.21	-	-	Gamma
Health state cost - Mild	31.50	-	-	Gamma
Health state cost - Moderate	31.50	-	-	Gamma
Health state cost - High	75,937.74	-	-	Gamma
Health state cost - DCC	151,707.49	-	-	Gamma
Health state cost - HCC	122,882.85	-	-	Gamma
Health state cost - Pre-LT	0.00	-	-	Gamma
Health state cost - LT	1,013,286.72	-	-	Gamma
Health state cost - Post-LT	24,517.53	-	-	Gamma
Health state cost - Re-emergence of PBC	75,937.74	-	-	Gamma
AE unit cost - pruritus	3,785.73	-	-	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
AE unit cost - urinary tract infection	2,624.19	-	-	Gamma
AE unit cost - fatigue	1,044.00	-	-	Gamma
Elafibranor mild itch total cost	1,077.18	-	-	Gamma
UDCA mild itch total cost	1,077.18	-	-	Gamma
Elafibranor clinically significant itch total cost	1,923.18	-	-	Gamma
UDCA clinically significant itch total cost	1,923.18	-	-	Gamma
End of life costs: DCC	84,433.47	-	-	Gamma
End of life costs: HCC	84,433.47	-	-	Gamma

Appendix H. Literature searches for the clinical assessment

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

As described in section 5.1, the evidence for efficacy and safety of elafibranor compared to placebo is based on the head-to-head study ELATIVE. Therefore, a SLR for the clinical assessment was not conducted.

Table 62 Bibliographic databases included in the literature search

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

Abbreviations: N/A: Not applicable

Table 63 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Abbreviations: N/A: Not applicable

Table 64 Conference material included in the literature search

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

Abbreviations: N/A: Not applicable

H.1.1 Search strategies

Not applicable.

Table 65 of search strategy table for [name of database]

No.	Query	Results
N/A	N/A	N/A

Abbreviations: N/A: Not applicable

H.1.2 Systematic selection of studies

Not applicable.

Table 66 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Abbreviations: N/A: Not applicable

