Medicinrådet

Bilag til Medicinrådets anbefaling vedr. epcoritamab til behandling af diffust storcellet B-cellelymfom

Efter to eller flere linjer systemisk behandling

Vers. 1.0

Bilagsoversigt

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

Høringssvar til Medicinrådets vurdering af epcoritamab (Tepkinly)

AbbVie ønsker at takke for muligheden for at kommentere på Medicinrådets vurdering af epcoritamab. Vi ønsker at fremhæve nogle centrale punkter vedrørende data til sammenligning, vurderingskonsistens og håndtering af usikkerhed, patientoverførbarhed og behovet for nye behandlinger i 3. linje DLBCL i Danmark.

Vi bemærker dog, at Medicinrådet anerkender at epcoritamab har en overlevelses- og QALY-gevinst i alle fire scenarier præsenteret i vurderingsrapporten.

I vurderingen anvender Medicinrådet IPD data fra en subgruppe, som Abbvie ikke har haft mulighed for at inkludere i ansøgningen. Vi mener at der er væsentlige problemer med at anvende disse data og dermed også de konklusioner Medicinrådet drager

Usikkerhed i data

Medicinrådet anerkender, at der ikke findes evidens for at anbefale et bestemt regime til behandling i 3. linje, hvor patienter tilbydes den bedst tilgængelige behandling. Den bedste tilgængelige standardbehandling i dag for 3. linje DLBCL er R-kemoterapi (R-DHAP, R-GemOX, R-GDP, R-ICE), stråleterapi eller palliativ behandling. Derudover, kan patienter indgå i kliniske studier, og for nylig er CAR-T (Yescarta) blevet godkendt til behandling i 3. linje, men det forventes at få patienter vil være kandidater i denne linje.

For bedst at repræsentere dansk standardbehandling i 3. linje DLBCL baserede AbbVie den indirekte analyse i ansøgningen på SCHOLAR-1, et internationalt, multikohorte retrospektivt observationsstudie, som er bredt anvendt i tidligere medicinske evalueringer – både i Danmark og internationalt – SCHOLAR-1 er desuden refereret som et relevant datagrundlag i danske kliniske retningslinjer til at illustrere effekten af R-kemoterapi.

Medicinrådet har valgt at sammenligne epcoritamab (EPCORE-NHL-1-data) med data fra et dansk retrospektivt observationsstudie (Al-Mashhadi et al., 2023) som reference for standardbehandling.

AbbVie mener det er bemærkelsesværdigt at Medicinrådet påpeger usikkerheder ved AbbVies indirekte sammenligning mellem epcoritamab og SCHOLAR-1, men samtidig selv anvender data fra et retrospektivt observationsstudie uden at justere for væsentlige prognostiske variabler eller baseline-karakteristika såsom primær refraktær status eller refraktær i flere linjer (negativ prognostisk variabel), som Medicinrådet også selv nævner i rapporten er patienterne i epcoritamab armen også tungere behandlet end patienterne som indgår i det danske studie. Den manglende justering for parametre med betydning for overlevelsesudfald kan skabe bias i vurderingen af effektiviteten mellem epcoritamab og eksisterende behandling.

Derudover fremhæver Medicinrådet, at EPCORE-NHL-1 inkluderer patienter, der er yngre og har færre komorbiditeter sammenlignet med danske patienter. Det er dog uklart, om denne observation hviler på faktiske data, da baseline-karakteristika for subgruppen som Medicinrådet anvender (n=68) ikke er præsenteret, hvilket vanskeliggør en transparent vurdering af sammenligningen.

Vi mener, at datagrundlaget burde være mere konsistent og omfatte justering for relevante prognostiske variabler for at reducere usikkerheden i vurderingerne.

Overførbarhed af data til danske patienter

Medicinrådet fremhæver gentagne gange manglende overførbarhed af data fra EPCORE-NHL-1 til danske patienter på baggrund af forskelle i alder og komorbiditet. AbbVie er uenige i denne vurdering.

Vi mener, at EPCORE-NHL-1 er repræsentativt for danske patienter, og 14 ud af de 157 patienter (ITT populationen) er fra Danmark. Man kan argumentere for at poulationen er selekteret pga. inklusions- og eksklusionskriterierne i studiet, men dette er tilfældet for langt de fleste kliniske studier. Derfor vælger Medicinrådet også at anvende subpopulationen af patienter der anses som ”egnede til at indgå i kliniske studier” (n=68) til at sammenligne med epcoritamab.

Problemet med at anvende denne population, som er "egnede til at indgå i kliniske studier" er, at mange af patienterne rent faktisk har indgået i kliniske studier. Medicinrådet påpeger, at 28 % af population, har modtaget behandling i kliniske studier, som potentielt inkluderede bispecifikke antistoffer – muligvis epcoritamab. Det indebærer dermed, at Medicinrådet sammenligner epcoritamab med behandlinger der endnu ikke er anbefalet som standardbehandling i Danmark, men som må forventes at have bedre effekt end nuværende standardbehandling. I denne subpopulation er median overlevelsen 13 måneder, mens den i SCHOLAR-1 er 6,3 måneder. Man kunne forestille sig at den lange median overlevelse i det danske studie til dels er drevet af de 28% af patienterne der har modtaget behandling i kliniske studier (potentielt epcoritamab og andre bispecifikke antistoffer). Desværre er data for denne subpopulation ikke tilgængelig for AbbVie, så vi kan ikke udføre en analyse der kan belyse dette.

Samlet set fremstår denne vurderingsmetode inkonsekvent og problematisk, især fordi der ikke er foretaget justering for nogen prognostiske variabler, fordi baseline-karakteristika for subgruppen, de 68 patienter fra Al-Mashhadi et al. ikke er tilstrækkeligt beskrevet og ikke mindst fordi en stor andel af patienterne i Medicinrådets "komparatorarm" har modtaget behandling med lægemidler der ikke er standardbehandling i Danmark og sandsynligvis har en bedre effekt end den behandling danske patienter modtager idag.

Afventende fase III-data

Medicinrådet henviser i vurderingen til det igangværende fase III-studie GCT3013-05 for epcoritamab monoterapi sammenlignet med R-GemOX. Det er AbbVies forventning at resultaterne fra dette studie vil understøtte de allerede positive data for epcoritamab og give yderligere dokumentation for dets effekt og sikkerhed.

Medicinrådets scenarier

Vedrørende Medicinrådets scenarie 4, hvor OS-data for epcoritamab ekstrapoleres med Gamma og OS-data for kemoterapi ekstrapoleres med Generalised Gamma, observeres det, at kurverne krydser hinanden flere gange. I denne sammenhæng fremstår det ikke klinisk plausibelt, at overlevelsen for patienter med kemoterapi overstiger overlevelsen for patienter behandlet med epcoritamab fra år 3,5 og frem. Dette indikerer, at den pågældende ekstrapolering ikke afspejler de kliniske data korrekt. Samtidig har Gamma ekstrapoleringen for epcoritamab-armen det dårligste statistiske fit på data og valideret klinisk til ikke at afspejle forventningen af epcoritamab. Abbvie vurderer, at scenarie 1 er det mest relevante grundlag for at vurdere omkostningseffekten på. Scenarie 1 vurderingen bygger på, at samtlige statistiske test indikerer, at log-normal kurven giver det bedste fit til epcoritamabs data, og blev også valideret af eksterne kliniske eksperter. Samtidig vurderes log-logistisk ekstrapolering for kemoterapi at være mere klinisk plausibel, når den sammenholdes med eksisterende publicerede data.

Behovet for epcoritamab i 3. linje DLBCL

Epcoritamab har demonstreret bedre overlevelse sammenlignet med eksisterende behandlingsmuligheder i 3. linje DLBCL, en patientgruppe med meget dårlig prognose j.f. Al-Mashhadi et al. Ifølge danske hæmatologer er behovet blandt danske patienter for nye behandlingsmuligheder stort, da langt fra alle patienter kan modtage CAR-T og ofte må inkluderes i kliniske studier for at få adgang til lægemidler med nye virkningsmekanismer, men ikke alle patienter opfylder inklusionskriterier til kliniske studier, og der er færre pågående kliniske studier end tidligere. AbbVie påskønner Medicinrådets arbejde, men vi opfordrer Medicinrådet til grundigt at inddrage usikkerhederne ved den naive sammeligning med danske data man har valgt at lave, så man ikke undervurderer den effekt epcoritamab har vist i kliniske studier. Vi er indforstået med at Medicinrådet anser fase II data uden kontrolarm som meget usikre, men vi opfordrer til at Medicinrådet forsøger at håndtere den usikkerhed på en måde der kan komme danske patienter til gavn nu.

Med venlig hilsen,
AbbVie

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06.03.2025
CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.03.2025
Leverandør	AbbVie
Lægemiddel	Tepkinly (epcoritamab)
Ansøgt indikation	Behandling af diffust storcellet B-celle lymfom (DLBCL) efter to eller flere linjer systemisk behandling
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende to pristilbud på Tepkinly (epcoritamab):

Pristilbud 1:

Leverandøren tilbyder en pris baseret på en betinget anbefaling.

[redacted]

Tabel 1: Forhandlingsresultat, betinget anbefaling

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP	Ny forhandlet SAIP (DKK)	Ny forhandlet rabat ift. AIP
Tepkinly	48 mg (1 stk.)	49.264,51	[redacted]	[redacted]	[redacted]	[redacted]
Tepkinly	4 mg/0,8 ml (1 stk.)	4.105,38	[redacted]	[redacted]	[redacted]	[redacted]

Pristilbud 2:

Amgros har forhandlet følgende flade rabat på Tepkinly (epcoritamab):

Tabel 2: Forhandlingsresultat, flad rabat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Tepkinly	48 mg (1 stk.)	49.264,51	[redacted]	[redacted]
Tepkinly	4 mg/0,8 ml (1 stk.)	4.105,38	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Hvis Medicinrådet ikke anbefaler Tepkinly, indkøbes lægemidlet til AIP.

Aftaleforhold

Pristilbud 1 og 2 er betinget af en anbefaling. Ved en anbefaling, vil Amgros indgå en aftale med leverandøren som gælder fra den 01.03.2025. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

[redacted]

Information fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ikke andre bispecifikke antistoffer godkendt til DLBCL i 3. linje. Medicinrådet anbefalede ikke Columvi (glofitamab) i august 2024.
[redacted]

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tepkinly (pristilbud 1)	48 mg (1 stk.)	SC injektion i henhold til doseringsplan for optrapning, efterfuldt af anbefalet dosis på 48 mg hver 4. uge*	[redacted]	[redacted]
Tepkinly (pristilbud 2)	48 mg (1 stk.)	SC injektion i henhold til doseringsplan for optrapning, efterfuldt af anbefalet dosis på 48 mg hver 4. uge*	[redacted]	[redacted]

*Se SPC

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Under vurdering	Link til vurdering

Opsummering

[redacted].