Table 67 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A: Not applicable

H.1.3 Excluded fulltext references

Not applicable

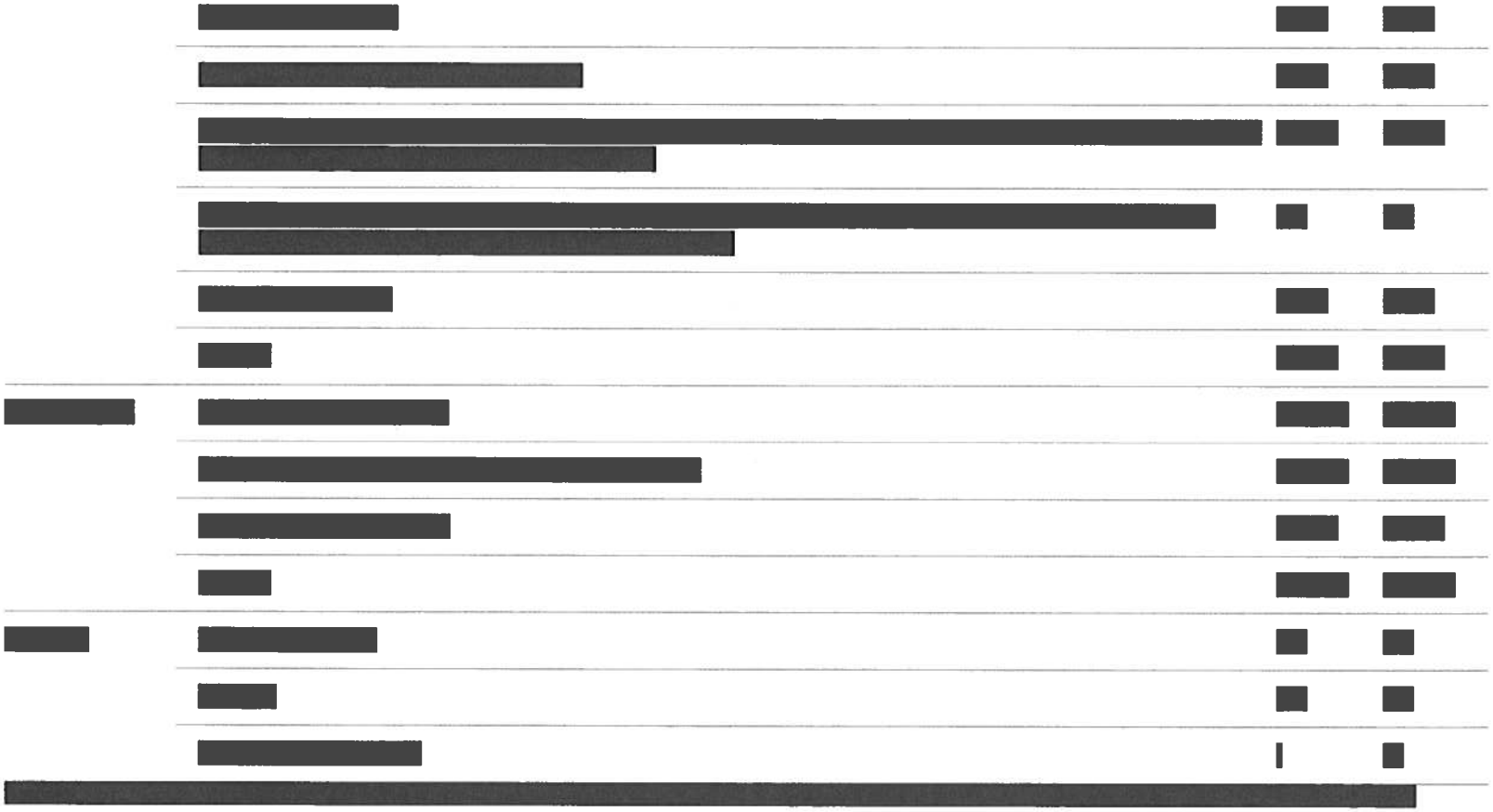
H.1.4 Quality assessment

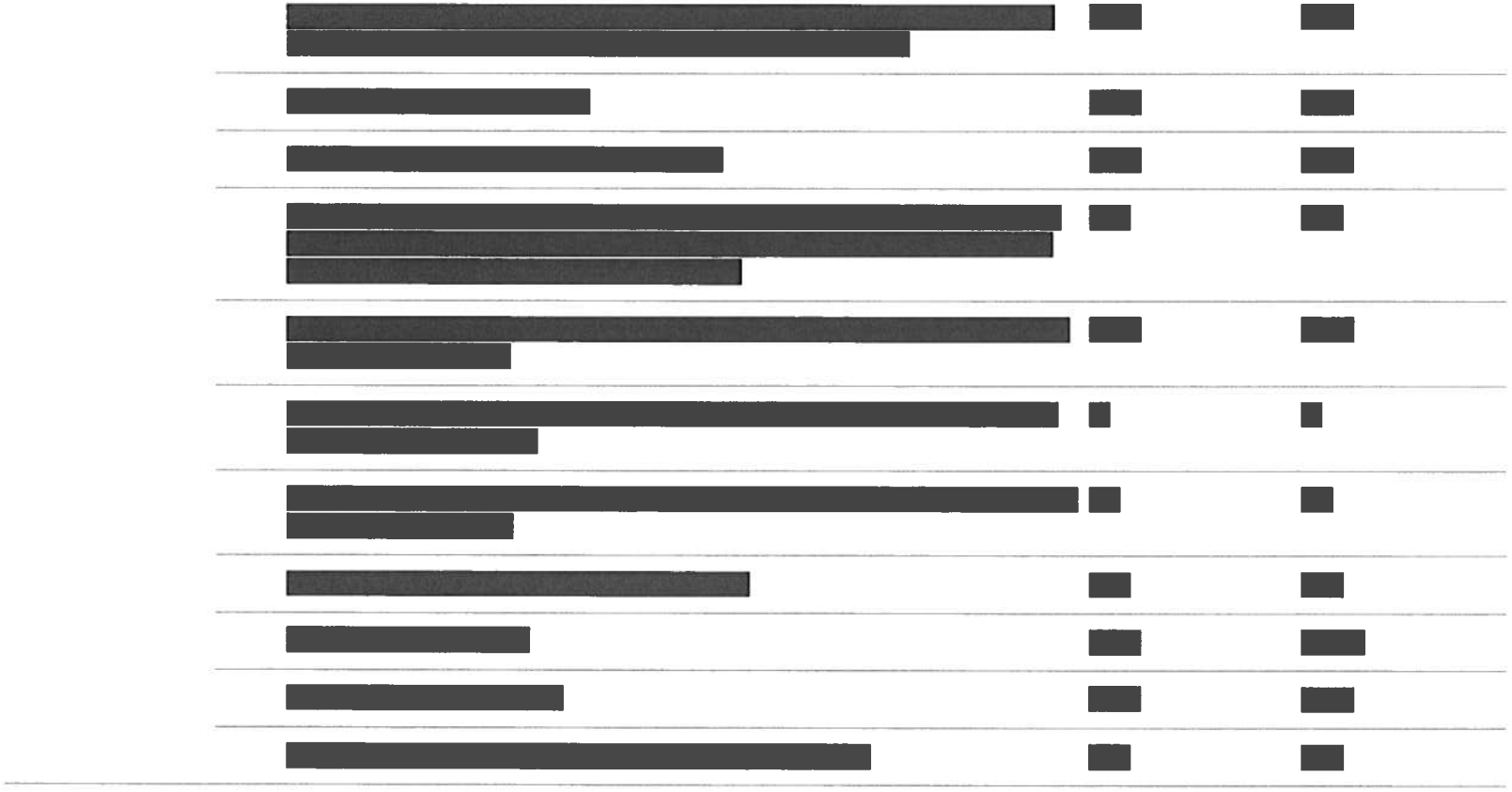
Not applicable

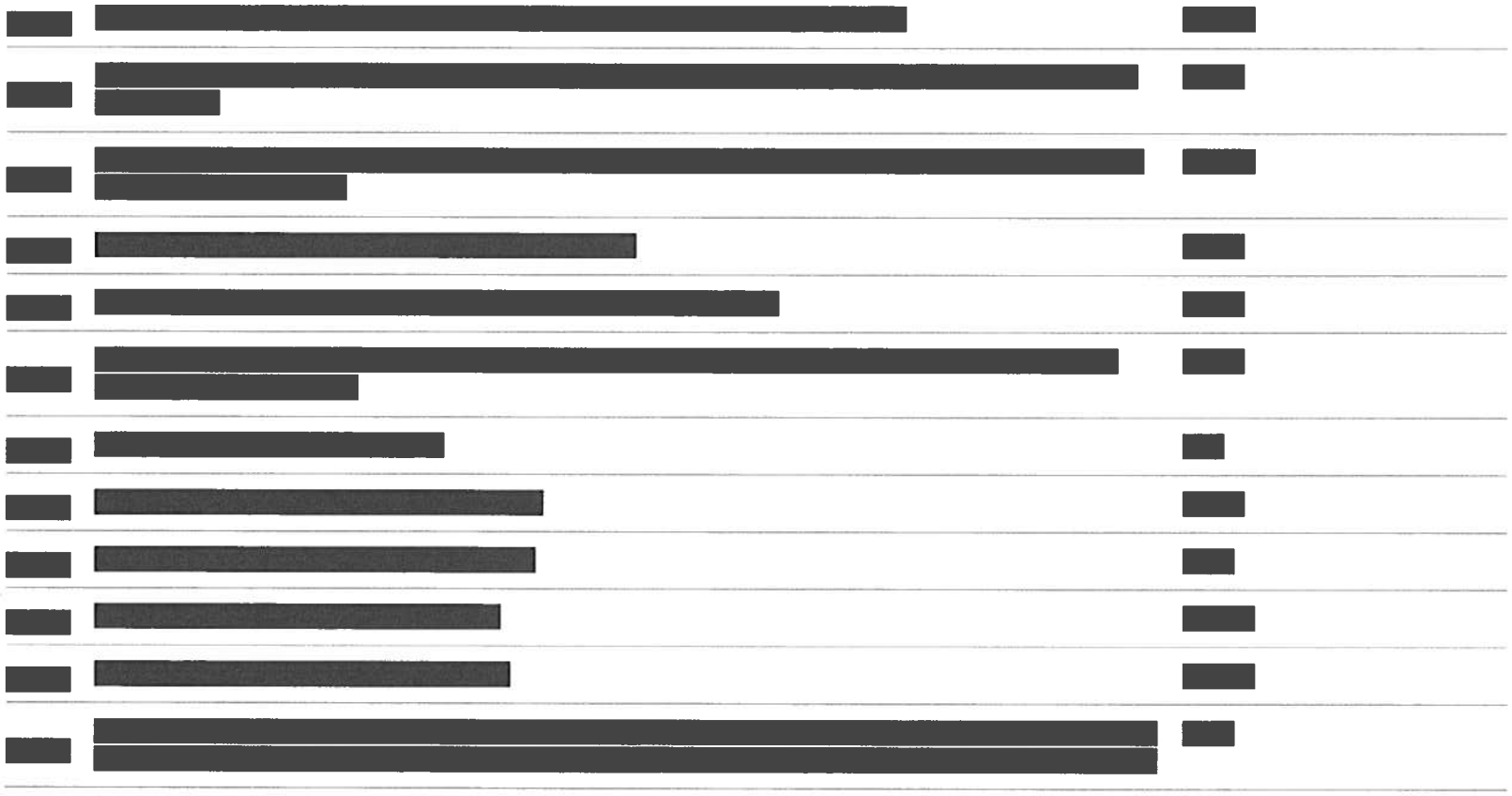
H.1.5 Unpublished data

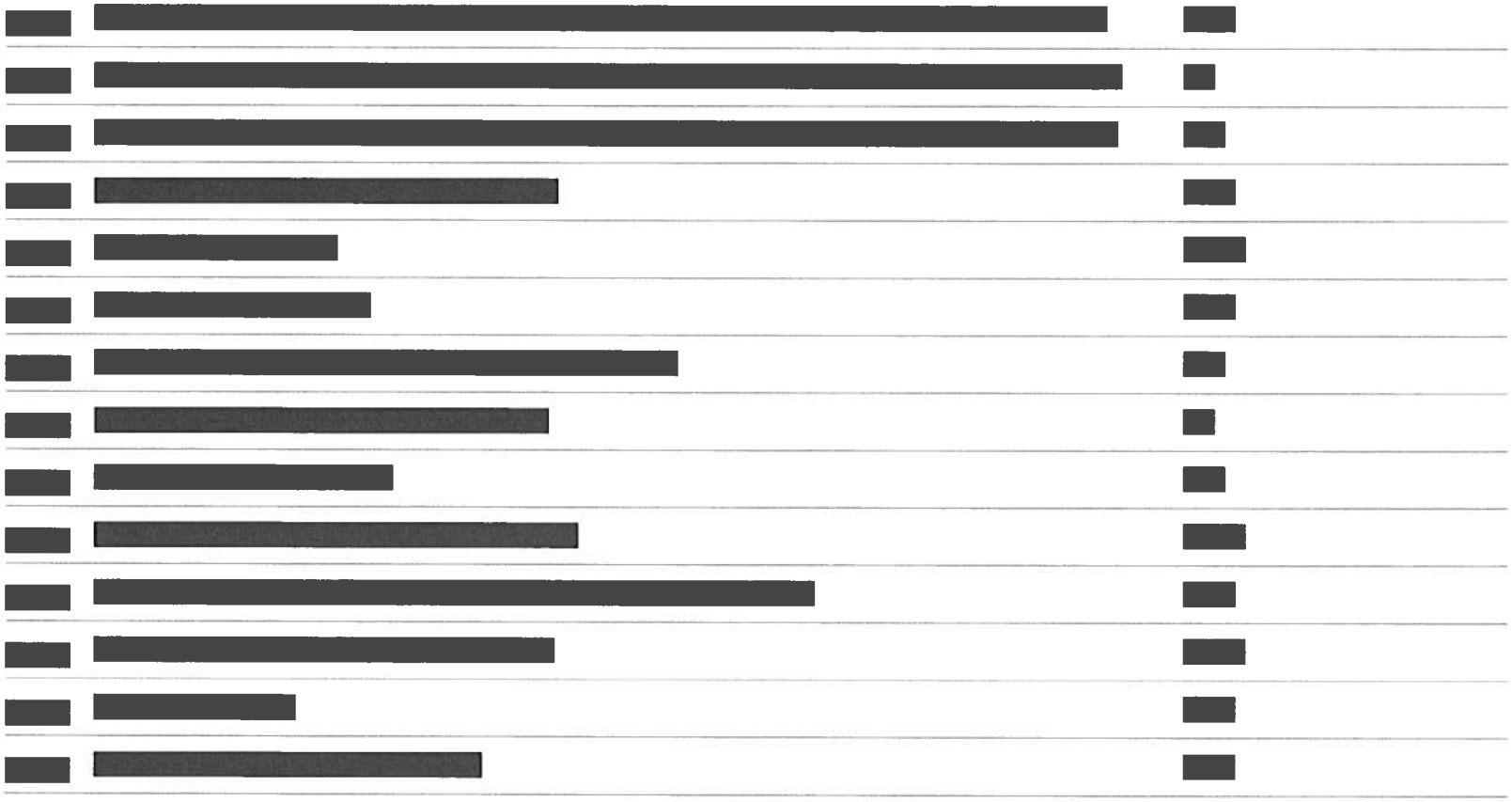
Not applicable.

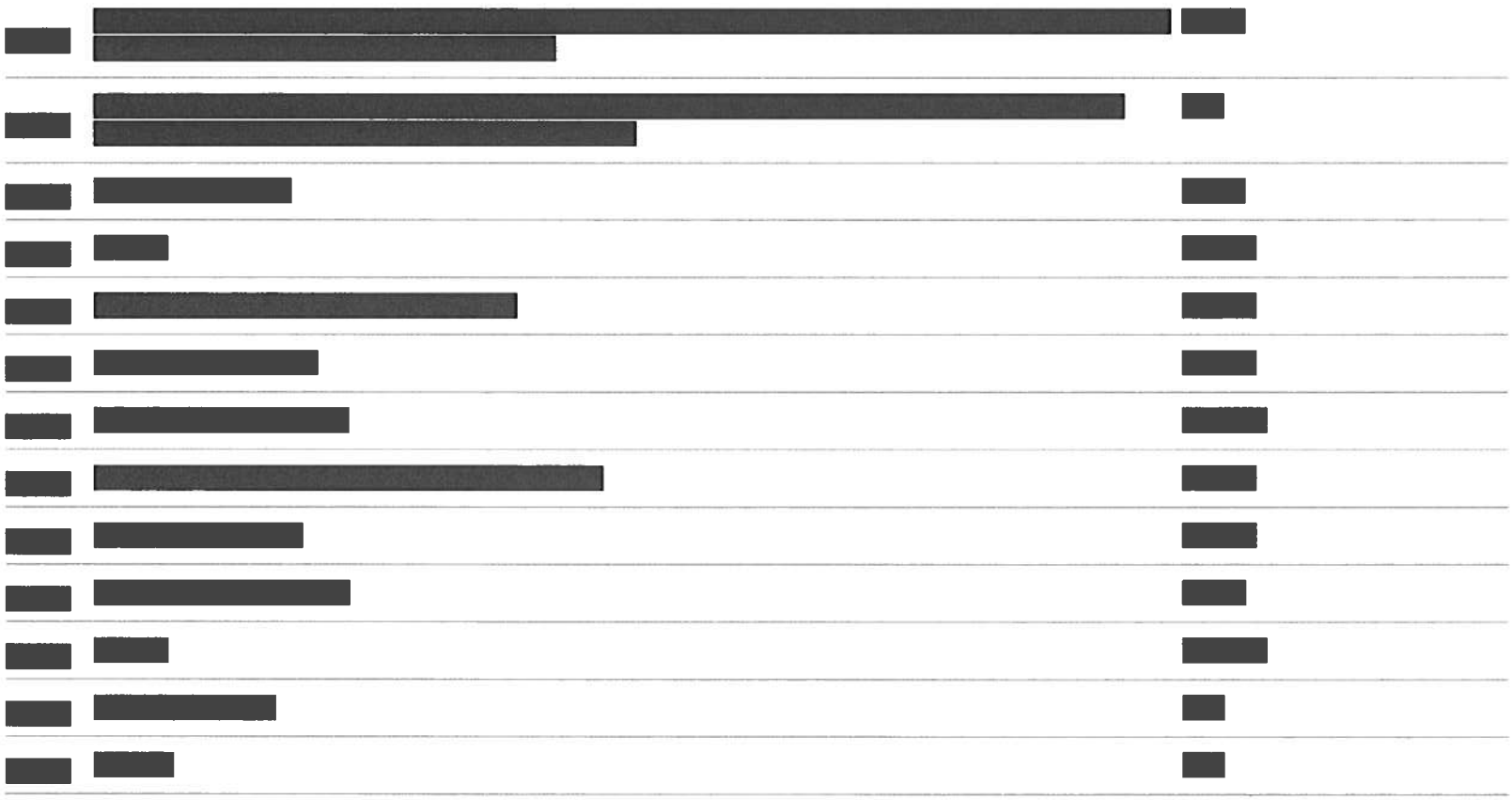
[redacted]

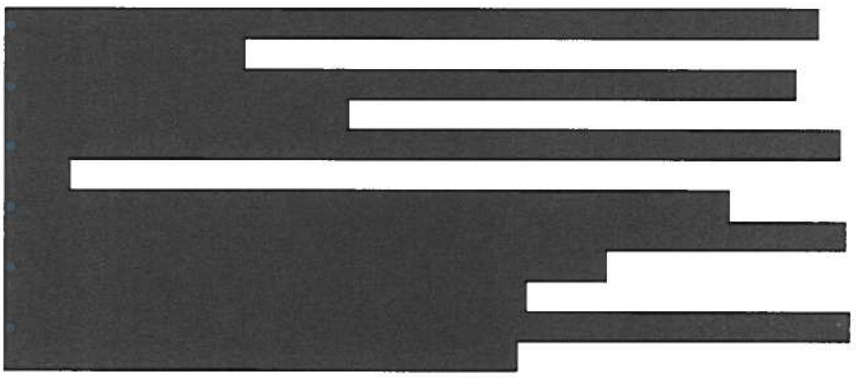


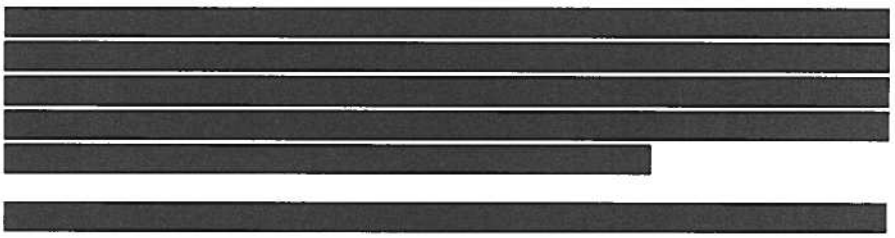


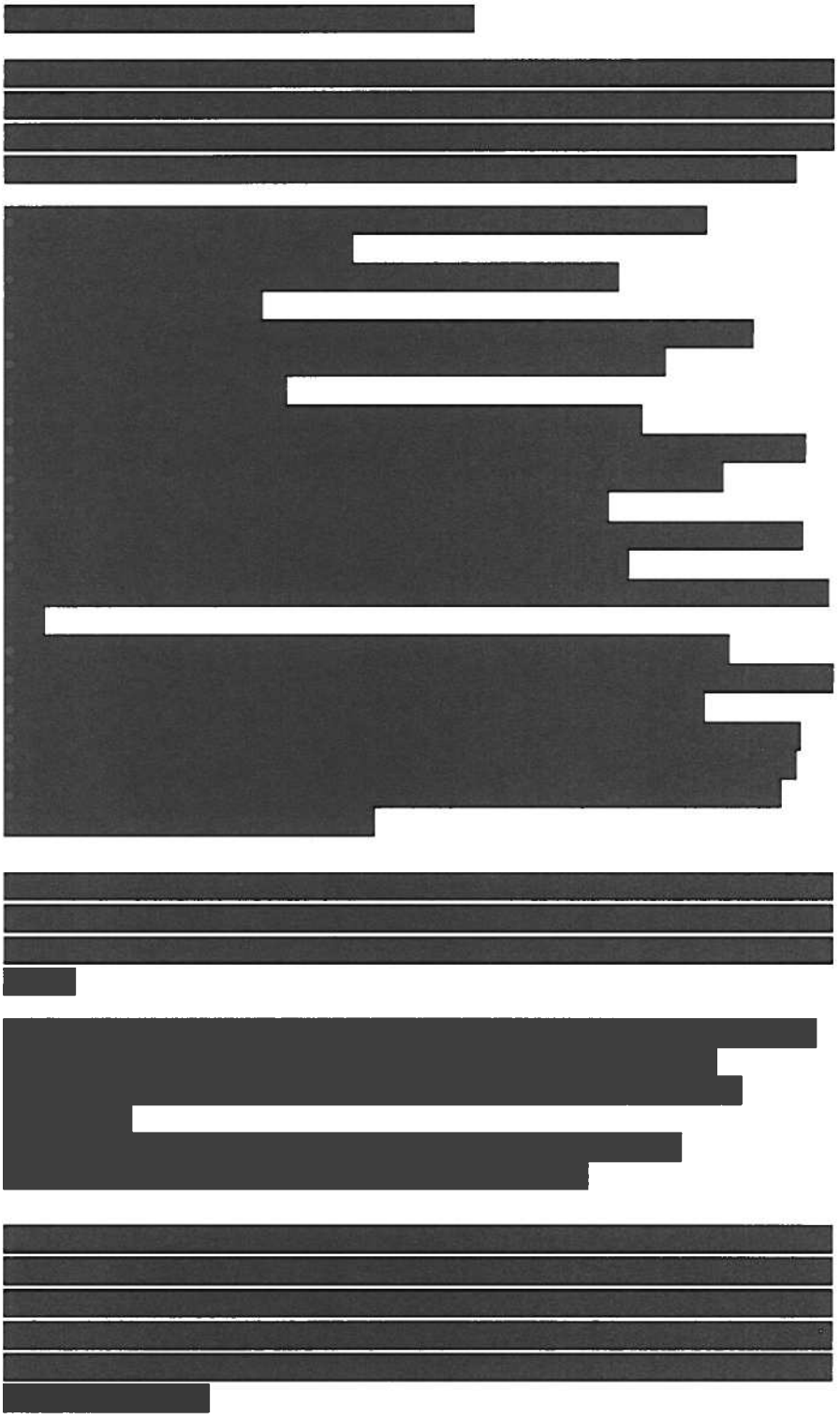


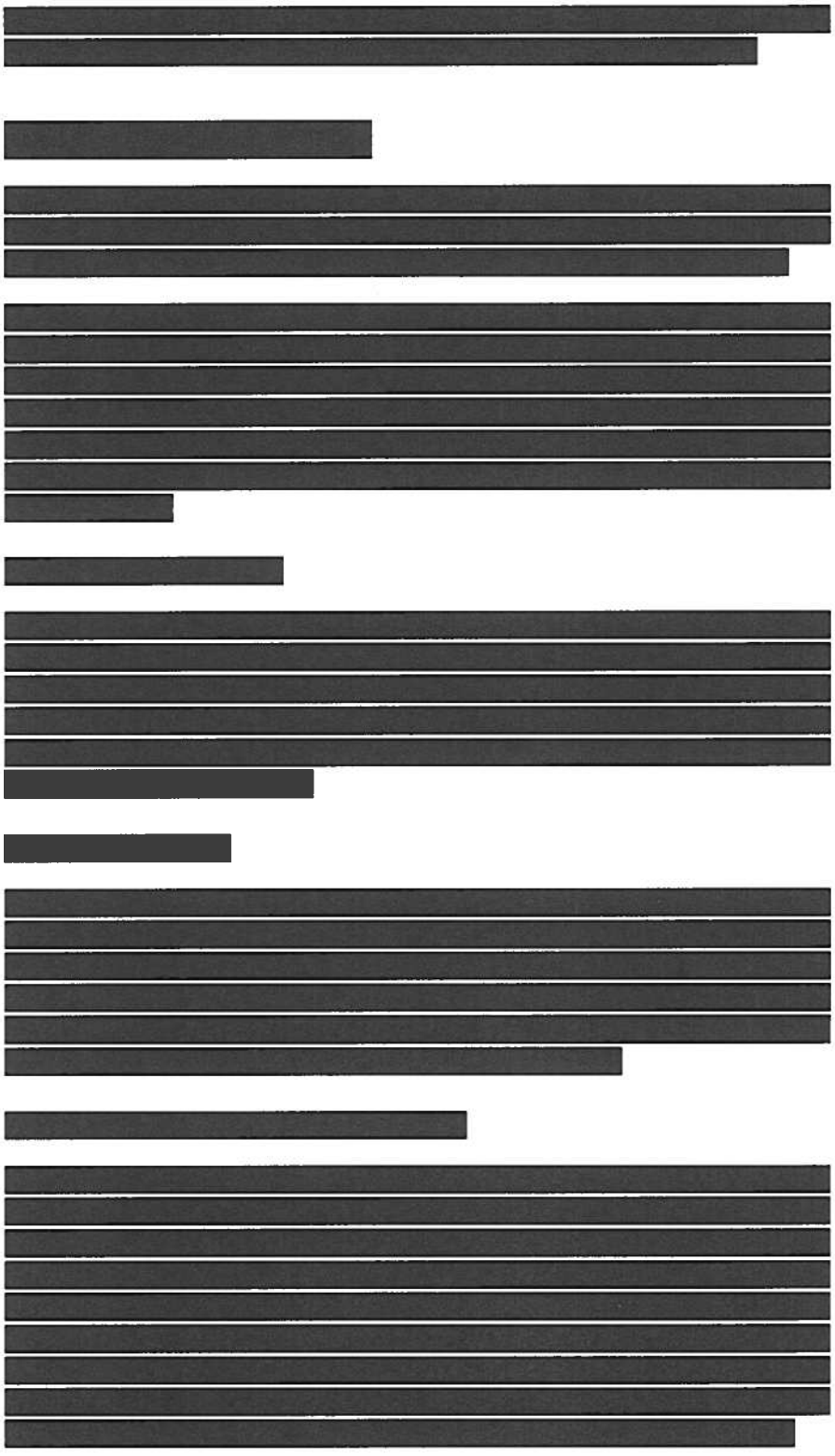












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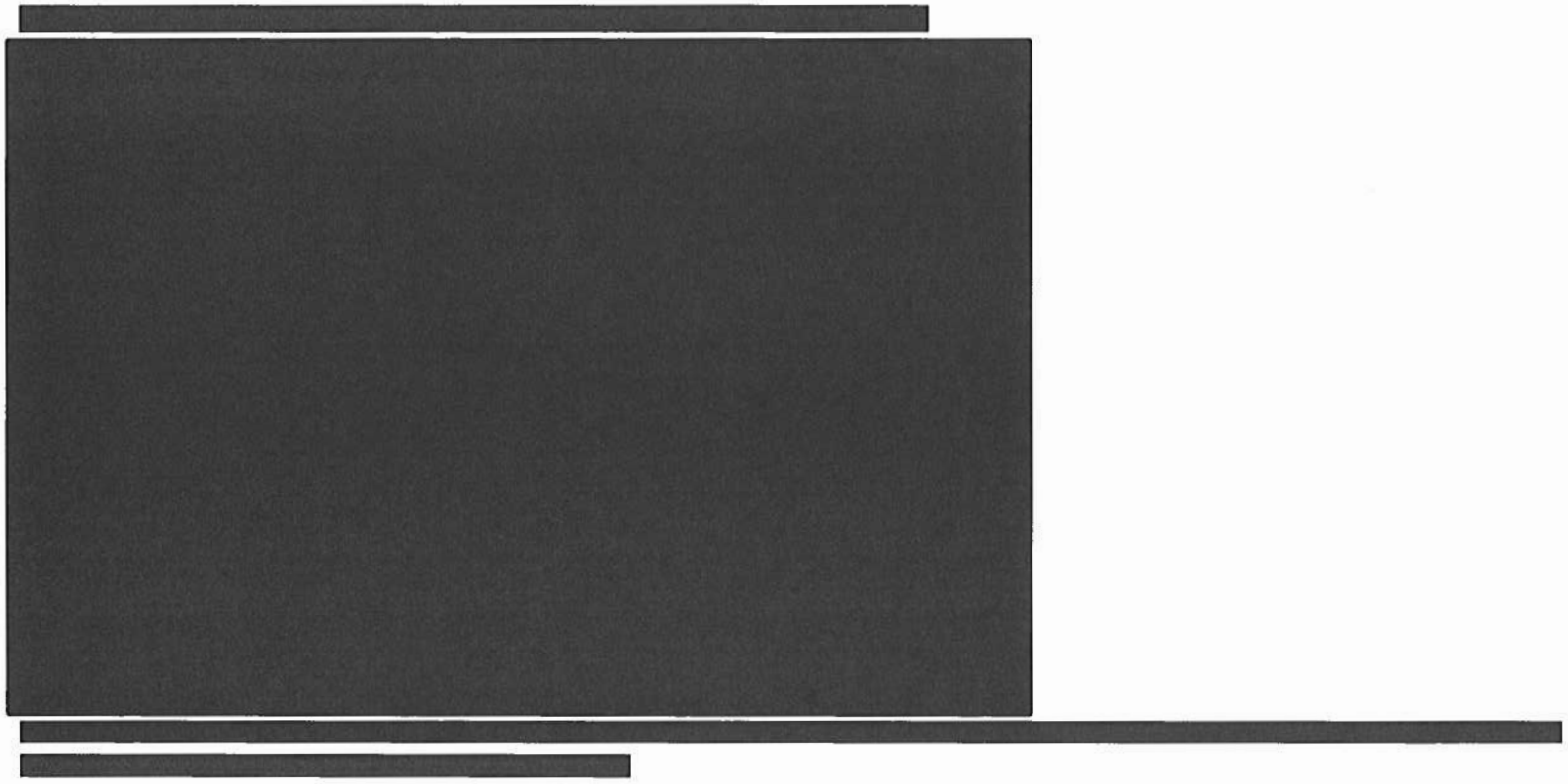