Application for the assessment of epcoritamab (Tepkinly) for relapsed or refractory diffuse large B-cell lymphoma

Contact information

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Table of contents

Tables and Figures

Tables:

Figures:

Abbreviations

Abbreviation	
1L	First line
2L	Second line
3L	Third line
AE	Adverse events
AESI	Adverse event of special interest
AIC	Akaike information criteria
ASCT	Autologous Stem Cell Transplantation
AUC	Area under the curve
BCL	B-cell lymphoma
BCL2	B-cell lymphoma 2
BCL6	B-cell lymphoma 6
BIC	Bayesian information criteria
BMT	Bone marrow transplant
BR	Bendamustine + rituximab
BSC	Best supportive care
CAR-T	Chimeric antigen-receptor T-cell therapy

CD20	Cluster of differentiation 20
CEAC	Cost-effectiveness acceptability curve
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release response
DCI	Danish clinical input
DLBCL	Diffuse large B-cell lymphoma
DLG	Danish Lymphoma Group
DoR	Duration of response
DMC	Danish Medicines Council
DRG	Diagnosed related groups
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicine Agency
EPAR	European public assessment report
ESS	Effective sample size
FACT-Lym	Functional assessment of Cancer Therapy-
FIH	First in human
FL	Follicular Lymphoma
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICANS	Immune effector cell-associated neurotoxicity
IPD	Individual patient level data
IPI	Inventory Performance index
IRC	Investigator response controlled
IV	Intravenous
KM	Kaplan Meier
LBCL	Large B-cell Lymphoma
LDH	Lactate Dehydrogenase
MAIC	Matching adjusted indirect comparison
MUGA	Multiple-gated acquisition
MZL	Marginal zone lymphoma
NA	Not applicable
NE	Noneevaluable
NHL	Non-Hodgkin lymphoma
NMA	Network meta-analysis

NR	Not reached
OS	Overall survival
ORR	Overall response rate
PD	Progression of disease
PET-CT	Positron Emmissons Tomography
PH	Proportional hazard
PFS	Progression-free survival
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Per oral
Pola+BR	Polatuzumab + bendamustine and Rituximab
PPS	Post-progression survival
PR	Partial response
PSM	Partitioned survival model
RCT	Randomized clinical trial
R/R	Relapsed or refractory
R-DHAP	Rituximab + Dexamethasone + Cytarabine +
R-GDP	Rituximab + Gemcitabine + Cisplatin +
R-GemOX	Rituximab + Gemcitabine + Oxaliplatin
R-ICE	Rituximab + ifosfamide, Carboplatin and
RP2D	Recommended phase-2 dose
SC	Subcutanous
SCT	Stem cell transplantation
SD	Stable disease
TTD	Time to treatment discontinuation
TTNT	Time to next treatment

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	TEPKINLY
Generic name	Epcoritamab
Marketing authorization holder in Denmark	Abbvie A/S
ATC code	L01FX27
Pharmacotherapeutic group	Bispecific antibody
Active substance(s)	IgG1-bispecific antibody
Pharmaceutical form(s)	Subcutaneous (SC)
Mechanism of action	Epcoritamab is a humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B-cells and to CD3 on T-cells. The activity of epcoritamab is dependent upon simultaneous binding of CD20-expressing tumor cells and CD3-expressing T cells. Simultaneous binding to CD20 and CD3 induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells
Dosage regimen	Epcoritamab monotherapy SC in cycles of 4 weeks, i.e., 28 days administered as follows: • Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22 • Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22 • Cycles 4-9: epcoritamab 48 mg on Days 1 and 15 • Cycles 10 and beyond: epcoritamab 48 mg on Day 1
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Prednisolone and analgesics

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	1 packages of 48 mg vial 1 packages of 4 mg vial
Orphan drug designation	*EMA has granted an orphan drug designation*

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	R/R diffuse large B-cell lymphoma
Dosage regiment and administration:	Epcoritamab monotherapy SC in cycles of 4 weeks, i.e., 28 days administered as follows: • Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22 • Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22 • Cycles 4-9: epcoritamab 48 mg on Days 1 and 15 • Cycles 10 and beyond: epcoritamab 48 mg on Day 1
Choice of comparator	Chemotherapy (R-CIT)
Prognosis with current treatment (comparator)	Studies have shown that with the current available therapy (various chemotherapy options) for patient with R/R DLBCL median OS is approximately 6 months and 2y OS is around 20%.
Type of evidence for the clinical evaluation	ITC
Most important efficacy endpoints (Difference/gain compared to comparator)	- ORR - PFS - OS - Health related quality of life (HQoL)
Most important serious adverse events for the intervention and comparator	Cytokine release syndrome (CSR), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), Febrile neutropenia
Impact on health-related quality of life	Clinical documentation: EQ-5D-3L and FACT-Lym Health economic model: Better
Type of economic analysis that is submitted	Type of analysis is CUA

Summary	
	Type of model is a partitioned survival model
Data sources used to model the clinical effects	EPCORE-NHL-1 SCHOLAR-1
Data sources used to model the health-related quality of life	Excel
Life years gained	[redacted] years
QALYs gained	[redacted] QALY
Incremental costs	[redacted] DKK
ICER (DKK/QALY)	[redacted] DKK/QALY
Uncertainty associated with the ICER estimate	Clinical efficacy and HR value
Number of eligible patients in Denmark	Incidence: Not known Prevalence: 41 (estimated from clinicians) eligible patients in Denmark per year
Budget impact (in year 5)	[redacted] mio. DKK

DLBLC is the most common aggressive Non-Hodkins Lymphoma (NHL) subtype, and the prognosis is generally poor for the patients who develop relapse/refractory (RR) DLBCL. Studies have shown that with the current available therapy (various chemotherapy options) for patients with R/R DLBCL, the median OS is approximately 6 months, and 2-year OS is around 20%. There is no evidence to recommend one standard treatment regimen in 3L(+)(1). According to the Danish guidelines, consultations with Danish clinical experts and a published Danish study, multiple chemotherapy regimens can be considered for 3rd line DLBCL. The comparator for epcoritamab will be chemotherapy (CIT) combined with rituximab (R). Newer treatment options such as Chimeric antigen-receptor T-cell therapy (CAR-T) and polatuzumab (pola)-bendamustin+rituximab (BR) has not been recommended by the DMC for the treatment of R/R DLBCL in Denmark and are therefore not available.

Epcoritamab (Tepkinly) as monotherapy is indicated for relapsed and refractory DLBCL who has received 2 prior lines of therapy. Epcoritamab is a stable, of the shelf, subcutaneous (SC) administered, novel bispecific antibody targeting CD20 on the malignant B-cells and CD3 on the T-cells, and has demonstrated high efficacy and a manageable safety profile in R/R DLBCL patients. Epcoritamab offers a new treatment modality and treatment option in the 3rd L (+) landscape in DLBCL patients who has a high unmet need for new treatment options. The EMA approval is based on results from the EPCORE-NHL 1 study, that included patients with relapsed, progressive, and/or refractory

mature B-cell lymphoma. This trial included 139 patients with DLBCL who have had a median of three prior treatment lines.

The relative efficacy of epcoritamab compared to R-CIT have been calculated using indirect treatment comparisons (ITC). This analysis showed an overall survival that was significantly better for epcoritamab compared to CIT ([redacted]) and a complete response for epcoritamab that was [redacted] significantly higher than CIT. The efficacy and cost between epcoritamab and R-CIT has been evaluated in a Cost-utility analysis. The CUA resulted in an ICER of [redacted] DKK/QALY.

Epcoritamab is expected to provide a significant benefit to patients with deep and durable treatment effects and offer an advantage clinically meaningful to patients and clinicians when compared with currently available therapies.

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

3.1 Diffuse large B-cell lymphoma (DLBCL)

DLBCL is the most common aggressive non-Hodgkin's Lymphoma (NHL) subtype accounting for almost 30% of all NHL cases (2,3).It develops from B-cell precursors and is characterized morphologically by having large cancerous lymphocytes and a diffuse growth pattern(4). It can arise *de novo* or via transformation from an indolent NHL(5). Approximately 30–40% of patients have extranodal disease at presentation(3).
DLBCL arises from molecular events leading to over-proliferation of precursor cells in the pathway towards development of mature B-cells involved in antibody production and B memory cells(4). The molecular events result from oncogenic changes that alter cell cycle regulation and B-cell maturation. The oncogenes most frequently involved in the pathogenesis of DLBCL include *BCL2(B-cell lymphoma gene 2), BCL6 (B lymphocytes chemoattractant gene 6)* and *MYC. MYC* rearrangements are seen in approximately 12% of DLBCL tumors and occur together with a rearrangement of *BCL2* and/or *BCL6* in 4–8% of tumors(4). Such tumors are termed **double- or triple-hit lymphomas**.(3,6,7)

In addition to chromosome translocations leading to overexpression of oncogenes, overexpression in the absence of translocations is seen for *MYC* in approximately 45% of cases and *BCL2* in 65% of cases, with overexpression of both occurring in approximately 30% of cases, known as double-expressor lymphomas(4).

3.1.1 Clinical presentation and diagnosis

The symptoms of DLBCL at presentation are diverse and depend upon the sites of involvement, i.e., whether extra nodal or not and the specific extra nodal sites involved. General symptoms associated with DLBCL include pain in the chest, abdomen or bones, weight loss, fever, skin rash and fatigue.(1,8) The most common initial symptom is swelling of the lymph nodes e.g. in the neck, under the arms, in the groin or stomach, while symptoms associated with specific extra nodal sites include diarrhea or bleeding resulting from development in the abdomen; chest pain, breathlessness and cough if the chest is involved, and headaches if there is Central Nervous System (CNS) involvement. If the bone marrow is affected, this may manifest as anemia (extreme fatigue), increased risk of infection and bleeding problems. The constellation of fever, night sweats and unintentional weight loss are known as B-symptoms (8,9).

Accurate diagnosis is important to distinguish between NHL subtypes as treatment options and outcomes vary considerably between different lymphomas.(10)

A lymph node biopsy is essential for the diagnosis of DLBCL and includes involvement of a hematopathologist. An anamnesis and clinical examination are recorded with the important information on the duration and growth of lymph nodes or tumor and whether symptoms on extra nodal involvement e.g., CNS and B-symptoms (night sweats, weight loss and fever) are present. The Performance status (ECOG PS) are registered under the objective examination(1). Furthermore, a number of laboratory test[1] are required and a PET-CT of the whole body is used for diagnostic as well(1).

Disease risk category are used to guide therapy. A number of prognostic systems have been developed, including the International Prognostic Index (IPI) and/or age-adjusted IPI (aaIPI). The IPI defines four risk categories, based on age, Lactate Dehydrogenase (LDH), performance stage (PS), stage of disease at diagnosis and extra nodal involvement(1).

Table 1 international prognostic index (PI) (1,10)

International prognostic index (IPI)			Estimated 3-year overall survival (95% CI)
Risk factors Each of the risk factors is scored as yes=1, no=0, with total scores ranging from 0 to 5	Age >60 years		
	Serum LDH > normal		
	Stage III–IV		
	Performance status 2–4		
	Extranodal sites >1		
Risk categories	Low	0–1	91 (89–94)
	Low	2	81 (73–86)
	High	3	65 (58–73)

[1] a full list of laboratory test is found in the Danish Clinical Guidelines ver. 2.0 for DLBCL page 4

	High	4-5	59 (49–69)
Age-adjusted international prognostic index (aaIPI) in patients ≤60 years			
Risk factors	Serum LDH > normal		
	Stage III–IV		
	Performance status 2–4		
Risk categories	Low	0	98 (96–100)
	Low	1	92 (87–95)
	High	2	75 (66–82)
	High	3	

Determination of the stage of disease and risk category are also performed as part of the initial assessment of a patient(1,10). Staging determines the extent of spread of disease and is usually classified according to the Ann Arbor staging system which defines four stages of disease(1,11).

Table 2 Ann Arbor staging system(11)

Stage	
I	Involvement of a single lymphatic region (I) or localized involvement of single extra lymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extra lymphatic organ or site and of one or more lymphatic regions on the same side of a diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extra lymphatic organs with or without lymphatic involvement

DLBCL is an aggressive disease that progresses rapidly in the absence of appropriate therapy. Overall, 5-year relative survival for DLBCL has been reported to be approximately 55–65%. However, OS varies widely according to response to therapy with up to 60% of patients achieving long-term remissions, while 30–40% are refractory to or relapse after standard first-line chemoimmunotherapy (CIT) and have a much poorer OS(12).

3.2 Patient population

A study based on a Danish population-based registry investigated the OS and progression-free survival (PFS) from the initiation of 3rd line therapy. For the entire cohort (192 patients) the 2-year OS and PFS were 22% (95% CI 16-28) and 12% (95% CI 7-17) respectively, and the median OS was 6 months (95% CI 4.8-7.8). Patients with high IPI (4-5) had worse outcomes than patients with low IPI (0-1) with 2-year OS of 13% (95% CI 6-28) versus 40% (95% CI 40-95). Younger patients (< 70 years) had a 2-year OS and PFS of 27% (95% CI 18-41) and 16% (95% CI 9-28) respectively, which was significantly better than patients ≥ 70 years (p = 0.03) with an OS of 19% (95% CI 13-28) and PFS of 9% (95% CI 5-17) observed in these patients. . This study highlights the major unmet need for novel therapeutics, that is not yet readily available, for patients suffering from DLBCL who experience relapse or refractory disease(13).

The estimated 5-year prevalence (5 year since diagnose) of NHL was 5.727 patients in the year 2020 and has been increasing over time(14). The incidence was estimated to an average from 2016-2020 of 1.457 patients per year, see Table 3, and the predicted incidence for 2023 is 1.514 new NHL patients(14).In Denmark, approximately 450 new patients are diagnosed with DLBCL/year; excluding DLBCL patients with primary CNS lymphoma (out of scope). In a large nationwide population-based study from Sweden the proportion of DLBCL patients who were treated in first line had a 2y incidence of relapsed/refractory disease at 18.9% and the 5-year incidence was 23.1% (15). A recent publication based on the Danish LYFO-register states that 17% of DLBCL patients experience disease progression after median follow

-up of 77 months, and 2-year OS was 35% after 79 months (16).

Table 3 Incidence and prevalence (total years since diagnosis) for 5 years (2016-2020) of NHL patients(14).