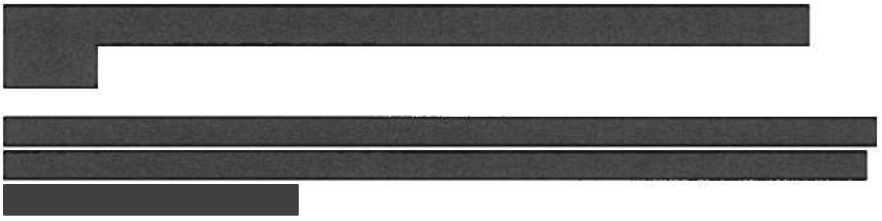

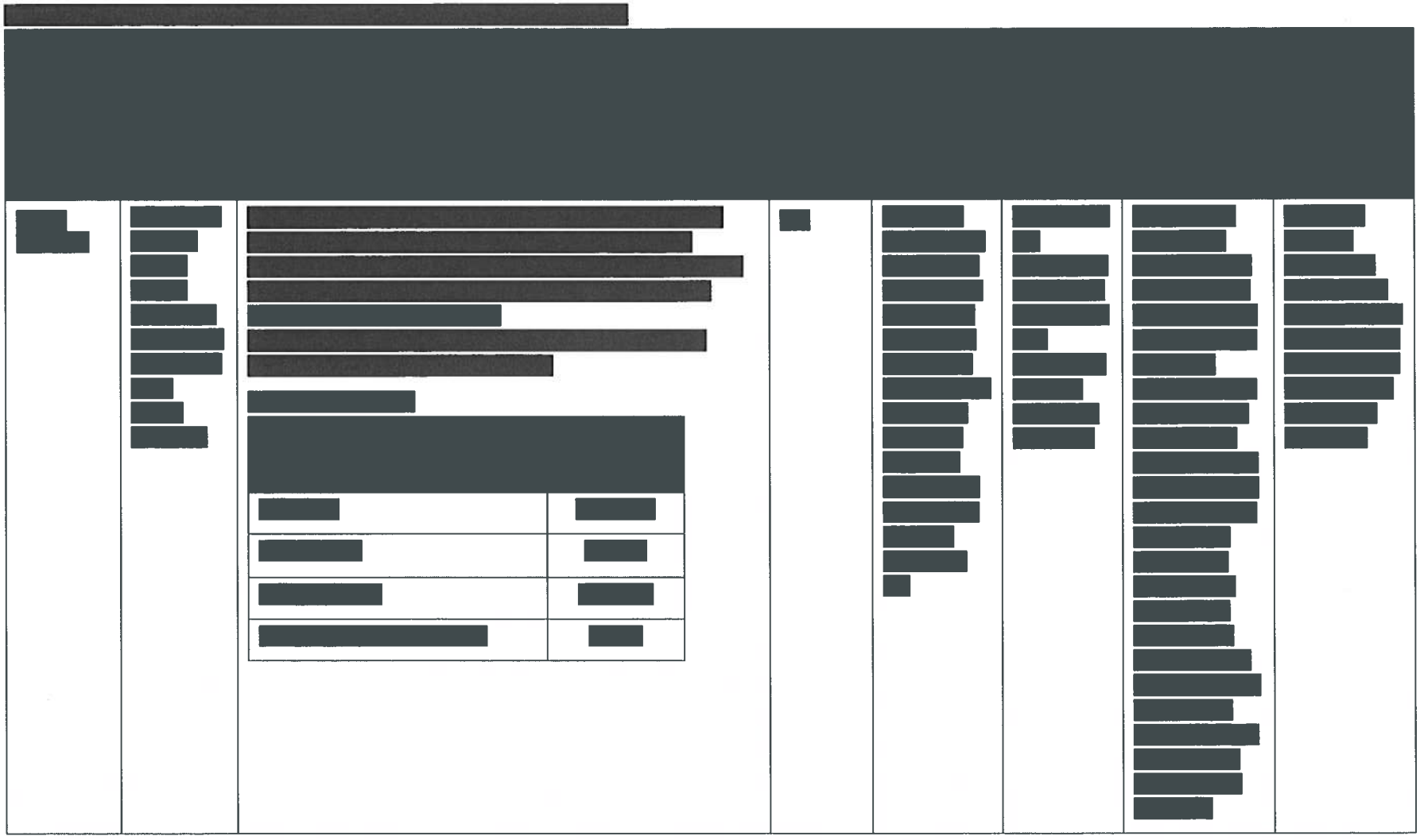

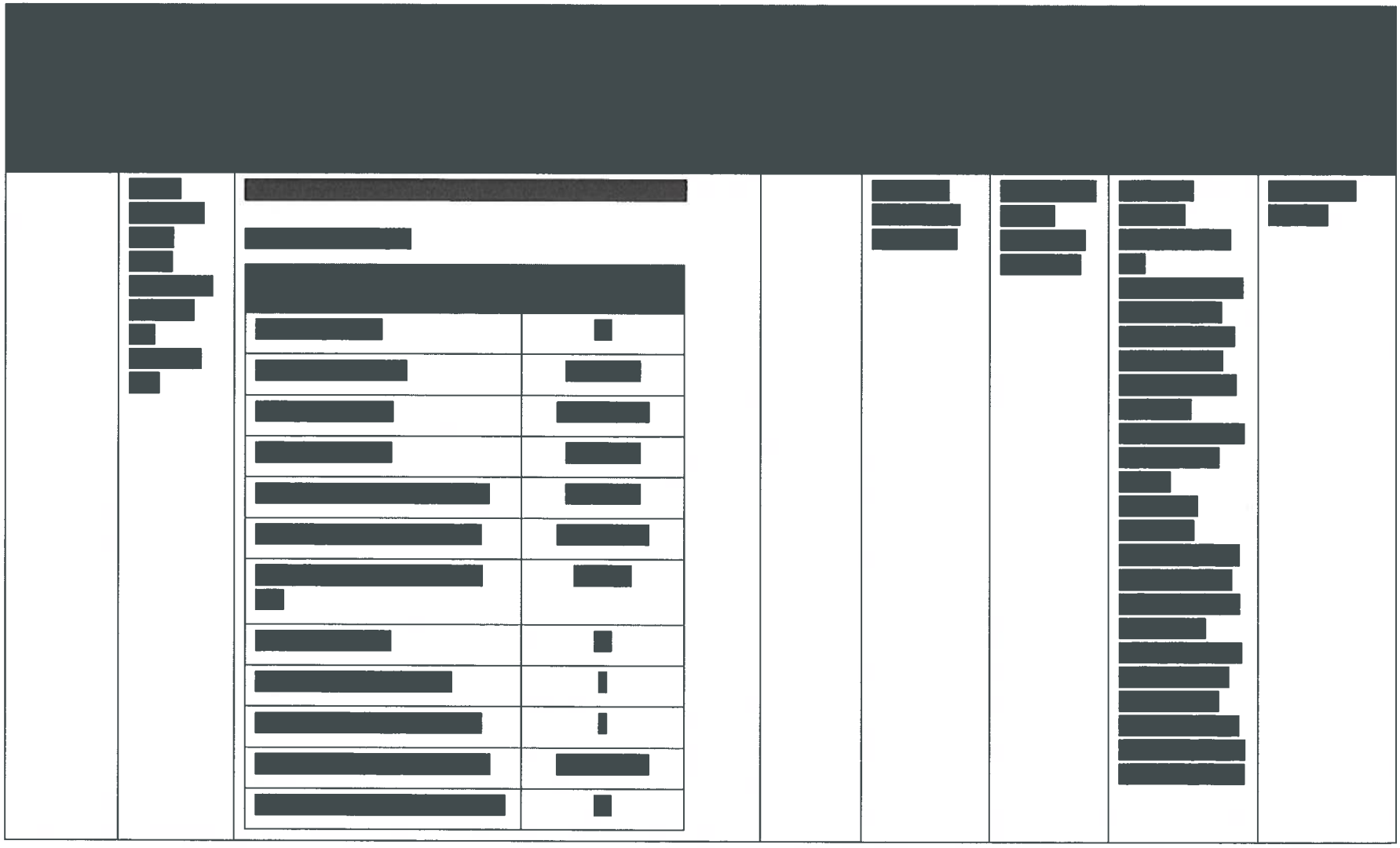

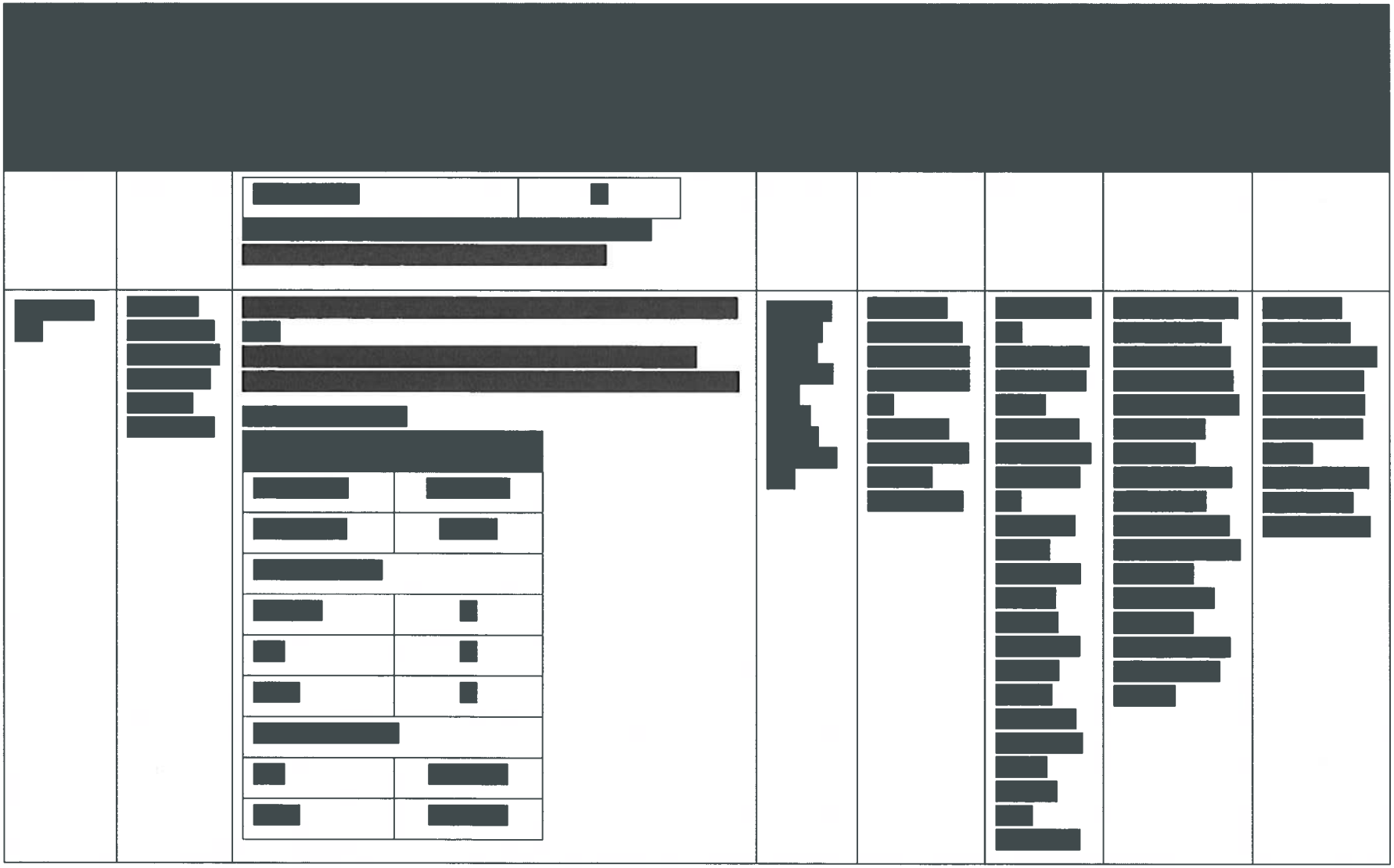

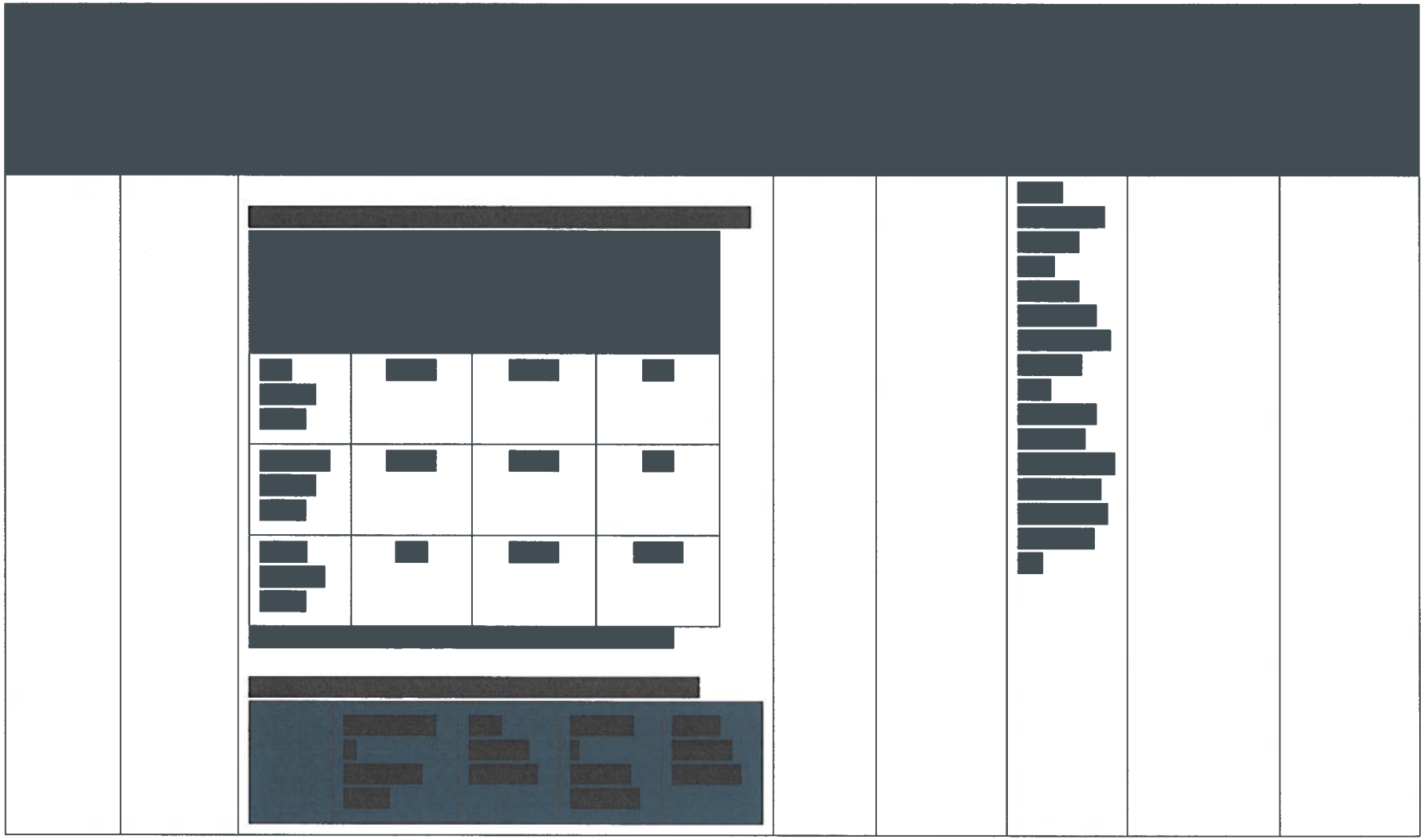

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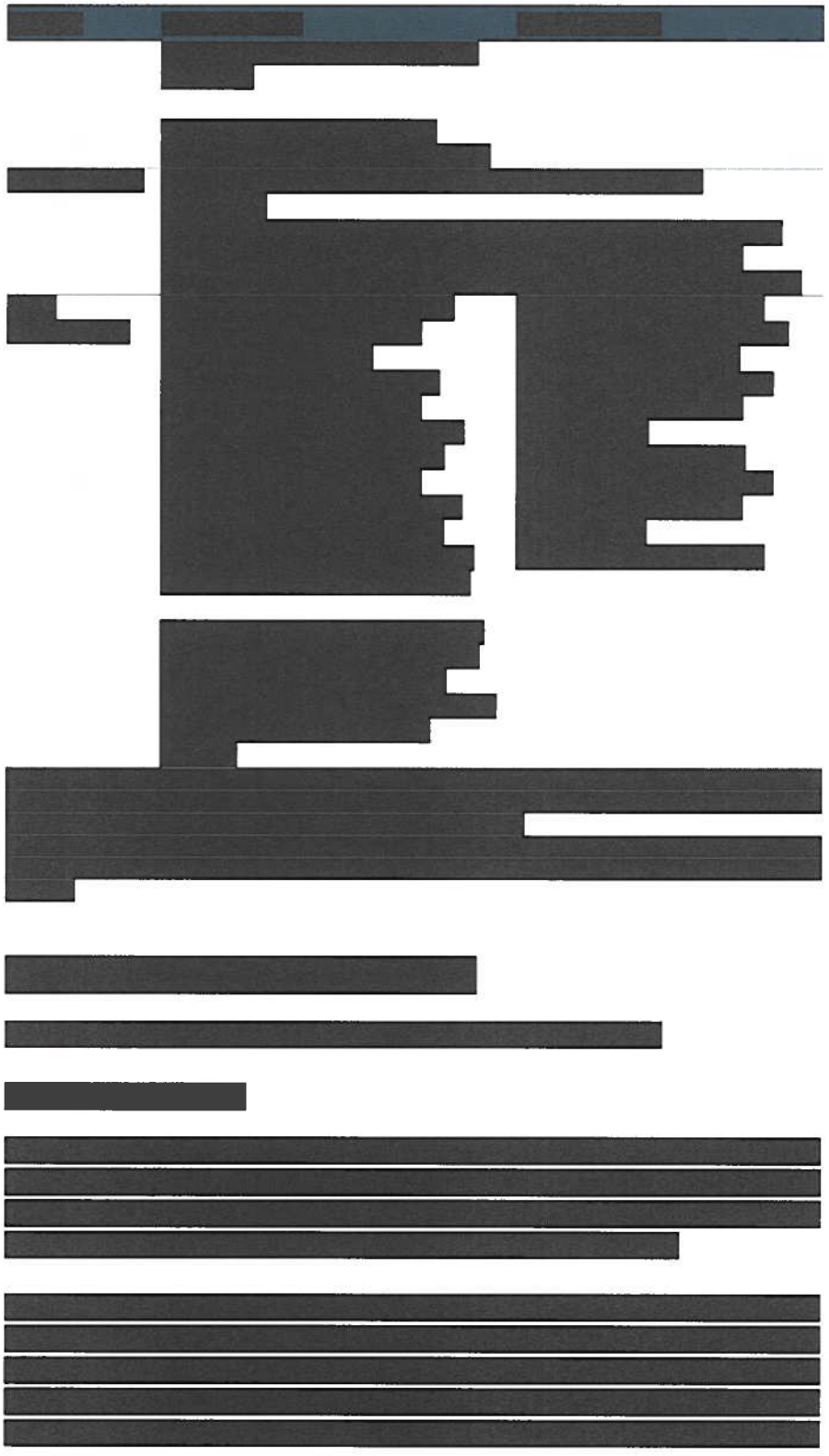

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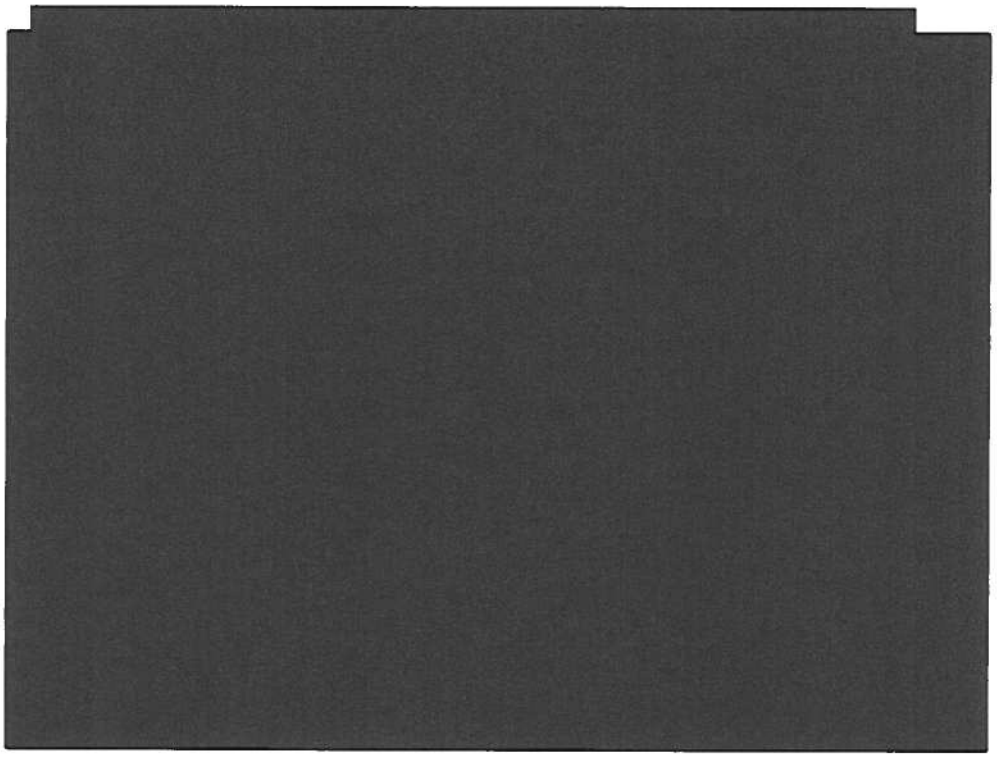
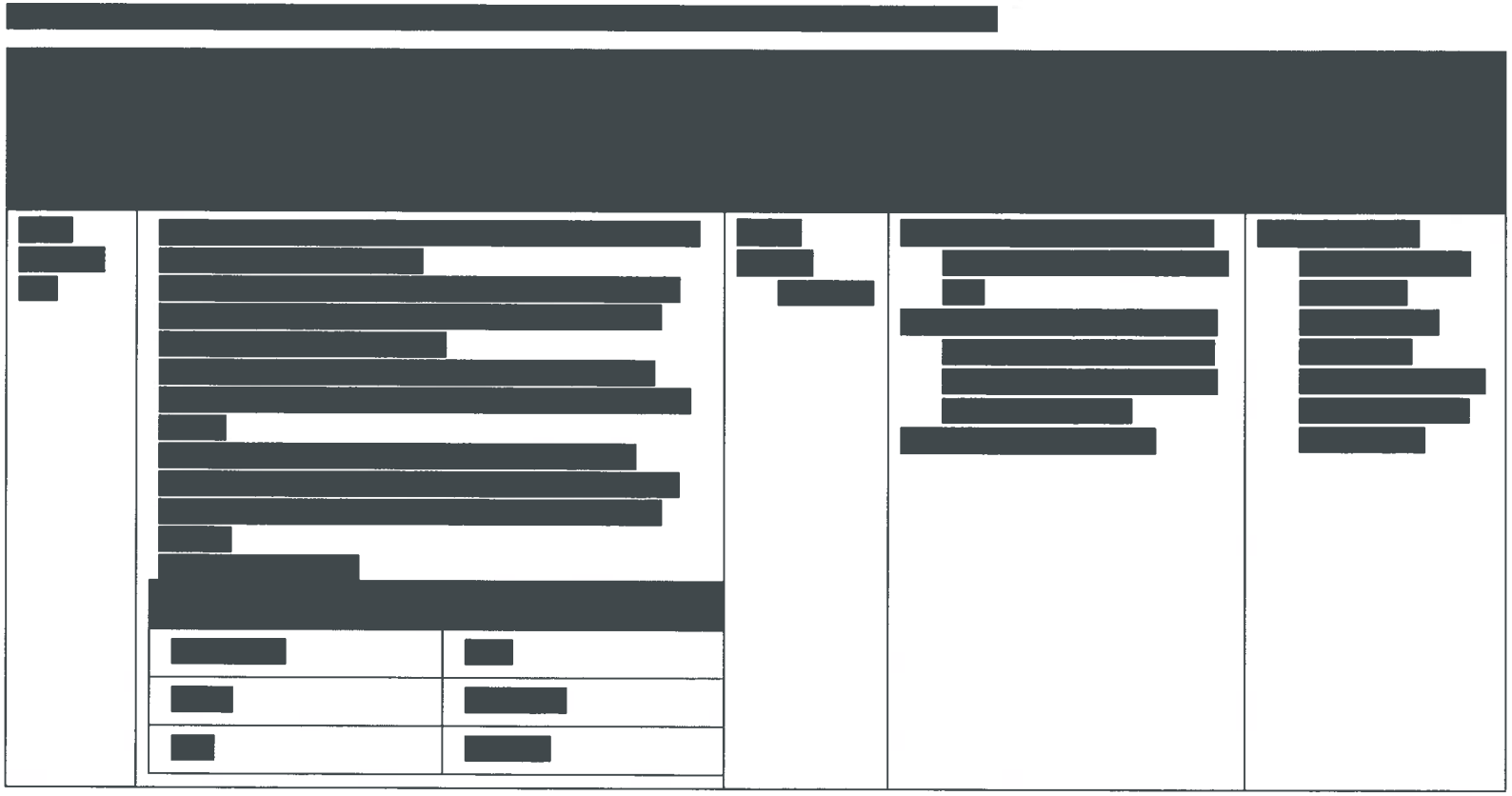