Year	2016	2017	2018	2019	2020
Incidence NHL in Denmark	1.472	1.487	1.443	1.440	1.442
Prevalence NHL in Denmark	11.828	12.546	13.137	13.717	14.246

3.2.1 Patient populations relevant for this application

Epcoritamab as monotherapy is indicated for relapsed and refractory DLBCL who has received 2 prior lines of therapy.

The EMA approval is based on results from the EPCORE-NHL 1 study, that included patients with relapsed, progressive, and/or refractory mature B-cell lymphoma.

In Denmark, the 2L treatment is split into patients being eligible for high-dose therapy – autologous stem cell transplant (HDT-ASCT) and patients ineligible for this treatment. For the latter there are no Standard of care (SOC) for this patient population, but patients who

are in a good performance, curative intended treatment can be considered such as Rituximab + following combination therapies: Gemcitabin+Dexamethasone+Cisplatin (GDP), Dexamethasone+cytarabine+cisplatine (DHAP), Gemcitabine+Oxaliplatine (GemOx), ifosfamide+carboplatin+etoposide phosphate (ICE). In either group 50% of patients do experience relapse of their disease(17).

Patients who do not respond, or relapse early (< 6 months) and hence are refractory to their 2L therapy, or patients who later relapse and proceed to 3L therapy are in scope for this application.

There is no evidence to recommend one standard treatment regimen in 3L(+)(1). In Denmark, the patients will be offered a clinical trial if available and relevant for the patient, other options are to consolidate treatment after relapse from ASCT with allogenic Bone marrow transplant (BMT) if chemosensitive disease, chemoimmunotherapy (CIT) or Best Supportive Care (BSC) for vulnerable patients. Newer treatment options such as Chimeric antigen-receptor T-cell therapy (CAR-T)and polatuzumab (pola)-bendamustin+rituximab (BR) has not been recommended by the DMC for the treatment of R/R DLBCL (CAR-T 3rd line) in Denmark and are therefore not available. However, recently CAR-T has been reimbursed for patients with DLBCL who are relapsed/refractory <12 month from completion of first-line therapy. From a recent abstract presented at ASH 2022, patients treated in 3L in Denmark, have a poor outcome; the 2-year OS and PFS were 22% (95% CI 16-28) and 12% (95% CI 7-17) respectively, demonstrating the clear unmet need for R/R DLBCL patients in Denmark who fail HDT-ASCT or are ineligible to this treatment(13).

It is estimated that approximately 100 patients with DLBCL in Denmark are refractory or relapsed after 2 or more lines of systemic treatment. Of those approximately 41 patients will be eligible to epcoritamab treatment.

See **Error! Reference source not found.** and Table 4.

Table 4 Estimated number of patients eligible for treatment.

Year	2024	2025	2026	2027	2028
Number of expected patients in Denmark eligible for treatment per year	41	41	41	41	41

3.3 Current treatment options

The DLBCL group under the Danish Lymphoma Group (DLG) and the Danish Multidisciplinary Cancer Groups (DMCG) has prepared the clinical treatment recommendations for DLBCL(1).

Before treatment initiation patient history and physical examination are performed, performance scores are obtained, registration of any B-symptoms or symptoms of CNS involvement (if CNS involvement different treatment guidelines apply) as well as all pathological parameters will be described.

1L treatment

Patients are scanned by PET-CT and have a biopsy performed to inform on the diagnosis. Patients are risk stratified by the IPI score (or aaIPI). Treatment recommendations are based upon stage (Ann Arbor) at diagnosis (or relapse) and the prognostic IPI score.

The choice of treatment in 1L is CIT as standard of care (SOC) – most often R-CHOP. The number and length of the R-CHOP cycles varies and depends on patient' age and stage of the disease. Radiation therapy can be offered to elderly patients with localized disease. For high-risk patients with aaIPI 2-3 addition of etoposide to CHOP is recommended(1).

For elderly >80 years the treatment depends on fitness of the patients (fit, frail, or vulnerable). Fit patients are treated with R-CHOP or R-miniCHOP, frail with R-miniCHOP and vulnerable patients with best supportive care (BSC)(1).

2L treatment

Even though the 5y survival rates in DLBCL is high in 1L – between 60% to 70%, almost 50% of patients do become refractory or relapse after treatment(18). Patient who are either refractory to their R-CHOP or have an early relapse (≤ 12 months after therapy or ASCT) or patients who relapse within the first 2 years have a poor prognosis (18) and many of the patients do not have any curative treatment options, hence there is a high unmet need for new treatment options for these patients (19). Recently CAR-T has been reimbursed for patients with DLBCL who are relapsed/refractory <12 month from completion of first-line therapy.

In Denmark, the recommendation for patients, who are below 65 to 70 years of age without significant comorbidity who experience a chemosensitive relapse, is to offer induction treatment with either R-DHAP (rituximab -dexamethasone, cytarabine and cisplatin) or R-ICE (rituximab – ifosfamide, carboplatin and etoposide) followed by high

dose therapy (HDT) ASCT, if the patient responds to the induction treatment. For ASCT eligible patients the above treatment regimen is the best option for a curative treatment in 2L; however, 50% of patients do relapse post transplantation (1,18,20,21).

For ASCT ineligible patients due to e.g., poor fitness, coexisting medical condition or no response to salvage therapy or who relapse after ASCT(19) there are no treatment recommendations in Denmark as SOC(1,3). Patients who fulfill inclusion criteria will be offered a clinical trial if available. For patients in good performance potential curative intended treatment should be considered such as R-GDP (rituximab – gemcitabine, dexamethasone, cisplatin), R-DHAOx, R-GemOX or R-ICE.

A Real world evidence (RWE) study from the US demonstrated that survival is significantly longer for patients who undergo ASCT compared with those who do not. Patients that did not receive ASCT had a median OS of 10.1 month at a median follow-up of 12.7 months. (22,23). Most of the patients who did not undergo ASCT relapse early on or after second-line therapy (R-CIT) (18,20).

However, only approximately 30% of patients receiving ASCT achieve long-term remission (24). Response prior to the ASCT is a key determinant of survival, with 5-year OS being 49% in those achieving complete response (CR) but only 13% in those achieving partial response (PR), respectively. For those who relapse post-ASCT, disease progression is generally rapid, with median OS being approximately 6 months(18).

3L+ treatment

3L treatment is rarely curative for DLBCL patients. The choice of treatment considered for the patients should be based on efficacy and the potential adverse events for the patient. There is no SOC recommended as 3L treatment in Denmark or in international guidelines(10). If the patient meets the inclusion criteria a clinical trial can be offered if it is available. Allogeneic BMT can be offered to consolidate the treatment of an ASCT relapse – if the patient has a chemosensitive disease. The outcome after allogeneic transplantation is very dismal and survival depends on the donor, conditioning, performance score and disease status and control of the disease(1).

CAR-T is a valid treatment option for patient who are refractory to 2L treatment or relapse ASCT, however in Denmark the DMC has not recommended the use of CAR-T in R/R DLBCL patients after ≥ 2 lines of systemic therapy(1).

Epcoritamab is a novel bispecific antibody targeting CD20 on the malignant B-cells and CD3 on the T-cells, has demonstrated high efficacy and a manageable safety profile in R/R DLBCL patients and offers a new treatment modality and treatment option in the 3rd L (+) landscape in DLBCL to these patients who has a high unmet need for new treatment options and are difficult to treat.

3.4 The intervention epcoritamab

Table 5 Overview of epcoritamab

Overview of intervention	
Therapeutic indication relevant for the assessment	Refractory or relapse DLBCL 3rd line
Method of administration	Subcutaneous
Dosing	Epcoritamab monotherapy SC in cycles of 4 weeks, i.e., 28 days administered as follows: • Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22 • Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22 • Cycles 4-9: epcoritamab 48 mg on Days 1 and 15 • Cycles 10 and beyond: epcoritamab 48 mg on Day 1
Dosing in the health economic model (including relative dose intensity)	Same as above, RDI 99%
Should the pharmaceutical be administered with other medicines?	Prednisolone and analgesics in the beginning to avoid side effects
Treatment duration / criteria for end of treatment	Median Time to Treatment Discontinuation (TTD) from EPCORE-NHL-1 Criteria for end of treatment were adverse events or progression of disease
Necessary monitoring, both during administration and during the treatment period	Regular follow ups within the disease area, see Danish clinical guidelines
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	All test currently applied in Danish clinical practice – same for intervention as for comparator
Package size(s)	1 packages of 48 mg vial 1 packages of 4 mg vial

3.4.1 The intervention in relation to Danish clinical practice

The indication for epcoritamab in patients with R/R DLBCL is:

- Epcoritamab is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

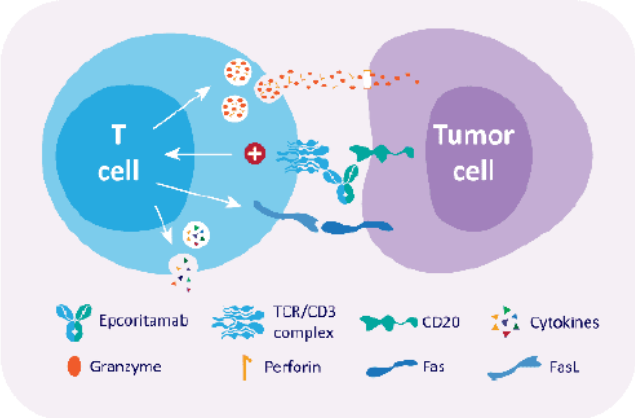
Epcoritamab is a stable, of the shelf, subcutaneous (SC) administered, bispecific antibody (bsAb) that harness the patient's own immune system to potently kill CD20+ malignant B cells. Epcoritamab binds to a unique epitope on CD20, expressed on the surface of normal and malignant B-lymphocytes, and simultaneously binds CD3, a protein complex that is part of the T-cell receptor, involved in the activation of T-cells; only simultaneous binding to CD20 and CD3 will activate T-cells and induce potent T-cell mediated killing of CD20+ malignant B cells. (25–27)

- **CD3** is a component of the T-cell receptor signaling complex expressed on all T cells. Targeting CD3 enables epcoritamab to specifically recognize and activate T-cells once bound to CD20 expressing B-cells.
- **CD20** is expressed on B-cells, specifically those of the B-cell lineage from pre-B-cells to plasma blasts, as well as many B-cell malignancies, including DLBCL. Targeting CD20 enables epcoritamab to minimize DLBCL tumor cells. Resistance rarely arises due to loss of CD20 in patients treated with anti-CD20 agents, indicating the suitability of CD20 as a B-cell target. Furthermore, epcoritamab induces potent T-cell–mediated killing even when CD20 expression levels on target B cells are very low(26,28).

The simultaneously binding of epcoritamab to CD3 on T cells and CD20 on B cells creates a trimer formation, seeFigure 1. This cross-linking of CD3 triggers T-cell activation, including proliferation and initiation of cytotoxic activity through the release of perforin and granzymes, ultimately leading to tumor cell death(26,28). Thus epcoritamab recruits the patient's T-cells to act as cytotoxic effectors against tumor cells. The process is strictly dependent on epcoritamab binding to both targets, thereby minimizing off-target effects(26,28).

Epcoritamab was designed to minimize the risk of inducing the production of anti-epcoritamab antibodies or cytokine release syndrome (CRS). Epcoritamab's silent $\mathbf{F_c}$ region means unnecessary recruitment of other effector cells is circumvented. This change may prevent unwanted adverse side effects resulting from an overactive immune system such as cytotoxicity/phagocytosis and complement dependent cytotoxicity (26).

Figure 1 Epcoritamab mechanism of action(26)



Posology and MoA(29)

Epcoritamab was administered SC in 28-day cycles starting with once-weekly dosing, then moving to q2w and finally q4w. In the dose escalation phase, once weekly dosing was given during cycles 1 and 2, 2qw dosing was given cycles 3–6 and q4w dosing was employed from cycles 7 onward; the schedule for the dose expansion phase was slightly different as given below:

- Cycles 1 to 3: Days 1, 8, 15, and 22 (qw)
- Cycles 4 to 9: Days 1 and 15 (q2w)
- Cycle 10 and beyond until unacceptable toxicity, PD, or withdrawal of consent: Day 1 (q4w)

Epcoritamab was continued until disease progression or unacceptable toxicity. Dose modifications were not permitted, although dose interruptions were permitted. A patient could resume epcoritamab therapy if the severity of the dose-limiting toxicity decreased to a maximum of grade 2 or the baseline level within 4 weeks.

In the EPCORE NHL-1 study patients were hospitalized for 24 hours after the first full dose of epcoritamab (this planned hospitalization was not to be reported as an serious adverse events (SAE). (29)

After the first dose there is no treatment specific monitoring needed. The disease management is dependent on patient's disease stage, i.e., whether the patient is progressing or staying progression free.