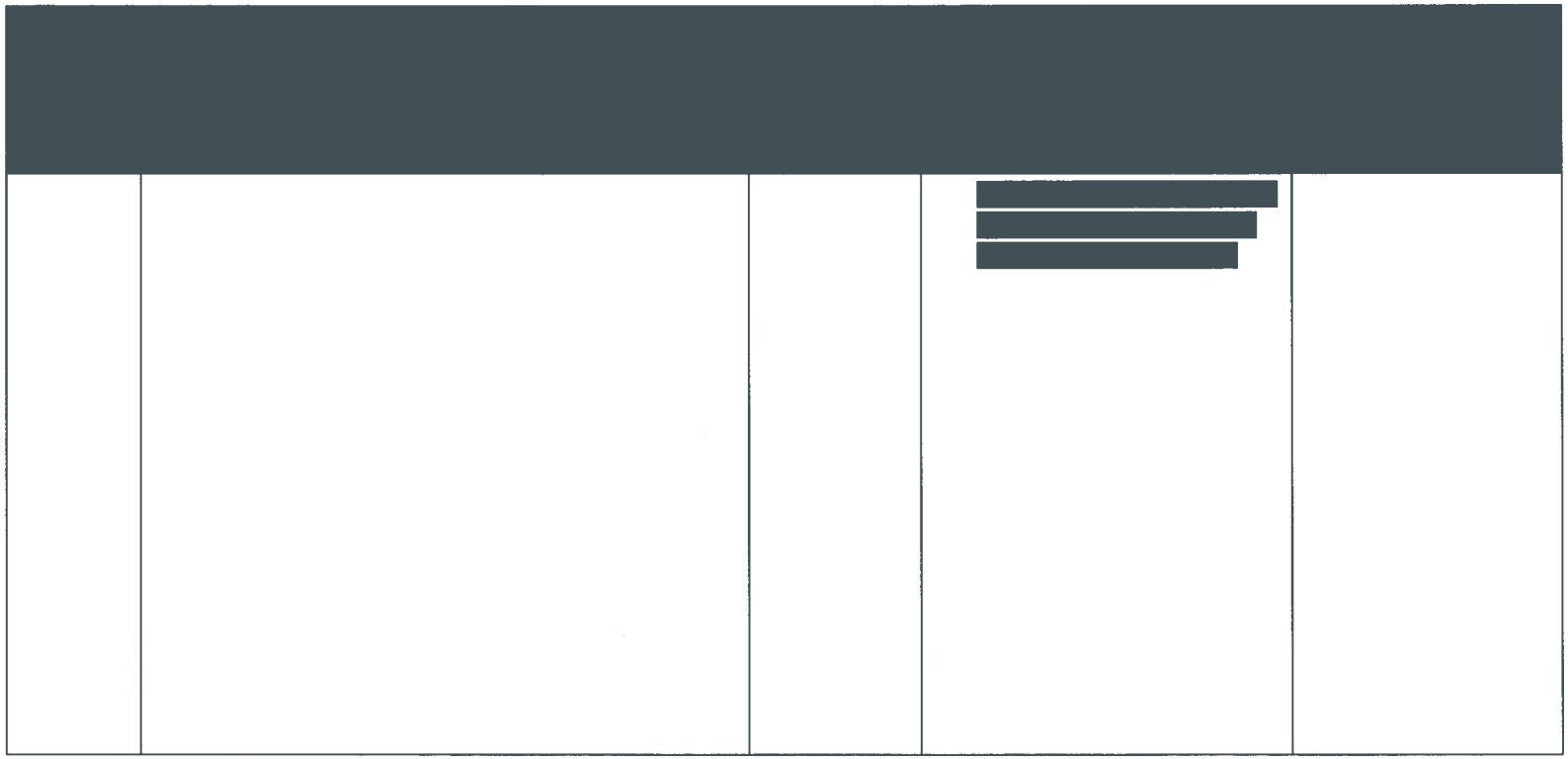
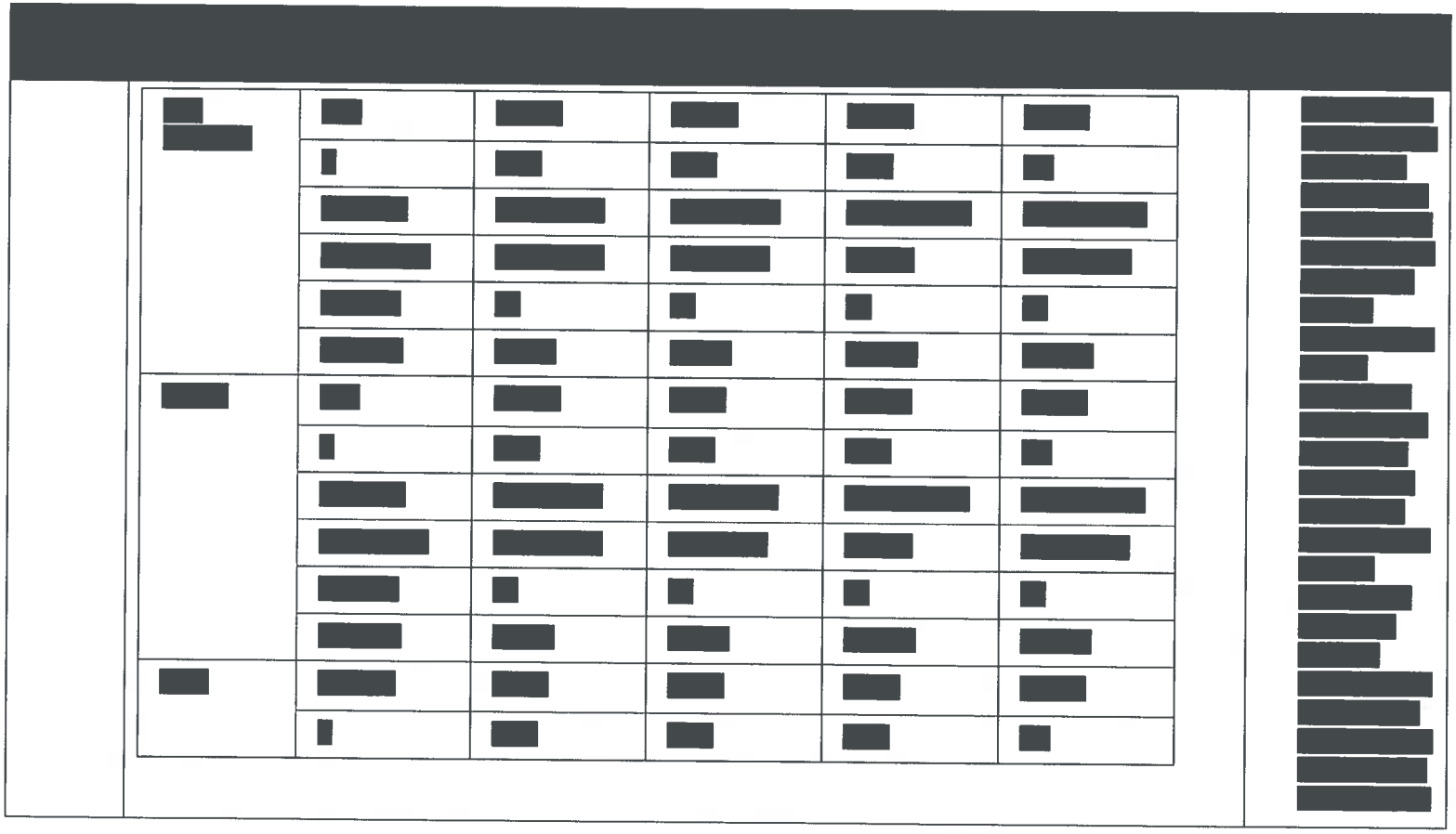
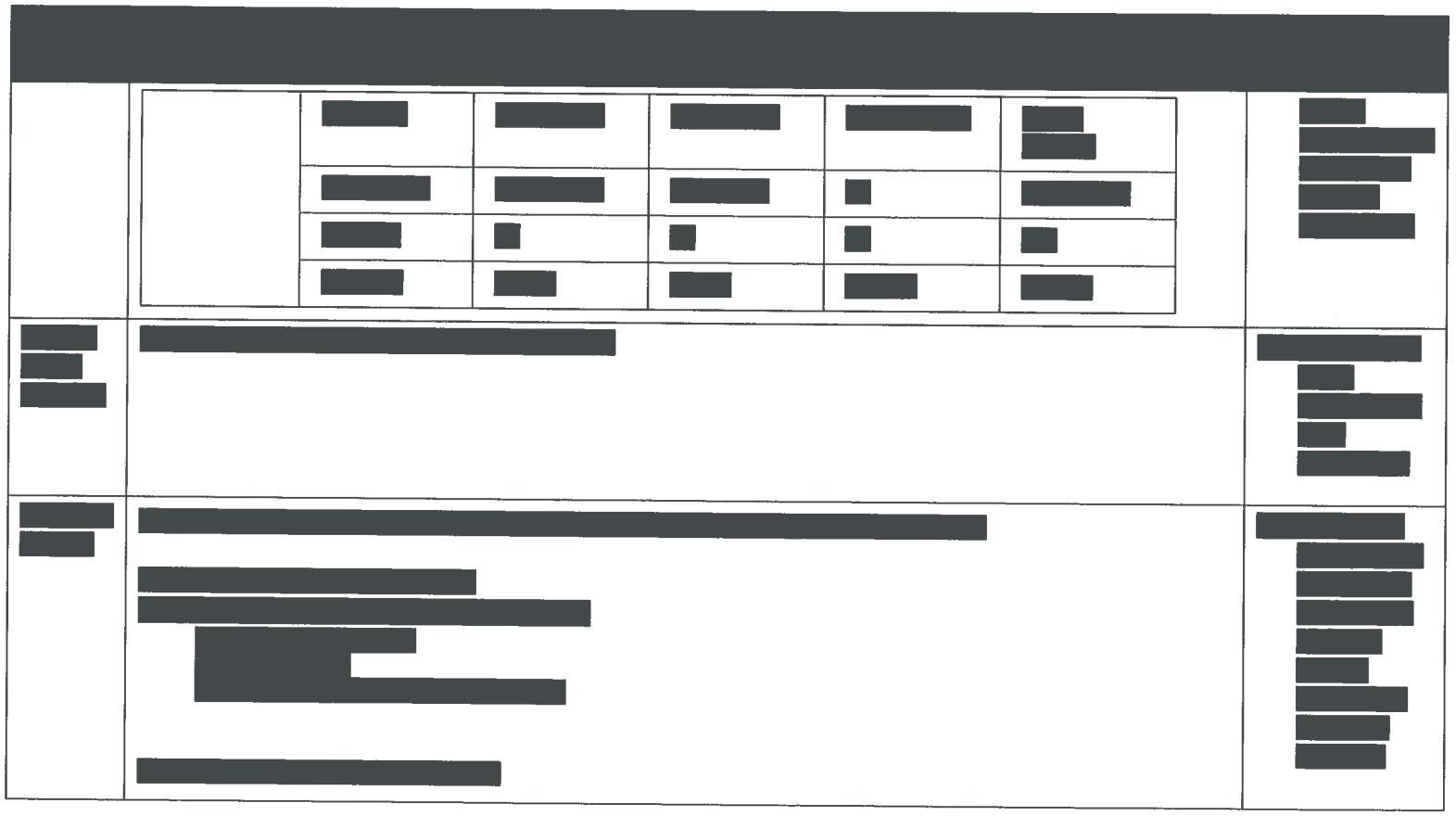
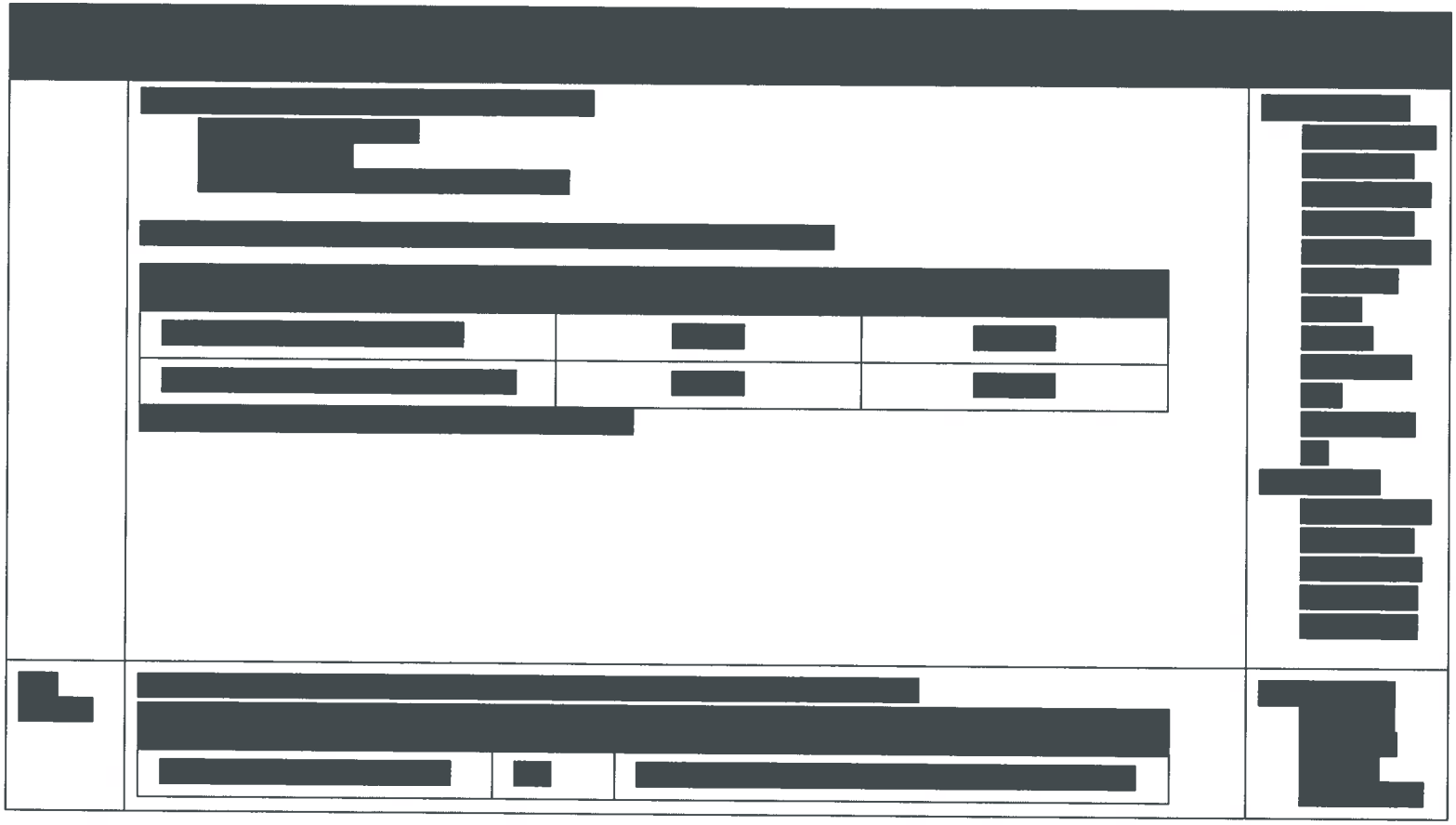