3.5 Choice of comparator(s)

Patients who are eligible for this indication in Denmark and relevant for this assessment are the following (validated by Danish clinical experts):

1) patients who are eligible for ASCT but will fail conditioning therapy

2) patients who fail treatment with ASCT after conditioning regimen,

3) patients who are not eligible for ASCT and have failed 2L treatment with chemotherapy (+/- R)

According to the Danish guidelines (se section 3.3), consultations with Danish clinical experts and a published Danish study, multiple chemotherapy regimens can be considered for 3rd line DLBCL and both R-GemOX, R-GDP and R-DHAP are potential treatment options. The comparator for epcoritamab will be chemotherapy combined with rituximab. R-GemOx, R-DHAP and R-GDP will be described separately by each component followed by description of each regime. Dosing and treatment duration are based on Danish clinical experts.

3.5.1 Rituximab (ATC L0XC02)(30)

Table 6 Rituximab information

Overview of comparator	
Generic name	Rituximab
ATC code	L0XC02
Mechanism of action	Rituximab is a human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences

Overview of comparator	
Method of administration	Concentrate for solution for infusion
Dosing	Rituximab should be administered as intravenous infusion through a dedicated line under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Recommended dosage is 375 mg/m^2 body surface area. Recommended initial rate for infusion is 50 mg/h; after first 30 minutes it can be escalated to 50 mg/h increments every 30 minutes, to maximum 400 mg/h. subsequent doses of rituximab can be infused at initial rate of 100 mg/h and increased by 100 mg/h increments at 30 minutes intervals to a maximum of 400 mg/h. RDI: 100%
Dosing in the health economic model (including relative dose intensity)	375 mg/m^2 body surface area
Should the pharmaceutical be administered with other medicines?	Premedication consisting of Prednisolone an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine should be given 30-60 minutes before each administration in non-Hodgkin's lymphoma.
Treatment duration/ criteria for end of treatment	Average 4 cycles (in health economic model), discontinuation if adverse events or side effects
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	supplied at a concentration of 10 mg/mL in 100 mg/mL or 500 mg/mL vials

3.5.2 Gemcitabine (ATC code: L01BC05)

Table 7 Gemcitabine information

Overview of comparator	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Gemcitabine is a pyrimidine antimetabolite and shows cytotoxic effects against a variety of cultured murine and human tumor cells. It kills cells that are undergoing DNA-synthesis and under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary.
Method of administration	Solution for infusion, IV
Dosing	Gemcitabine should be administered intravenous and should prescribed by a physician qualified in the use of anti-cancer chemotherapy. The recommended dose is 1000 mg/m^2, given by 30 minutes infusion. It should be given on days 1 and 8 of each 21-day cycle.
Dosing in the health economic model (including relative dose intensity)	100 mg/m^2, body surface area, RDI 100%

Overview of comparator	
Should the pharmaceutical be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	4 cycles, average
Need for diagnostics or other tests (i.e. companion diagnostics)	All patients must be monitored before each dose for platelet and granulocyte counts.
Package size(s)	10 mg/ml, 38 mg/ml, 40 mg/ml

3.5.3 Oxaliplatin (ATC: L01XA03)

Table 8 Oxaliplatin information

Overview of comparator	
Generic name	Oxaliplatin
ATC code	L01XA03
Mechanism of action	Oxaliplatin is a cytostatic, a platinum complex with mainly alkylating effect.
Method of administration	Solution for infusion, IV
Dosing	Gemcitabine should be administered intravenous and should be prescribed by a physician qualified in the use of anti-cancer chemotherapy. The recommended dose is 1000 mg/m^2, given by 30 minutes infusion. It should be given on days 1 and 8 of each 21-day cycle.
Dosing in the health economic model (including relative dose intensity)	The recommended dose for oxaliplatin is 100 mg/m^2 intravenously repeated every 2 weeks. Oxaliplatin is administered over 2 hours. RDI: 100%
Should the pharmaceutical be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	4 cycles, average
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	5 mg/ml at 10 ml, 20 ml and 40 ml

3.5.4 Dexamethasone oral tablets (ATC: (H02AB02)

Table 9 Dexamethasone information

Overview of comparator	
Generic name	Dexamethasone, oral tablets
ATC code	H022AB02
Mechanism of action	Dexamethasone is a synthetic glucocorticoid which reduces inflammation and suppresses the migration of neutrophils and decreasing lymphocyte colony proliferation.
Method of administration	Tablets

Overview of comparator	
Dosing	Initial dose for non-Hodgkin's lymphoma is 40 mg or 20 mg once per day. The dose and administration frequency varies within therapeutic area and treatments. Local guidelines should be followed. Dexamethasone Soluble Tablets should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided.
Dosing in the health economic model (including relative dose intensity)	40 mg tablets (clinical input)
Should the pharmaceutical be administered with other medicines?	Should be swallowed with water. Can be crushed.
Treatment duration/ criteria for end of treatment	4 cycles, average
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	1 mg and 4 mg at 20 pc., 100 pc., 40 mg at 10 pc.

3.5.5 Cisplatin (ATC: L01XA01)

Table 10 Cisplatin information

Overview of comparator	
Generic name	Cisplatin
ATC code	L01A01
Mechanism of action	Cisplatin is a cytostatic, a platinum complex with mainly alkylating effect.
Method of administration	Concentrate for solution for infusion, IV
Dosing	Cisplatin should be administered intravenously and should be prescribed by a physician qualified in the use of anti-cancer chemotherapy. The recommended dose is 50-100 mg/m^2 every 3-4 weeks. The cisplatin should be administered by intravenous infusion over a period of 6 to 8 hours.
Dosing in the health economic model (including relative dose intensity)	100 mg/$m^{2,}$ RDI 100%

Overview of comparator	
Should the pharmaceutical be administered with other medicines?	Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realized by intravenous infusion of one of the following solutions: Sodium chloride solution 0.9%. Mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1). Hydration prior to treatment with cisplatin: Intravenous infusion of 100 to 200ml/hour for a period of 6 to 12 hours. Hydration after termination of the administration of cisplatin: Intravenous infusion of another 2 liters at a rate of 100 to 200 ml per hour for a period of 6 to 12 hours. Forced diuresis may be required should the urine secretion be less than 100 to 200 ml/hour after hydration. Forced diuresis may be realised by intravenously administering 37.5g mannitol as a 10% solution (375 ml mannitol solution 10%), or by administration of a diuretic if the kidney functions are normal. The administration of mannitol or a diuretic is also required when the administrated cisplatin dose is higher than 60 mg/m^2 of body surface.
Treatment duration/ criteria for end of treatment	4 cycles, average
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	1 mg/ml, at 50 ml conc. And 100 ml. conc.

3.5.6 Cytarabine (L01BC01)

Table 11 Cytarabine information

Overview of comparator	
Generic name	Cytarabine
ATC code	L01BC01
Mechanism of action	Cytarabine is a cytostatic, a platinum complex with mainly alkylating effect.
Method of administration	Solution for infusion, IV
Dosing	Cytarabine is administered by intravenous infusion or injection, or subcutaneous injection. Dosage recommendation is 2000 mg/m^2 at the first day, and once again after 12 hours.
Dosing in the health economic model (including relative dose intensity)	Cytarabine is administered by intravenous infusion, 2000 mg/m^2, body surface area, twice at day 1, RDI: 100%

Overview of comparator	
Should the pharmaceutical be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	4 cycles, average
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	100 mg/ml at 10 ml, 100 mg/ml at 20 ml, 20 mg/ml at 5x5 ml and 20 mg/ml at 5 ml.

3.5.7 Per comparator used in the health economic model

The posology and treatment duration are based on communication with clinicians.

Table 12 Posology and treatment of R-GemOX in Danish clinical practice(31)

Comparator: R-GemOX	
Generic name	Rituximab, gemcitabine and oxaliplatin
Posology	Rituximab 375 mg/m^{2,} 90 minutes infusion, day 1 Gemcitabine 1000 mg/m^2, 100 minutes infusion, day 1 and 8 Oxaliplatin: 100 mg/m^2, 2 hours infusion, day 1
Treatment duration	In cycles 21-days for average 4 cycles

Table 13 Posology and treatment of R-GDP in Danish clinical practice(32)

Comparator: R-GDP	
Generic name	Rituximab, gemcitabine, dexamethasone, and cisplatin
Posology	Rituximab 375 mg/m^{2,} 90 minutes infusion day 1 Gemcitabine 1000 mg/m^2, 100 minutes infusion at day 1 and 8 Dexamethasone 40 mg day 1-4 Cisplatin 100 mg/m^{2,} 1 hour infusion, day 1
Treatment duration	In cycles of 21-days for average 4 cycles

Table 14 Posology and treatment of R-DHAP in Danish clinical practice(33)

Comparator: R-DHAP	
Generic name	Rituximab, Dexamethasone, Cytarabine and cisplatin
Posology	Rituximab 375 mg/m^{2,} 90 minutes infusion day 1 Dexamethasone 40 mg day 1-4 Cytarabine 2g/m^2 2 hours infusion, twice day 2 Cisplatin 100 mg/m^2 1 hour, day 1
Treatment duration	In cycles of 21-days for average 4 cycles

3.6 Cost-effectiveness of the comparator(s)

As mentioned in section 3.2.1 and section 3.3 cost-effectiveness analysis will be performed on epcoritamab compared to R-CIT (GDP, DHAP and GemOX). This comparator has been considered as established standard of care in Danish clinical practice and it would be arguably unethical to withhold a therapy of proven efficacy from any patient. Associated costs for R-CIT are considered low. No cost-effectiveness analysis of placebo will be included in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

As outcomes validated by independent review committee (IRC) can be seen as inherently more reliable and reduce the risk of bias, PFS and response outcomes (Lugano definition) from EPCORE NHL-1 were based on the IRC. Whenever available, IRC definitions were used for comparators but when not available - investigator-assessed.

Table 15 Efficacy outcome measures relevant for the application

Outcome measure	Definition	How was the measure investigated/method of data collection
ORR [EPCORE-NHL-1] [SCHOLAR-1]	ORR was defined as the proportion of patients who achieved best overall response of complete response (CR) or partial response (PR)	Lugano response criteria by IRC, Time-to-event, subgroup DLBCL
DoR [EPCORE-NHL-1]	Duration of Response defined as time from first documentation of response to the date of progression or death	Determined by the Lugano and LYRIC response criteria assessed by IRC, Time to event
PFS [EPCORE-NHL-1]	Defined as time to first documented PD or death	Determined by the Lugano criteria and LYRIC and reviewed by IRC, Kaplan meier
Overall survival (OS) [EPCORE-NHL-1] [SCHOLAR-1]	OS is defined as the time from randomization to death from any cause.	Determined by the Lugano criteria and reviewed by IRC , Kaplan meier
HQoL EQ-5D-3L [EPCORE-NHL-1]	A difference in EQ-5D-3L, Change from baseline, start and to end follow-up	
HQoL – FACT-Lym [EPCORE-NHL-1]	A difference in FACT-LYM, Change from baseline in health related quality of life (HRQoL) over time in relation to treatment, start and to end follow up	Changes in lymphoma symptoms as measured by FACT-Lym
AE [EPCORE-NHL-1]	Patients who experience at least 1 serios adverse events, Grade 3,4 and 5 ICANS and CRS.	

OS and health related quality of life (EQ-5D-3L and FACT-LYM) has previously been validated as relevant efficacy outcome measures in DMC's assessments(34).

4. Health economic analysis

A cost-utility model was developed to assess the cost-effectiveness of Epcoritamab vs. relevant comparator for relapsed/refractory DLBCL who received 2 or more prior lines of therapy. The comparators that reflect Danish clinical practice is R-CIT. R-GemOX, R-DHAP and R-GDP are relevant to represent the current standard care for the population in this application.

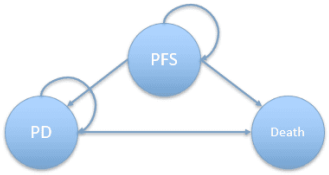
4.1 Model structure

The model used in the health economic analysis is a partitioned survival model (PSM) and included three different health states: progression-free survival (PFS), progressive disease (PD), and death. The proportion of patients within each health state was determined by OS and PFS curves via an area-under-the-curve (AUC) approach.

All patients started in the PFS state at the model start. The proportion of patients in the PFS state of the model was set to be equal to the PFS curve of each treatment. The PD state included alive patients who progressed . The proportion of patients in the PD state was set to be equal to the difference between the proportion of living patients, which was based on the OS curve, and the proportion of PFS patients. The model also include on and off treatment (TTD) for epcoritamab, where patients under the TTD curve was in progression-free state and on treatment, the patients between the TTD and PFS curve are in progression-free state but off-treatment.

During each cycle, patients were redistributed among the three health states, with death being the absorbing state. Each cycle are 28 days and half-cycle correction was applied.

Figure 2 Partitioned survival model structure



The model has been validated by clinical experts and is a typical approach in modelling oncology products. The time horizon was set to 30 years, to capture all differences in cost and clinical outcomes between epcoritamab and comparators. Background mortality for the Danish population was included to make sure that the Overall survival did not exceed the general mortality.

The model approach for comparison is PSM but made more flexible by allowing to capture the variation in hazards.. If this exist, it is very important to take the timepoint when different hazard ratio (HR) between intervention and comparator occurs into consideration. In this model both the log-cumulative hazard plot and input from clinical experts has been used to assist HR over time and it has been concluded by the experts that it seems clinically plausible to use same HR value in the model's time horizon.

For Denmark clinical input show that the Danish clinicians for now considers using epcoritamab until progression, however, they also stated that they have seen patients stopping treatment due to other reasons than progression and that those patients stayed in long term remission. Due to this the clinicians also gave the input that they will stop treatment for patients in long-term remission if there are specific reasons for the patient to do this such as toxicity burdens. To treat until progression differs from statements of clinicians in several countries (including Sweden, Norway and UK) where the clinicians have given the input that they will stop treatment when the patients have been in long-term remission for 2-3 years. Therefore, the model allow for long-term remission for the patients staying in progression free state but this had not been included in the base case analysis in this application but it is included in a scenario analysis.

4.1.1 Target population used in the application

The target population for this application is described in section 3.2 and will be based on the R/R (treatment with at least two prior lines) DLBCL population from the EPCORE-NHL-1 study, no prior CAR-T. The restriction to the no prior CAR-T patient population in the study was implemented to ensure comparability between the populations in EPCORE-NHL-1 and standard of care in Denmark. Recently CAR-T has been reimbursed for patients with DLBCL who are relapsed/refractory <12 month from completion of first-line therapy. However, clinical experts provided input indicating that prior CAR-T treatment is an important prognostic factor that could potentially influence the outcomes of the study. Since there were no previous studies conducted with the standard of care in Denmark that included patients who had received CAR-T treatment, it was necessary to exclude this population to maintain consistency in the data analysis.
Out of the total 139 patients with DLBCL included in the study, [redacted] had previously received CAR-T treatment. For detailed information and data regarding full population including the prior CAR-T patient population, please refer to section 6.1.2.2.

4.2 Model features

The perspective of the analysis is a limited societal perspective, considering all relevant treatment related costs as drug costs, drug administration costs, monitoring, management of AEs, subsequent treatment costs and disease management costs. Also, patient time- and transportation costs were included. Cost and utilities were assigned to the health states PFS and PD states, and disutilities for AEs not connected to a specific health state or treatment, but to the AE occurring.

The inputs were based on Danish sources where possible. The efficacy of epcoritamab was based on the target population R/R DLBCL with 2 or more prior lines, and no CAR-T. The

efficacy for R-CIT was based on SCHOLAR-1, see section 5 for the literature used for the clinical assessment.

A discount rate of 3,5% on both utilities and cost was used as specified in Danish guidelines(35).

R-CIT dosing, frequency and test are based on Danish clinical experts.

Efficacy inputs are presented in section 7 and cost inputs are presented in section 11.

Table 16 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with DLBCL, 2 prior lines of therapy	NA
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population (66 years). Validated by Danish clinical expert
Cycle length	28 days	Consistent with length of treatment cycle
Half-cycle correction	Yes	
Discount rate	3.5 %	According to methods guide
Intervention	Epcoritamab	
Comparator(s)	R-CIT as: R-GemOX R-DHAP R-GDP	According to national treatment guidelines. Validated by Danish clinical expert
Outcomes	OS, PFS, Utilities (EQ-5D-3L)	For a CUA as Partitioned survival model

5. Overview of literature

5.1 Literature used for the clinical assessment.

A systematic literature research was performed in PubMed and Cochrane Library to identify studies used as relevant treatment comparison to epcoritamab. The inclusion and exclusion criteria as well as search strategy and PRISMA flow diagram can be found in Appendix H.

All studies included for selection based on full article review were discussed with clinical experts.

Studies to be considered in the assessment and for inclusion are based on following criteria:

- Patients that had received two or more prior lines of therapy.
- Reported key baseline characteristics.
- Included KM curve for OS.
- Reported outcomes similar to EPCORE-NHL-1

If no appropriate data available, the comparator population that was most representative of the epcoritamab population was selected. Following feedback from clinicians, the most important effect modifiers were age, refractoriness, prior lines, and disease stage.

Several studies were screened for the best comparable efficacy against epcoritamab based on which patient population that best match the EPCORE-NHL-1 study. Patient characteristics were validated by clinical input, and especially heavily refractoriness was pointed out to be an important effect modifier in the EPCORE-NHL-1, for this reason one of the studies (CORAL) that was found comparable to epcoritamab was excluded based on missing information on important prognostic factors and effect modifier. In conclusion, one study was found to be relevant in the efficacy comparison to epcoritamab which was SCHOLAR-1 and this study was included in the clinical assessment of epcoritamab. This study has also been investigated and assessed in previous NICE and TLV decisions and EMA accepted it as comparator when evaluating Yescarta(36).

Recently, a Real-World Evidence (RWE) study was conducted based on Danish registries, focusing on patients with relapsed/refractory DLBCL.(37) The study included 189 patients who had received at least three lines of therapy. The findings revealed that the 2-year OS and PFS estimates for all patients were 25% and 12%, respectively. Several patient characteristics were identified as predictors of poor outcomes, including age ≥ 70, central nervous system (CNS) involvement, elevated LDH levels, and ECOG performance status ≥ 2. The median follow-up period was 31 months.
Of the patients included, 76% were refractory to the previous line of therapy, and those who were refractory to the most recent treatment line experienced particularly poor outcomes. Excluding patients who received best supportive care (BSC) and palliative radiotherapy, 182 patients were considered potential candidates for third-line trials. Among them, 68 patients met the eligibility criteria for clinical trials, with 19 enrolled, although the specific treatments they received were unknown.
The study was explored for the possibility of conducting a MAIC using this patient population. However, only two patient characteristics, age ≥65 years and IPI, were available for analysis, which limited the ability to accurately adjust the EPCORE-NHL-1 patients to match. Additionally, it should be noted that the study included a mix of DLBCL, High-grade B-cell Lymphoma (HGBL), and Primary Mediastinal B-cell Lymphoma (PMBCL), which does not align with the patient population specified in the label for epcoritamab.
For a naïve comparison between epcoritamab and the standard of care in Denmark, please refer to Appendix O, which utilizes the EPCORE-NHL-1 dataset with an April data cut, along with the study conducted by AL-Mashhadi et al.

The SCHOLAR-1 was found to be most representative as this study is the biggest retrospective observational study to evaluate outcomes in DLBCL. The SCHOLAR study patient population represent a clinical meaningful patient population compared to the Danish DLBCL patient population, as information on patients refractory status was

included. Also, the CORAL-study population was included in this trial, giving an even bigger representation of patients when looking at patient characteristics which could be of relevance when looking at unadjusted sensitivity analysis.

Compared to the SCHOLAR-1 CIT population, the EPCORE NHL-1 cohort had a greater proportion of patients older than 65 (61.6% vs. 16.5%), with disease stage III-IV (74.4% vs. 64.5%) and with more than 3 prior lines (52.3% vs. 28.8%). Also, more patients in the EPCORE NHL-1 trial were refractory to >=2 consecutive lines of therapy (62.8% vs. 50%); fewer patients relapsed within 12 months after ASCT (11.6% vs. 21.8%).

All those aforementioned factors are known to impact baseline risk and treatment effect, rendering that the inclusion of the SCHOLAR-1 trial is a conservative approach in terms of relative difference in efficacy vs epcoritamab.

See Figure 18 in Appendix H for the PRISMA flow-diagram.

Table 17 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial; Catherine Thieblemont et. Al, Journal of Clinical Oncology, 2023(38)	EPCORE NHL-1; GCT3013-01	NCT03625037	Start: June 26, 2018 Est. completion date: January 2025	Epcoritamab vs. Chemotherapy in R/R DLBCL 3rd line.
Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Crump M. et al; -1 (18)	SCHOLAR-1	N/A - retrospective study	N/A	Epcoritamab vs. Chemotherapy in R/R DLBCL 3rd line.

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

For the literature search of Health-related quality of life data, a global economic SLR was performed. The main objective was to identify economic evidence as inputs (i.e., economic models, healthcare resource use [HCRU], cost and utility/health-related quality of life [HRQoL] values) for the development of a cost-effectiveness model for epcoritamab treatment in ≥3rd line LBCL or DLBCL, see Appendix I for further description of the literature research of HRQoL.

For the assessment of HRQoL for this application, only DLBCL where in scope of the application. All studies that included HRQoL on DLBCL included comparators not relevant for this application. Therefore, this assessment will be of HRQoL only from the EPCORE-NHL-1 study, concerning the intervention of this application.

The two outcomes that will be included can be seen in Table 18.

Table 18 Relevant literature included for 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
EPCORE-NHL-1 study Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial; Catherine Thieblemont et. Al, Journal of Clinical Oncology, 2022(38)	Utilities, EQ-5D-3L FACT-LYM	Section 10

5.3 Literature used for inputs for the health economic model

The objective of the economic SLR was to identify all available evidence as input for the development of a cost-effectiveness model for epcoritamab in patients with ≥3rd line R/R LBCL including DLBCL. Therefore, this SLR was conducted in line with the guidelines set out by Cochrane and the Centre for Reviews and Dissemination (CRD)26 and the 27-item 2020 PRISMA Statement checklist.

The main objective was to identify economic evidence as inputs (i.e., economic models, healthcare resource use [HCRU], cost and utility/health-related quality of life [HRQoL] values) for the development of a cost-effectiveness model for epcoritamab treatment in ≥3rd line LBCL or DLBCL. For more details see Appendix J.

All relevant literature used in the health economic model can be seen in Appendix J.

Table 19 Literature used in the clinical assessment

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
EPCORE-NHL-1 (data cut [redacted])(39) Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody in Relapsed or Refractory Large B-	OS PFS TTD AE QALY	Systematic literature review, intervention for the assessment	Section 7.1.3, 8.1 and 9.1.2

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Cell Lymphoma: Dose Expansion in a Phase I/II Trial; Catherine Thieblemont et. Al, Journal of Clinical Oncology, 2023(38)			
SCHOLAR-1 Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Crump M. et al; 2017 (18)	Comparative efficacy, HR value used for OS and PFS	Systematic literature review, comparator for the assessment	Section 7.1.3
Single Technology Appraisal Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576] (40)	Incidence of AE's for R-CIT Disutilities for AEs	Literature review	Section 9.2.1 and 10.2.2
NICE TA559 National Institute of Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies*.(41)	Scenario analysis: Different utility values for health states PFS and PD	Literature review	Section 10.2.3 and 12.2.1
Hamadani et al. 2022(42)	Scenario analysis: Different Hazard ratio applied for the effectiveness	Manual search for estimates from the CORAL studies	Section 12.2.1 and Appendix K

6. Efficacy

6.1 Efficacy of epcoritamab compared to R-CIT for R/R DLBCL 3rd line

6.1.1 Relevant studies

The indication for epcoritamab is patients with R/R DLBCL after two or more lines of systemic therapy, hence the scope of this application. The EPCORE-NHL-1 study included an escalation part (to establish RP2D) and an expansion part. The expansion part is used in this application and any reference to the EPCORE NHL-1 trial refers to the expansion part. DLBCL was a prespecified subgroup in the study EPCORE-NHL-1. Therefore, in the below section the EPCORE NHL-1 study is described (covering the whole LBCL group) and in addition, a later data cut ([redacted]) will only describe results from patients with DLBCL as these results forms the basis of the relative efficacy and health economic model.

A description of the studies included is seen below. The studies are also described in detail in Appendix A.

The EPCORE NHL-1 is a first-in-human (FIH), open-label, phase I/II multicenter, dose escalation/expansion, multi-cohort, single arm trial in subjects aged 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma. The trial includes a Dose Escalation Part and an Expansion Part(27,43) whereas only the expansion part will be described as mentioned above.

A total of 157 subjects, including 139 with DLBCL and 18 subjects with other LBCL subtypes, were treated with the epcoritamab recommend phase 2 dose (RP2D). The primary endpoint was ORR and secondary endpoints included DOR, PFS, OS, TTNT, HRQoL and safety.