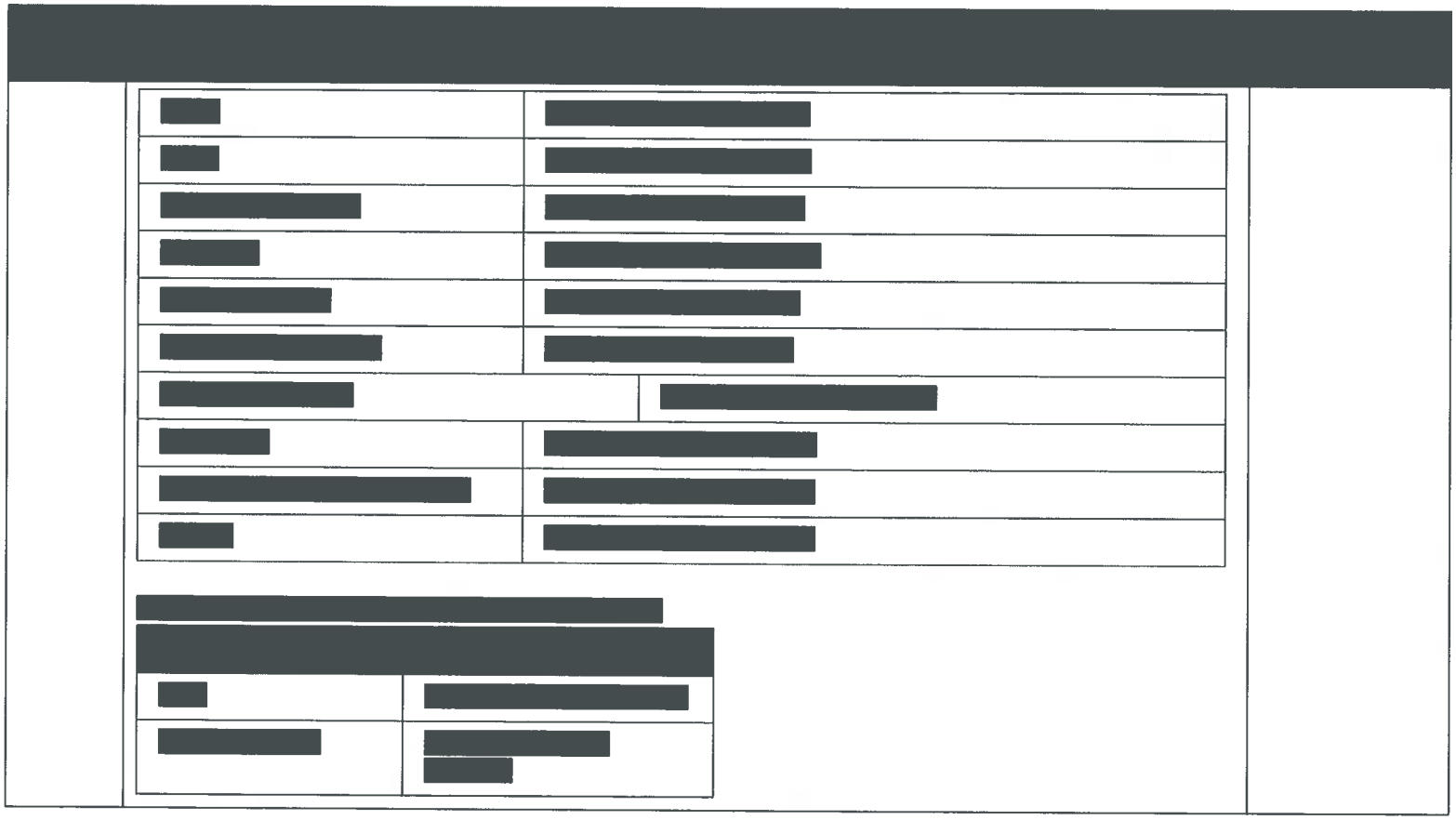


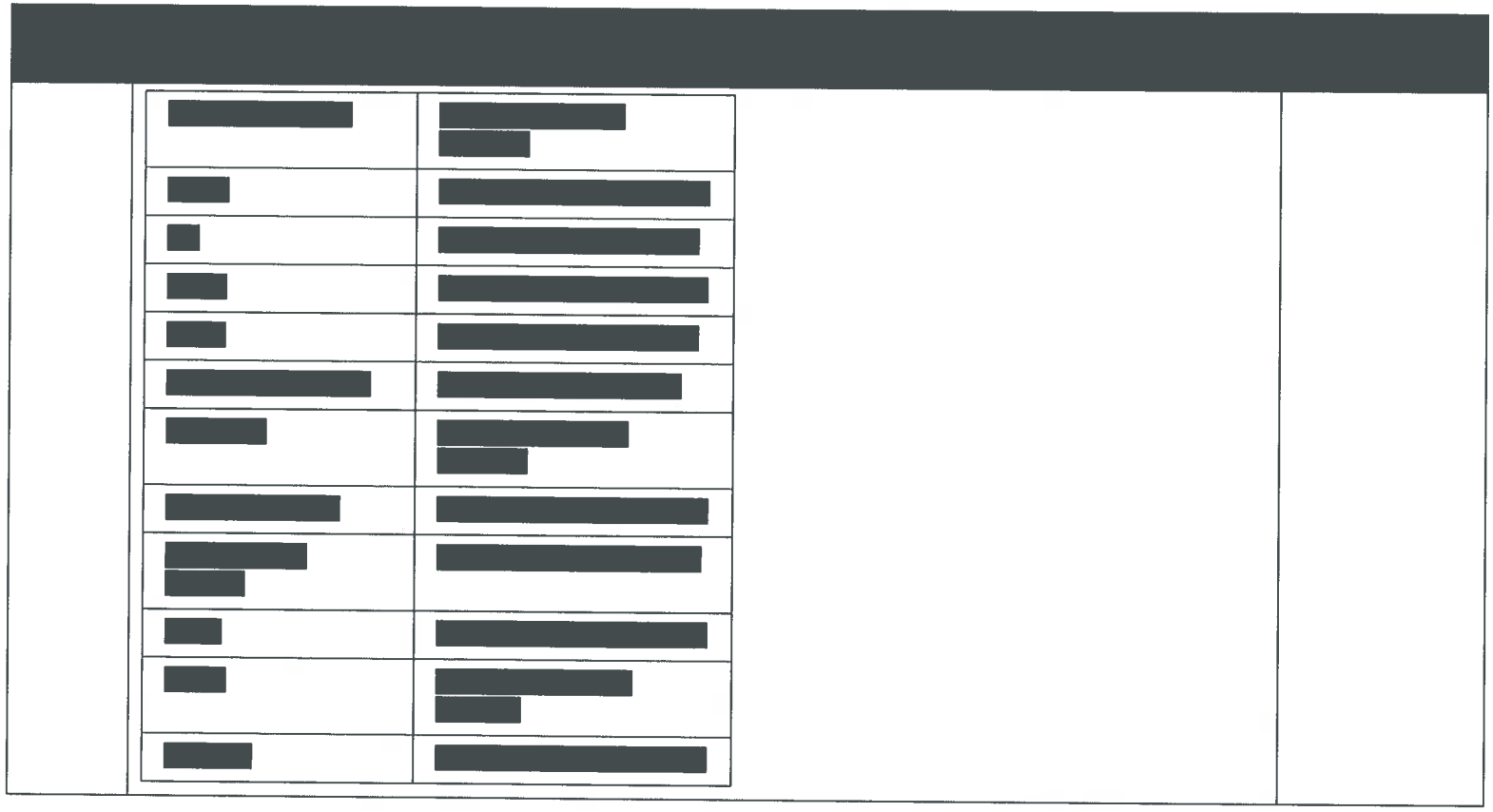


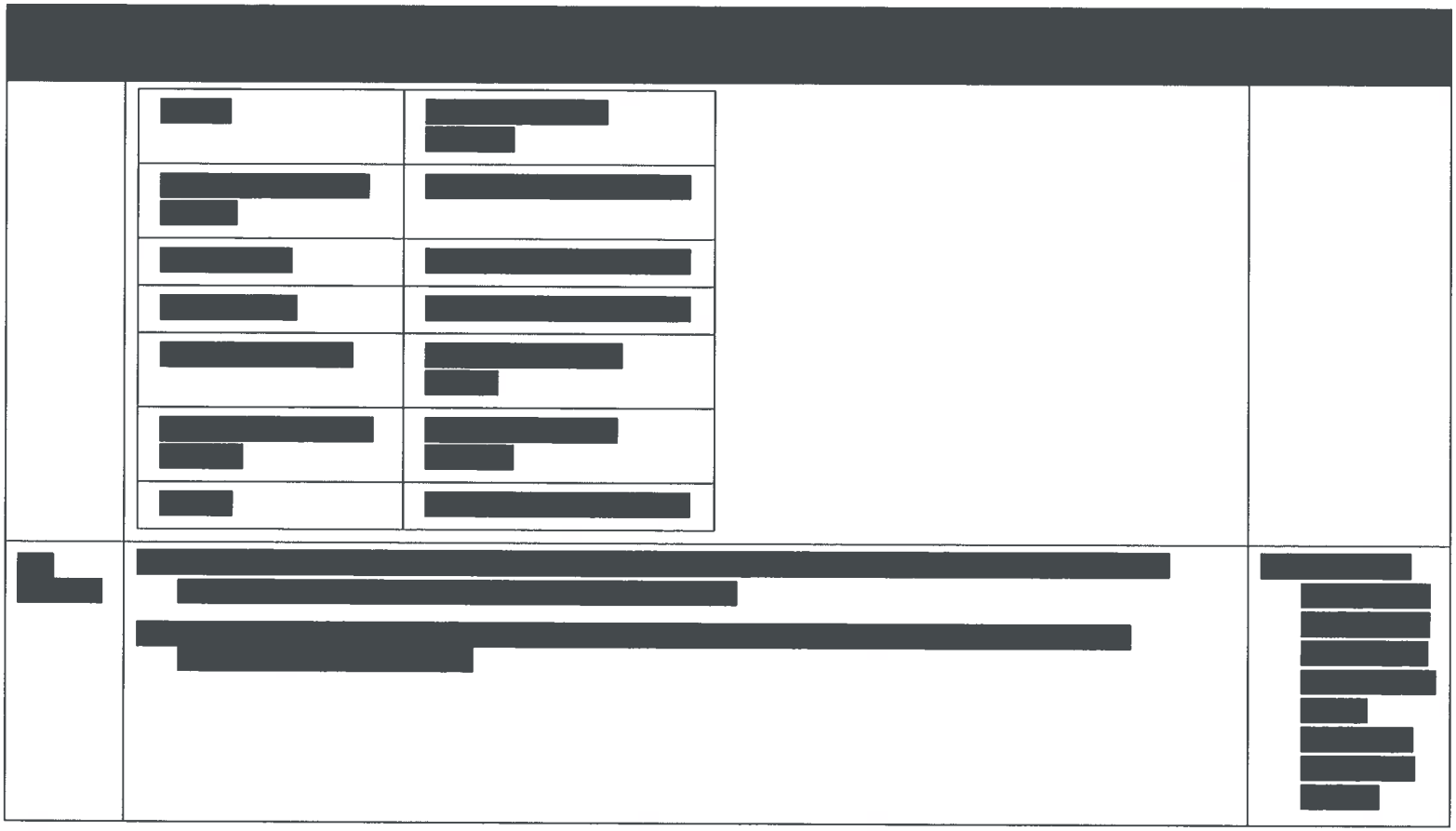


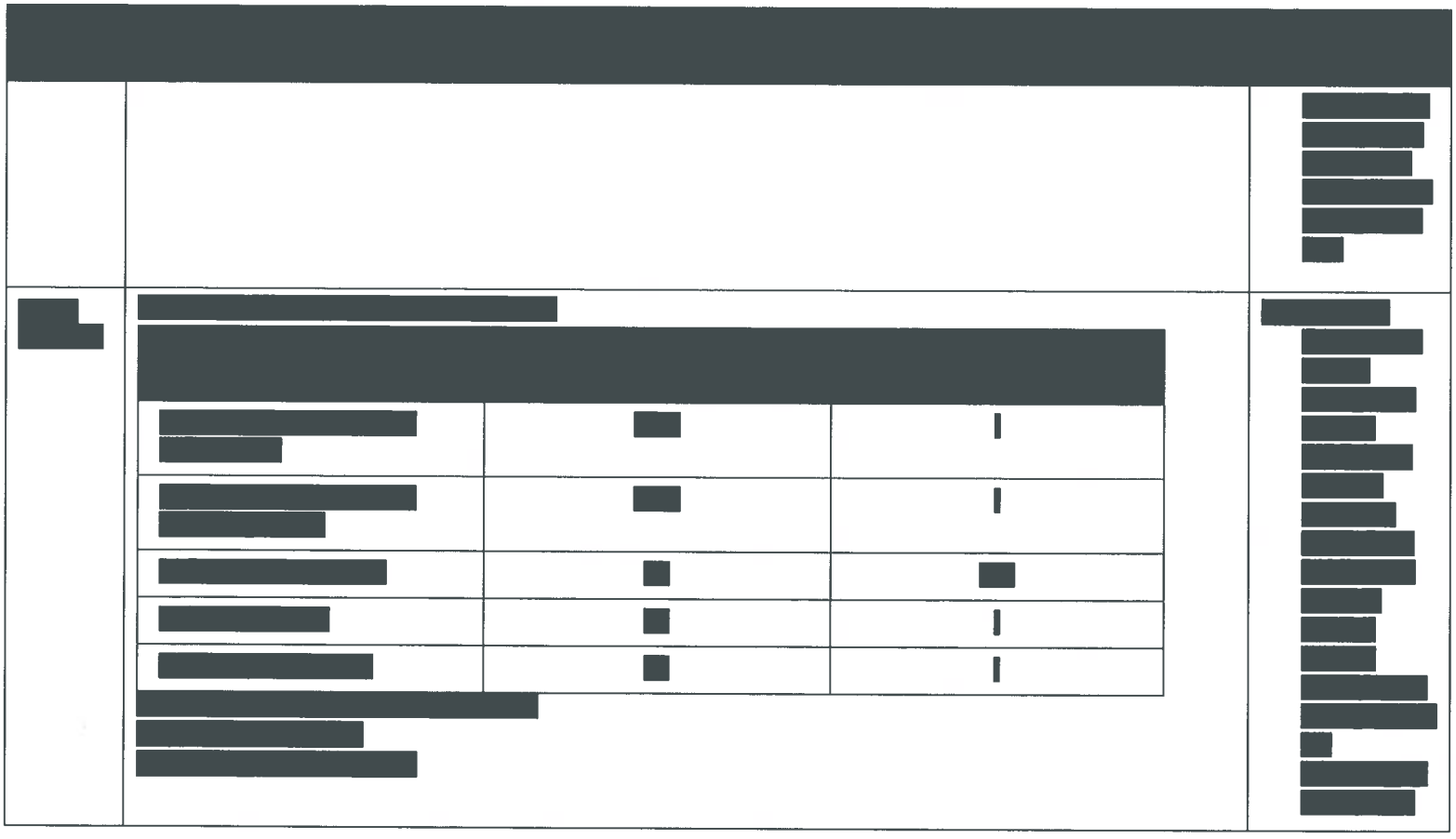










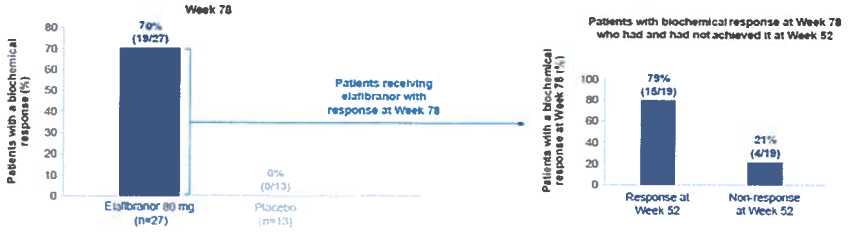


Appendix K. Long-term efficacy results from the ELATIVE trial

K.1 Biochemical response

Efficacy outcomes beyond Week 52, in the variable DB period of the ELATIVE trial, with a focus on Week 78, were presented at the European Association for the Study of the Liver (EASL) Congress 2024 (Table 7) (80). The Week 78 visit in the DB period was reached by 30/108 (28%) of patients receiving elafibranor and 13/53 (25%) of patients receiving placebo (80). At Week 78, 19/27 (70%) patients receiving elafibranor achieved a biochemical response compared with 0/13 (0%) patients receiving placebo. Out of these patients who received elafibranor, 4/19 (21%) patients had not achieved response by Week 52, and 15/19 (79%) patients had a sustained response from Week 52 (80). [redacted]

Figure 26 Percentage of patients with biochemical (cholestasis) response[a] to Week 78 (ITT analysis set)



Footnotes: [a] Cholestasis response was defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%.
Abbreviations: ALP: Alkaline phosphatase; ITT: intent-to-treat; mg: Milligram; TB: total bilirubin.
Source: Bowlus *et al.* 2024 (80)

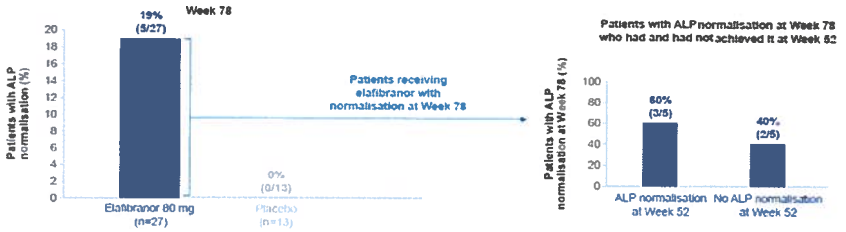
[redacted]

[redacted]

K.2 ALP normalisation

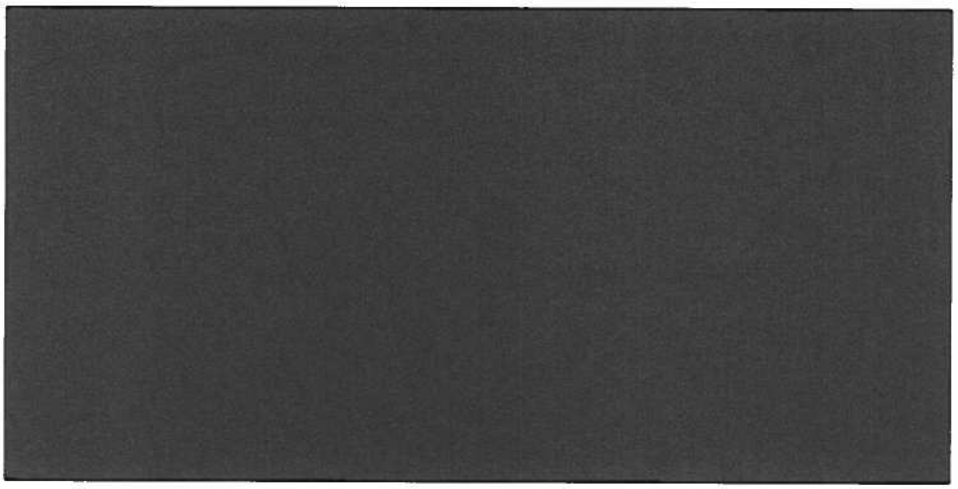
In the variable DB period at Week 78, ALP normalisation occurred in 5/27 (19%) patients receiving elafibranor compared with 0/13 (0%) patients receiving placebo (Figure 27) (80). Out of these patients who received elafibranor, 2/5 (40%) had not achieved ALP normalisation by Week 52; and 3/5 (60%) patients had sustained ALP normalisation from Week 52 (80).