The cohort of patients included a heavily pre-treated population with a medium number of three prior lines of therapy.

The SCHOLAR-1 study was an international, multicohort, retrospective non-Hodgkin's lymphoma research study, that evaluated the outcomes in patients with refractory DLBCL. This study defined refractory as progressive disease or stable disease as best response (at any time) to chemotherapy (> 4 cycles of 1L or 2 cycles of later-line therapy) or relapsed $\leq$ 12 months from ASCT. The SCHOLAR-1 study analyzed data from 636 patients, who were either refractory to 1L, 2L or later therapy or had relapsed ≤12 months after ASCT given as 2L therapy, reported an overall ORR of 26% in response to 3L therapy (18). This retrospective study collected data from two phase 3 trials (LY.12 and CORAL)(44) and two observational cohorts of patients (from the MD Anderson Cancer Center [MDACC] and the Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence [IA/MC])(45).

Table 20 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
Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial; Catherine Thieblemont et. Al, Journal of	Phase I/II, open-label, **dose-expansion** trial design	Median follow up period of 10.7 months, January 2022 data cut.	The dose-expansion part of the trial includes patients from 54 sites across Asia, Europe, North America and Australia. A total of 157 patients with LBCL; 139 patients with DLBCL Patients have received a median	Epcoritamab was administered once weekly during cycles 1 – 3, 2qw dosing was given, cycles 4–9 (days 1 and 15) and q4w dosing was employed from cycle 10 onward.	NA/Single-arm	Primary: ORR (Overall Response Rate) – determined by Lugano criteria as assessed by IRC. Secondary: DOR (Duration Of Response), CR (Complete Response), DOCR (Duration of complete response), PFS (Progression Free Survival), OS (Overall Survival), Time To Response (TTR), Time To Next anti-lymphoma Therapy (TTNT) and MRD (Minimal Residual Disease), Safety, PK parameters, Change in lymphoma symptoms assessed by the FACT-Lym.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
[redacted] data cut [redacted]		Median follow up [redacted] data cut, 25.5 months	of 3 prior lines of therapy. All had received an anti-CD-20 agent, anthracyclines and alkylating agents, and most patients were refractory to their last line of therapy. See incl. and excl. criteria in appendix.			Epcoritamab was continued until disease progression or unacceptable toxicity. Dose modifications were not permitted, although dose interruptions were permitted.
Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017.	Patient-level data collected from two large randomized phase 3 trials and two observational cohorts.	NA	Patients with RR DLBCL. Most patients had ECOG PS ≤1 and stage III-IV disease.	Observational cohorts: Second salvage therapy and subsequent treatments Phase 3 clinical trials: Randomly assigned to 1 of 2 salvage regimens.	Observational cohorts: Not applicable Phase 3 clinical trials: Randomly assigned to 1 of 2 salvage regimens.	Survival (mOS months, 1-year survival and 2-year survival) Response(CR and OR)

6.1.2 EPCORE-NHL-1 Dose-expansion (38)

In the following section results for the SCHOLAR-1 and EPCORE-NHL-1 will be presented.

For the EPCORE-NHL-1 further data will be presented:

- A later data cut [redacted] (only DLBCL).
- Details specifically on the DLBCL subgroup, relevant and in scope for this application

Data from the Expansion Part of the EPCORE NHL-1 trial are presented in this submission, as this represents the population that is consistent with the decision problem and the licensed indication for epcoritamab.

The EPCORE NHL-1 trial included patients from 54 sites across Asia, Europe, North America and Australia, and results have been reported from data cut-off for efficacy evaluations as of 31 January 2022, when the median follow-up was 10.7 months for patients with R/R LBCL.

The dose-expansion part of the EPCORE-NHL-1 (NCT03625037) trial was a phase I/II trial, single -arm, multicenter, open-label.

The primary objective of the trial was to evaluate clinical efficacy as determined by Lugano criteria(11), with a primary endpoint of ORR assessed by an independent review committee (IRC) and also to evaluate the safety of epcoritamab in patients with R/R LBCL at RP2D.

The trial involved adults with relapsed progressive, or refractory CD20+ mature B-cell NHL. This included patients with DLBCL and other LBCL subtypes, (such as patients with *de novo* or transformed FL BCL, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma (PMBCL), FL, MCL, small lymphocytic lymphoma, and marginal zone lymphoma (MZL)). All patients were required to have a documented $CD20^{+}$ mature B-cell neoplasm and patients were also required to have previously received an anti-CD20 therapy and to have received ≥2 prior lines of systemic therapy. Relapsed disease was defined as disease that had recurred ≥6 months after completion of therapy. Refractory disease was defined as disease that either progressed during therapy or progressed <6 months after completion of therapy.

A step-up dosing approach was employed, primarily to mitigate against the risk of development of serious CRS. Thus, patients received a priming dose (0.16 mg) of epcoritamab on day 1 of cycle 1 and an intermediate dose (0.8 mg) of epcoritamab on day 8 of cycle 1, before receiving administration of full doses for the remainder of the treatment period. Epcoritamab was administered subcutaneously (s.c.) in 28-days cycles. Epcoritamab was administered once weekly in cycles 1-3, once every 2 weeks during cycles 4-9 and once every 4 weeks from cycle 10. Epcoritamab was continued until disease progression or unacceptable toxicity.

The study enrolled a total of 157 patients which included 139 patients with DLBCL and 18 patients with other LCBL types. [redacted]. Patients were heavily pre-treated, having received a median of 3 prior lines of therapy

(range 2-11), of which 31,8% had 3 or more prior lines of therapy. All patients had received an anti-CD-20 agent, anthracyclines (except 3 patients) and alkylating agents, while 19,7% (n=31) had received an ASCT and 38.9% (n=61) had received a CAR T-cell therapy. Most 82,8% (n=130) patients were refractory to their last line of therapy. The median age was 64 years and almost all 96,8% (n=152) had an ECOG PS of 0 or 1. Detailed patient characteristics are found in Section 6.1.4.

Epcoritamab monotherapy demonstrated a high efficacy including a high rate of deep and durable responses in this difficult to treat patient population of LBCL patients (majority of patients having DLBCL) with refractory or relapsed disease, who had received a median of three prior lines of systemic therapy (including an anti-CD20 regimen). The ORR reported by the IRC (Lugano criteria) was 63.1% and a CR of 38.9 %.

6.1.2.1 Results for LBCL, Jan 2022 data cut:

Primary endpoint

ORR

The primary endpoint in the study was ORR, defined as the proportion of patients who achieved a best overall response of CR or PR, in all patients who received at least one dose of epcoritamab. The per IRC reported best overall response (by Lugano criteria) was 63.1% (n/N = 99/157) and 38,9% of patients achieved a CR (n/N = 61/157); the number of patients achieving a PR was 38 patients (n/N = 38/157; 24.2 %) (38).

5 patients had stable disease (SD) and 37 patients had progressed disease (PD) as their best overall response by IRC (n/N = 5/157; 3.2% and 37/157; 23.6% respectively). 16 patients (n/N = 16/157; 10.2%) were nonevaluable and 14 out of these patients had no response assessment done prior to discontinuation, one patient had a response assessment after a new anticancer treatment was initiated and was censored and one patient had no evidence of disease at baseline and remains on treatment (38). A table of primary and secondary outcomes are summarized in Table 21 below.

Patients who were primary refractory (n=96) achieved an ORR of 55,2% and the CR rate was 30,2 %. In patients without receiving prior CAR T-cell therapy (n=96) the ORR was 68,8% and the CR rate was 41,7%. The median DOR in these patients was 12.0 months (95% CI, 5,6 to not reach (NR)) and the median DoR in patients in CR was NR.

Secondary endpoints

Secondary efficacy outcomes where DOR, CR rate, duration of CR, PFS, time to treatment response (TTR) per IRC, OS, and safety).

Progression free survival (PFS)

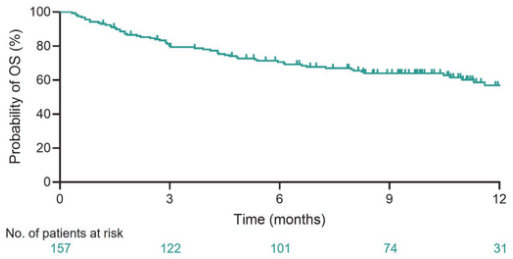
Median PFS was 4.4 months (95% CI: 1.0 - 8.4) for all responders and was not reached for complete responders (95% CI, 14,5 to NR).

[redacted] The PFS rate at 6 months was 43.9% (95% CI, 35.7 to 51.7).(38)

Overall Survival (OS)

At a median follow-up time of 10,7 months the median OS was not reached (95%CI, 11.3 to not reached).

Figure 3 Kaplan Meier plot OS Jan 22 data cut (data supplement (46)



An overall survival ad hoc analysis using the Mantel–Byar approach shows a hazard ratio (95% CI) for patients with CR versus nonresponders of 0.05 (0.01–0.14) and a hazard ratio (95% CI) for patients with PR versus nonresponders of 0.34 (0.18–0.61). CI, confidence interval; CR, complete response; OS, overall survival; PR, partial response.

Table 21 Summary of Efficacy End points, per IRC, in patients with LBCL (Jan 22 data cut)

End Point	Patients (N=157)
Best overall response per IRC, No. (%)	
Overall response of CR or PR, No. (%) [95% CI]	99 (63.1) [55.0 to 70.6]
CR	61 (38,9) [31,2 to 46,9]
PR	38 (24,2)
SD	5 (3,2)
PD	37 (23,6)
Nonevaluable	16 (10,2)
DOR, months, median (range) [95% CI]	12.0 (0.0+ to 15.5+) [6,6 to not reached]
DOR among complete responders months, median (range) [95% CI]	Not reached (1.4+ to 15.5+) [12.0 to not reached]
Duration of CR, months, median (range) [95% CI]	12.0 (0.0 to 14.9+) [9,7 to not reached]
PFS, months, median (range) [95% CI]	4,4 (0,0+ to 16,9+) [3,0 to 7,9]
OS, months, median (range) [95% CI]	Not reached (0,3 to 17,9+) [11,3 to not reached]
Time to response, months, median (range) [No.]	1,4 (1,0-8,4) [99]
Time to CR, months, median (range) [No.]	2,7 (1,2-11,1) [61]

NOTE. Data cutoff: January 31, 2022. The + sign indicates censored value.

Abbreviations: CR, complete response; DOR, duration of response; IRC, independent review committee; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

6.1.2.2 Results DLBCL, [redacted] data cut [redacted] (39)

All efficacy results are reported based on the [redacted] data cut-off, unless otherwise stated, with a median duration of study follow-up of [redacted] months.

The ORR in patients with DLBCL (N=139) was [redacted] with [redacted] and [redacted] achieving best response of CR and partial response (PR), respectively. Overall, results throughout the trial were consistent for patients with other LBCL subtypes and all patients with LBCL and the published data cut from January 2022.

For patients with DLBCL, the median DOR was [redacted] and median PFS was [redacted] based on IRC assessment determined by Lugano criteria. Among patients in CR, median PFS was [redacted] Median PFS was [redacted] among patients in PR when compared with non-responders ([redacted] versus [redacted]

Median OS among patients with DLBCL was [redacted] and median Time To next Treatment TTNT (time to next treatment) was [redacted]

Whilst on treatment, there were [redacted] in the total Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) score and the Functional Assessment of Cancer Therapy-Lymphoma Subscale (FACT-LymS) from Cycle 1 Day 1 to Cycle 9 Day 1.

Primary endpoint ORR

The per IRC reported best overall response (by Lugano criteria) was [redacted] and [redacted] of patients achieved a CR ([redacted].

[redacted] patients had stable disease (SD) and [redacted] patients had PD as their best overall response by IRC (n/N = [redacted] respectively). [redacted] patients (n/N = [redacted] were nonevaluable. Of [redacted] nonevaluable patients, [redacted] had no response assessment before discontinuation, one patient had a response assessment after new anticancer therapy was initiated and was censored, and one patient had no evidence of disease at baseline and remains on treatment.

Table 22 DLBCL response rates, [redacted] datacut(39)

	DLBCL ([redacted]
ORR	[redacted]
(95% CI)	[redacted]
CR rate	[redacted]
(95% CI)	[redacted]

Best Overall Response	
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
NE	[redacted]

Secondary endpoints

Table 23 Outcome Complete response, DLBCL, [redacted] datacut(39)

	DLBCL [redacted])
All responders (PR or CR)	
Number of responders	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
DOR (months)	
Min, max	[redacted]
25% quartile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75% quartile (95% CI)	[redacted]
Estimate percentage of patients remaining in response (95% CI)	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]
18-month	[redacted]
CR	
Number of patients with CR	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
DOR (months)	
Min, max	[redacted]
25% quartile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75% quartile (95% CI)	[redacted]
Estimate percentage of patients remaining in response (95% CI)	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]
18-month	[redacted]

Progression free survival

Median PFS was [redacted] ([redacted]) for all responders and the PFS rate at 6 months was [redacted] and [redacted].

Figure 4 KM plot of PFS, IRC assessment (Lugano Criteria), [redacted] data cut-off(39)

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma;
Source: Figure 14.2.1.12.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

Overall survival (OS)

At a median follow-up time of [redacted] months the median OS was [redacted]). The OS rate at 12 months and 18 months was [redacted]) and [redacted]

Figure 5 KM plot of OS. [redacted] data cut-off(39)

[redacted]

Summary of results

Table 24 Summary of results of outcomes DLBCL [redacted] datacut(39)

Outcome	**DLBCL (N=139)**
ORR (IRC, Lugano criteria)	[redacted]
(95% CI)	[redacted]
CR (IRC, Lugano criteria)	[redacted]
(95% CI)	[redacted]
DOR (months) all responders (IRC, Lugano criteria)	
Number of responders	[redacted]
Min, max	[redacted]
Median (95% CI)	[redacted]
PFS (months) (IRC, Lugano criteria)	
Number of events	[redacted]
Min, Max[c]	[redacted]
Median (95% CI)	[redacted]

OS (months)	
Number of events	[redacted]
Number of censored	[redacted]
Min, max	[redacted]
Median (95% CI)	[redacted]
TTNT (months)	
Number of events	[redacted]
Number of censored	[redacted]
Min, Max	[redacted]
Median (95% CI)	[redacted]

Epcoritamab is expected to provide a significant benefit to patients with deep and durable treatment effects and offer an advantage clinically meaningful to patients and clinicians when compared with currently available therapies. The introduction of epcoritamab is be expected to enhance equity to access as it will not be limited by manufacturing times and specialist delivery centers.

6.1.3 SCHOLAR-1 (18)

The SCHOLAR-1 study was an international, multicohort, retrospective non-Hodgkins lymphoma research study, that retrospectively evaluated the outcomes (response and OS) in patients with refractory DLBCL. This study defined refractory as progressive disease (PD) or stable disease (SD) as best response (at any time) to chemotherapy (> 4 cycles of 1L or 2 cycles of later-line therapy) or relapsed $\leq$ 12 months from ASCT. Most patients had an ECOG PS between 0-1 and stage III-IV disease and around one fourth of the patients had a high-intermediate or high-risk IPI risk classification. The SCHOLAR-1 study analysed pooled data for 636 patients, who were either refractory to 1L, 2L or later therapy or had relapsed ≤12 months after ASCT given as 2L therapy, reported an overall ORR of 26% in response to second-line or greater.(18) This retrospective study collated data from two phase 3 trials (LY.12(47) and CORAL(44)) and two observational cohorts of patients (from the MD Anderson Cancer Center [MDACC] and the Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence [IA/MC]).(18) Further analysis indicated that the ORR was higher (34%) for patients who had relapsed after autologous stem cell transplant (ASCT) compared with primary refractory patients (20%), but the differences were not statistically significant. The CR rate was 7% overall, ranging from 3% in patients with primary refractory disease to 15% in those relapsing after ASCT.

Overall, the pooled response rate was 26% which was similar across the four datasets (20%-39%). The pooled response rates from the three refractory subgroups (primary refractory, refractory to second line or later-line therapy and relapsed ≤ 12 months from ASCT) ranged from 20% to 39%. The low response rates were consistent across all three subgroups, with the lowest response rates in the primary refractory subgroup and the high-risk IPI subgroups. Patient who relapsed ≥ 12 months from ASCT had a higher response (34%) compared to the other two refractory groups; primary refractory (20%) and second or later-line therapy (26%).

Survival (from start of salvage therapy) for refractory disease was dismal for patients with refractory DLBCL, median OS 6.3 months (95% CI 5.9 -7.0 months) with a 1-year survival rate of 28% and at 2 years 20% of patients were still alive. OS rates were similar across the three subgroups, however a slightly lower median OS was found among patient who were refractory to second or later-line therapy (6,1 months) or who relapsed ≤ 12 months from ASCT (6,2 months) compared to primary refractory patients (7,1 months)

Patients achieving a CR after last salvage chemotherapy had a longer survival (median OS 14.9 months) compared with patients who were nonresponders (median OS, 4.6 months). The 2-year OS rate for nonresponders was 14%. Median OS was higher for patients who had undergone ASCT (180 patients) 14.4 months compared with patients who had not undergone ASCT (423 patients) 5.1 months and the 2y OS rate was 11% (95% CI, 8%-14%)

Table 25 Survival and response outcomes of relapsing/refractory patients from the SCHOLAR-1 study(18)

Endpoint	Refractory to 1L treatment, n=179	Refractory to ≥2L treatment, n=306	Relapse within 12 months of ASCT, n=118
% patients [a]	30	51	20
Survival			
mOS, months	7.1	6.1	6.2
1-year survival	29%	26%	32%
2-year survival	24%	17%	19%
Response			
OR	20%	26%	34%
CR	3%	10%	15%

[a] sums to >100 due to rounding errors

1L, first-line; 2L, second-line; CR, complete response; mOS, median OS; OR, objective response

6.1.4 Comparability of studies

6.1.4.1 Comparability of patients across studies

For the following, only the DLBCL population and [redacted] data cut will be described, as these data holds the foundation for the relative clinical assessment.

Patients in the EPCORE NHL-1 trial were heavily pre-treated with a median of 3 (range, 2–11) prior lines of therapy, 39% had prior chimeric antigen receptor T-cell (CAR T) therapy, 61% had primary refractory disease, and 83% were refractory to the last line of therapy.

Table 26

[redacted]

Characteristic, median (IQR) or n (%)	R/R DLBCL (EPCORE-NHL-1) (N=139)	SCHOLAR-1 Pooled (N=636)
Age, years)	[redacted]	55 (19-81)
Primary diagnosis	[redacted]	87%
Male	[redacted]	64%
ECOG PS		
0-1	[redacted]	73%
2-4	[redacted]	14%
Ann Arbor stage at Screening		
I-II	[redacted]	27%
III-IV	[redacted]	72%
IPI (at study entry)		
0-2	[redacted]	49%
≥3	[redacted]	33%
Unknown	[redacted]	18%
Not applicable	[redacted]	
Number of lines of previous therapy, median	[redacted]	
1	[redacted]	28%
2-3	[redacted]	49%
≥4	[redacted]	<1%
Prior radiotherapy	[redacted]	
Prior ASCT	[redacted]	
Previous systemic therapy		
Anti-CD20 monoclonal antibody	[redacted]	
Anti-CD19 monoclonal antibody	[redacted]	
Anthracyclines	[redacted]	
Alkylating agents	[redacted]	

CAR T therapy	[redacted]	
Median time (min, max) from end of last-line anti-lymphoma therapy to first dose of epcoritamab (months)	[redacted]	
Subjects with primary refractory disease	[redacted]	28%
Subjects refractory to ≥2 consecutive lines of prior anti-lymphoma therapy	[redacted]	50%
Last-line systemic antineoplastic therapy		
Refractory	[redacted]	78%
Relapsed	[redacted]	22%

In the relative efficacy analysis patient characteristics will be restricted to those patients treated with epcoritamab with DLBCL and no prior CAR-T (N=86) and patient characteristics from SCHOLAR-1 restricted to those presented in Neelapu et al.(48) The restriction to the no prior CAR-T patient population in the study was implemented to ensure comparability between the populations in the studies EPCORE-NHL-1 and SCHOLAR-1. Clinical experts provided input indicating that prior CAR-T treatment is an important prognostic factor that could potentially influence the outcomes of the study. Since there were no previous studies conducted with the standard of care in Denmark that included patients who had received CAR-T treatment, it was necessary to exclude this population to maintain consistency in the data analysis.
Out of the total 139 patients with DLBCL included in the study, [redacted] had previously received CAR-T treatment.

Table 27 Patient characteristics across studies used in the assessment for R/R DLBCL 3rd line

	EPCORE NHL-1 trial (DLBCL, no prior CAR-T, April 2023)	SCHOLAR-1(48)
DLBCL histology, %	[redacted]	NA
Median age, years	[redacted]	55[a]
Age ≥65 years, %	[redacted]	16
Male, %	[redacted]	68
ECOG <2, %	[redacted]	100
Median N of prior treatments (range)	[redacted]	NA
≥3 prior Tx, %	[redacted]	29
Primary refractory, %	[redacted]	37

Prior ASCT, %	[redacted]	NA
Disease stage III-IV, %	[redacted]	65

[a] *Assumed similar as median age in the original SCHOLAR-1 population presented by Crump et al[31]*

6.1.5 Comparability of the study population with Danish patients

Based on inputs from Danish clinicians and an Advisory Board organized ([redacted]), the experts provided feedback of the comparability of the study population in EPCORE-NHL-1.

Patient characteristic were presented based on DLBCL and no prior CAR-T data, and the experts stated that the baseline characteristics correspond to the Danish population, and therefore these inputs will be used in the health economic model. It was also stated that the patient population in the EPCORE-NHL-1 had a high number of refractory patients. [redacted]

Despite differences in the study populations between EPCORE-NHL-1 and SCHOLAR-1, the clinical experts considered the included populations to be representative of Danish patients with R/R DLBCL.

Table 28 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (39)
Age	Same as used in HE	65,67
Male	Same as used in HE	60.5 %
Patient weight	78,1 kg (based on previous evaluations)	73.6 kg
Patient M^2	1.92 m^2 (based on previous evaluations)	1,86 m^2

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

OS and ORR were included outcomes for the comparative analysis. Differences in outcomes were not addressed, as OS and ORR for R-CIT were based on pooled studies.

7.1.2 Method of synthesis

EPCORE-NHL-1 is a single-arm trial and no head-to-head trials with available data comparing epcoritamab to the relevant comparators were identified, see section 5.1. Therefore, an indirect treatment comparison (ITC), in the form of a matching-adjusted indirect comparison (MAIC) was conducted to inform about the relative efficacy estimates for epcoritamab versus R-CIT.

The feasibility of conducting a network meta-analysis (NMA) was explored to generate indirect evidence that could inform comparisons. The use of single arm data for EPCORE NHL-1 led to an incomplete and heavily restricted network and therefore generating indirect evidence for survival and response outcomes via a standard NMA approach was deemed not feasible. In the absence of a viable network of studies with sufficient comparability to inform an NMA, unanchored MAIC were pursued, which account for known imbalances in any effect modifiers or prognostic variables between the studies. The MAIC informing the base case analysis for the DLBCL population, and no prior CAR-T.

Relative effectiveness for epcoritamab versus comparator was evaluated by estimating hazard ratios (HR) for survival and mean differences for tumor responses. For this, we included selected patient characteristics in population-adjustment models rebalancing the EPCORE NHL-1 trial data to aggregate summary data reported in published comparator trials (i.e SCHOLAR-1). It is important that the choice of variables to be matched/weighted on should be carefully considered: including too many variables will reduce the effective sample size, negatively affecting the precision of the estimate; conversely, failure to include relevant variables will result in a biased estimate.

The selection of which patient characteristics to adjust for in the MAICs was determined based on review of the literature, empirical testing of prognostic status in the EPCORE NHL-1 trial as well as clinical expert input from an advisory board discussion as to whether patient characteristics are important characteristics to adjust for in the R/R DLBCL population, when available:

- **Age ≥65 years of age**
- **Gender**
- **DLBCL histology (including transformed follicular lymphoma) vs non DLBCL**
- **Primary refractoriness**
- **Refractory to ≥2 consecutive lines of therapy**
- **Refractory to last prior anti-CD20 agent**
    - **Refractoriness to last treatment instead when information on last prior anti-CD20 was not available**
- **Prior CAR T**
- **Prior autologous stem cell transplant**
- **Relapse within 12 months of autologous stem cell transplant**
- **ECOG performance status>1**
- **Disease stage III-IV**

Adjustment for cross-trial differences in patient characteristics in unanchored comparisons resulted in a smaller sample size for rebalanced EPCORE NHL-1 patients.

Compatibility assessment was performed to determine the feasibility of conducting indirect comparisons with the available data. Compatibility assessment included a comparative review of the trial design, population profiles and outcome measures of the relevant studies i.e. EPCORE-NHL-1 and SCHOLAR-1, see Table 29.