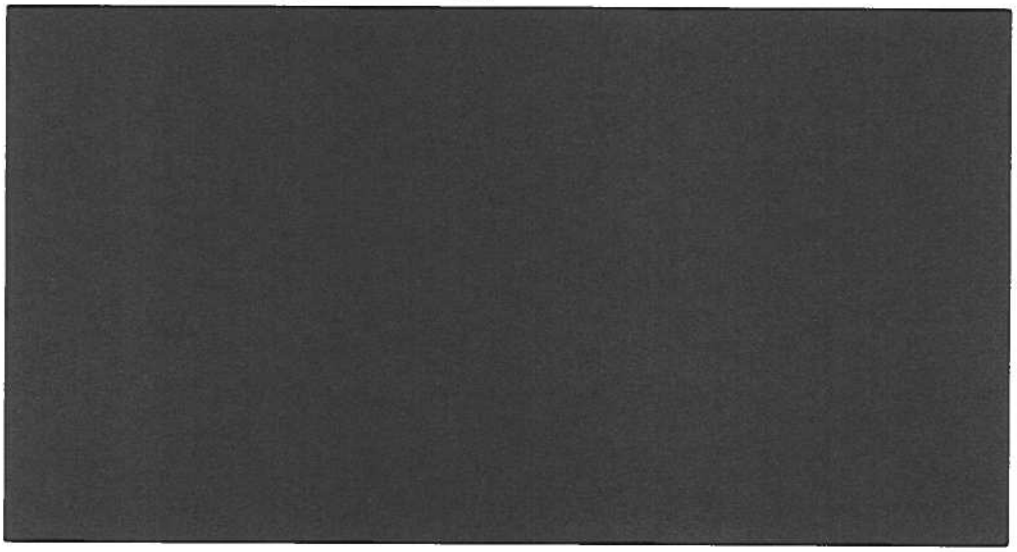
Figure 27 Percentage of patients achieving ALP normalisation to Week 78 (ITT analysis set)

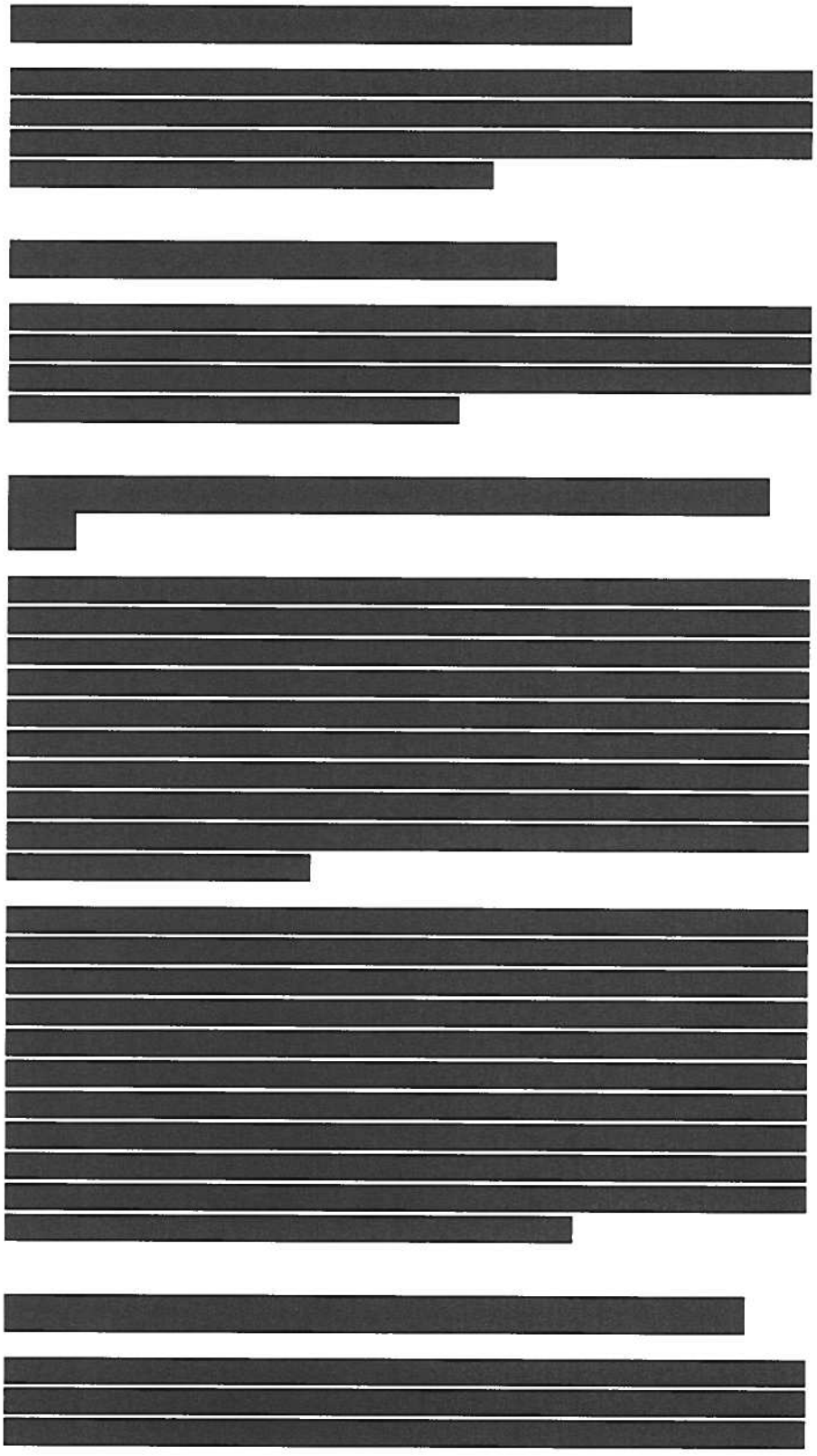


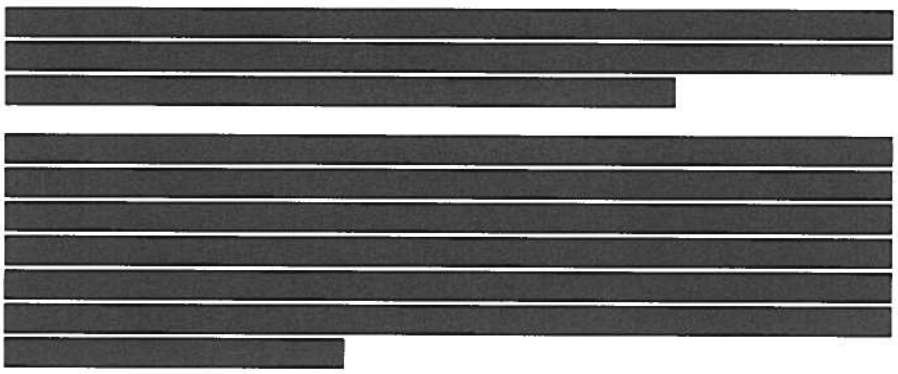
Abbreviations: ALP: Alkaline phosphatase; ITT: intent-to-treat
Source: Bowlus *et al.* 2024 (80)

[redacted]









Appendix L. Transition probabilities

L.1 PBC biomarker component

Table 78 Transition probabilities between baseline and Cycle 1 - elafibranor

[redacted]			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 79 Transition probabilities between Cycle 1 and Cycle 2 - elafibranor

[redacted]			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 80 Transition probabilities between Cycle 2 and Cycle 3 - elafibranor

[redacted]			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 81 Transition probabilities between Cycle 3 and Cycle 4 - elafibranor

[redacted]			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 82 Transition probabilities between baseline and Cycle 1 - UDCA

Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 83 Transition probabilities between Cycle 1 and Cycle 2 - UDCA

Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 84 Transition probabilities between Cycle 2 and Cycle 3 - UDCA

Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Table 85 Transition probabilities between Cycle 3 and Cycle 4 - UDCA

Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

Medicinrådet

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