Table 29 Summary of outcomes of EPCORE-NHL-1 and SCHOLAR-1

	EPCORE NHL-1 trial* [redacted]	SCHOLAR-1(48)
Type of ITC conducted	-	**Unanchored**
Median PFS, mo (IRC)	[redacted]	Na
Median PFS, mo (Investigator)	[redacted]	Na
Comparator in trial	No comparator	No comparator
HR for PFS for treatment vs comparator in trial	-	-
Outcome definition		
Median OS, mo	[redacted]	6.3
HR for OS for main treatment in trial	-	-
ORR, % (IRC)	[redacted]	-
ORR, % (Investigator)	[redacted]	34
CR, % (IRC)	[redacted]	-
CR, % (Investigator)	[redacted]	12

Individual patient-level event and censoring times for OS and PFS outcomes were extracted from the published Kaplan-Meier (KM) graphs of the comparator trials via a 2-step process. First, the numerical value of the survival curves at dozens of time points were obtained through a graphical digitization software, WebPlotDigitizer.[2] In the second step, these values were then used to create a "simulated" trial population using the algorithm published by Guyot et al.(49) This simulated trial is a collection of event and censored times equal to the number of patients in the trial and creating a KM curve whose values are closest to that of the digitized data. This means that even though we do not know the survival/censoring times for each patient in the trials, Guyot's algorithm provides a collective patient-level data set that approximates the survival data observed in the trial data.(50) These simulated patient-level data sets were then used in the ITC analyses. Where only summary statistics are available, the Guyot methodology has been recommended by NICE (Technical support document 14) in order to re-create patient level data.(51)[redacted]

Comparative efficacy data for epcoritamab relative to the comparator was derived for:

- Hazard ratio (HR) and 95% confidence interval (CI) of PFS
- Hazard ratio (HR) and 95% confidence interval (CI) of OS
- Kaplan Meier survival curves
- Mean difference (MD) and 95% CI of overall response (ORR)
- Mean difference (MD) and 95% CI of complete response (CR)

[2] https://automeris.io/WebPlotDigitizer/

As outcomes validated by independent review committee (IRC) can be seen as inherently more reliable and reduce the risk of bias, PFS and response outcomes (Lugano definition) from EPCORE NHL-1 were based on the IRC. Whenever available, IRC definitions were used for comparators but when not available - investigator-assessed. However, progression-free survival was not reported in the SCHOLAR-1, and as a result, an indirect treatment comparison (ITC) for this outcome was not conducted. To address this limitation, an assumption was made that the HR for PFS were similar to the HR for OS. It is important to note that PFS and OS measure the endpoint differently and can be influenced by various factors. However, there is evidence from a separate study that showed an association between PFS and OS in DLBCL and a linear correlation was observed between 1-year and 5-year PFS and 5-year OS. Additionally, this approach of assuming proportionality between PFS and OS has been validated by clinical experts who supported the plausibility of this assumption in the context of comparing epcoritamab and the comparator intervention (CIT).

Compared to the SCHOLAR-1 CIT population, the EPCORE NHL-1 cohort had a greater proportion of patients older than 65 (61.6% vs. 16.5%), with disease stage III-IV (74.4% vs. 64.5%) and with more than 3 prior lines (52.3% vs. 28.8%). Also, more patients in the EPCORE NHL-1 trial were refractory to >=2 consecutive lines of therapy (62.8% vs. 50%); fewer patients relapsed within 12 months after ASCT (11.6% vs. 21.8%), likely because ASCT was much lower to begin with in EPCORE NHL-1.

Adjusting the patient population where necessary to conduct a relative efficacy analysis that had included important effect modifiers and prognostic variables that affect the outcomes.

After adjusting the EPCORE NHL-1 cohort to the SCHOLAR-1 CIT population, the effective sample size was [redacted] for the EPCORE NHL-1 cohort. The adjustment weights were truncated at 1% and 99% because of outliers. See adjusted weight distributions in Appendix M.

The adjusted overall survival, after weight truncation, was significantly better for epcoritamab compared to SCHOLAR-1 CIT, ([redacted]. Additionally, the adjusted complete response for epcoritamab was [redacted] significantly higher than CIT in SCHOLAR-1, and the adjusted overall response rate was [redacted] significantly higher than CIT in SCHOLAR-1.

Table 30 Baseline characteristics for DLBCL, no prior CAR T population – pairwise comparison vs CIT from SCHOLAR-1)

	Unadjusted Epcoritamab DLBCL, no CAR-T [redacted]	Adjusted Epcoritamab DLBCL, no CAR-T [redacted]	SCHOLAR-1 CIT (n=340)
Age			
median (years)	69.5	[redacted]	55
>= 65 years	61.6%	[redacted]	16.5%

Male	60.5%	[redacted]	67.9%
ECOG PS 0-1 (vs 2)	96.5%	[redacted]	100.0%
Disease stage III-IV	74.4%	[redacted]	64.5%
IPI score >=3	54.7%	[redacted]	27.7%
Number of prior lines		[redacted]	
>=3 lines of chemo and ASCT	52.3%	[redacted]	28.8%
Primary Refractory	44.2%	[redacted]	37.1%
Refractory to >=2 consecutive lines of therapy	61.6%	[redacted]	50.0%
Relapse within 12 months of ASCT	11.6%	[redacted]	21.8%
SCT any time after refractory disease	7.0%	[redacted]	37.1%

[redacted]: ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor (CAR) T-cell therapy; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; SCT, stem cell transplant

7.1.3 Results from the comparative analysis

Table 31 Unadjusted and adjusted outcomes DLBCL, no prior CAR T population – pairwise comparison vs SCHOLAR-1

Epcoritamab vs SCHOLAR-1 CIT		
	Unadjusted Epcoritamab	**Adjusted Epcoritamab** [redacted]
	[redacted]	
Survival, HR [95% CI]		
Overall survival (OS)	[redacted]	[redacted]
Progression	Na	**Na**
Response rates, %		
Complete response (CR)	[redacted]	[redacted]
Difference, % [95% CI]	[redacted]	[redacted]
Overall response (OR)	[redacted]	[redacted]

Difference, % [95% CI]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CIT, chemoimmunotherapy; HR, hazard ratio; na, not applicable; N_{eff}, effective sample size;

Figure 6 OS EPCO (unadjusted and adjusted) to SCHOLAR-1

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

Based on DMC recommendation on extrapolation of time-to-event data following criteria was tested/conducted to document adequate adaption of the study's observed data.

- Assessment of the plausibility of PH based statistical test and graphical presentations (log-cumulative hazard plot and Schoenfeld-residuals)
- Log-cumulative hazard plot of the different parametric functions
- Test of Akaike's information criteria (AIC) and Bayesian information Criteria (BIC)
- Clinical and biological validity based on external data and clinical inputs

For further details, see Appendix D

AbbVie have conducted survival analyses of the individual patient data (IPD) to extrapolate clinical survival data from patients treated with epcoritamab in the EPCORE-NHL-1 (GCT3013-01) trial beyond the trial period.

PFS, OS, and TTD for epcoritamab are based on patient level data from the EPCORE-NHL-1 (GCT3013-01) trial, DLBCL no prior CAR-T using the outcome definitions as per the trial protocol and the [redacted] cut-off ([redacted]

Parametric survival curves for PFS, TTD, and OS for Epcoritamab were fitted to the KM curves from the EPCORE-NHL-1 (GCT3013-01) trial, using seven parametric distributions including the six key distributions identified in the NICE decision support unit (DSU). More information on the fitted parametric models can be found in section Appendix D.

The parametric models for OS and PFS for the patient population and comparators are presented below, see Table 32 for specification of the outcomes. The chosen distribution for the model is justified and AIC and BIC values are presented in Appendix D.

Table 32 Outcome definition used in relative efficacy

Outcome	Outcome definition	Endpoint
PFS	• Time between the date of randomization and the first date of the documented progression, or death due to any cause, whichever occurs first. • Participants who die without a reported progression (and die without start of subsequent anti-lymphoma therapy) will be considered to have progressed on the date of their death. • Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment on or prior to initiation of subsequent anti-lymphoma therapy. • Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization.	Progression, death, or censoring, whichever comes first.
Duration of treatment (mentioned as TTD in this report)	• Time from the start date of the first treatment until discontinuation, or death due to any cause, whichever occurs first. • A participant who has not discontinued will be censored at the last known alive date.	Treatment discontinuation, death, or censoring, whichever comes first.

OS	• Time between the date of randomization and the date of death due to any cause. • A participant who has not died will be censored at the last known alive date.	Death or censoring.

Proportional hazard (PH) assumption (PHA) was tested to indicate whether a hazard ratio (HR) can be applied to the epcoritamab curve to obtain the comparator curve. The PH assumption was investigated using both qualitative assessment and quantitative assessment, see Appendix D for further details and results.
It is important to note that when carrying out these tests, there is not one test which can assess whether PHs holds and so the final determination needs to be based upon the conclusions from all the tests. Based on the test it was concluded that PH cannot be rejected.

We found that a dependent model using the Cox Proportional Hazard model and corresponding HRs were the most justified approach to include the relative differences in efficacy between epcoritamab and R-CIT. This approach is commonly used for which access to individual patient level data (IPD) is not available, as is the case for the comparator R-CIT. Also, the HR and Piecewise HR approach for comparisons was the most informative base case to best control for differences in patient characteristics between EPCORE-NHL-1 population and SCHOLAR-1 population.

Only EPCORE NHL-1 data were extrapolated according to the 7 standard parametric distributions and hazard ratios (HRs), as calculated by the matching-adjusted indirect comparisons (MAICs), were applied on the EPCORE NHL-1 data to generate the comparator curves in the cost-effectiveness model. Based on clinical inputs, the expected efficacy outcomes will follow the patient until death.

The primary analysis concerned patients [redacted] treated with epcoritamab, restricted to those with diffuse large B-cell lymphoma (DLBCL) and no prior CAR-T.

The best fitting curves for epcoritamab are described in detail below. Any selected distribution for epcoritamab acts as a base case for the comparator (CIT) extrapolated curve.

8.1.1.1 Extrapolation of OS

The Extrapolation is based on the observed OS data [redacted] data cut, with observation up until 33 months (DLBCL patients and no prior CAR-T [redacted] The median observed OS is [redacted]. See Appendix D for the observed OS KM curve.

[redacted]

[redacted]

Error! Reference source not found. shows how the KM curve fits the survival extrapolations and **Error! Reference source not found.** shows the long term extrapolations of OS.

[redacted]

[redacted]

Distribution	Median (months)	12 months (95% CI)	24 months	48 months	60 months	120 months	180 months
Observed (95% CI)							
Exponential							
Gamma							
Generalized gamma							
Gompertz							
Log-logistic							

Log-normal	[redacted]						
Weibull	[redacted]						

[redacted]

Method/approach	Description/assumption
Data input	EPCORE-NHL-1 and SCHOLAR-1
Model	Partitioned Survival model
Assumption of proportional hazards between intervention and comparator	Yes, same distribution between epcoritamab and comparator, see section 7.1.2
Function with best AIC fit	Epcoritamab: Log-normal
Function with best BIC fit	Epcoritamab: Log-Normal
Function with best visual fit	Epcoritamab: Log-Normal/Generalized gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Log-normal
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Epcoritamab: Log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No, but shown in scenario

8.1.1.2 Extrapolation of PFS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Distribution	Median (months)	12 months (95% CI)	24 months	48 months	60 months	120 months	180 months
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 33 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	EPCORE-NHL-1 and SCHOLAR-1
Model	Partitioned Survival model
Assumption of proportional hazards between intervention and comparator	Yes, same distribution between epcoritamab and comparator, see section 7.1.2
Function with best AIC fit	Epcoritamab: Generalized Gamma
Function with best BIC fit	Epcoritamab: Log-Normal
Function with best visual fit	Epcoritamab: Log-Normal/Generalized gamma/log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Generalized Gamma
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Epcoritamab: Log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No, but shown in scenario

8.1.1.3 Extrapolation of TTD

[redacted]

[redacted]

Distribution	Median (months)	12 months (95% CI)	24 months	48 months	60 months	120 months	180 months
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For Denmark clinical input show that the Danish clinicians consider using epcoritamab until progression, however, they also stated that they have seen patients stopping treatment due to other reasons than progression and that those patients stayed in long term remission. Due to this the clinicians also gave the input that they will stop treatment in long-term remission if there are specific reasons for the patient to do this such as toxicity burdens. To treat until progression differs from statements from clinicians in several other countries (including UK, Sweden and Norway) where the clinicians has given the input that they will stop treatment when the patients have been in long-term remission for 2-3 years. The clinicians see the TTD curve as more representative for the treatment with epcoritamab.

[redacted]

Table 34 Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	EPCORE-NHL-1 and SCHOLAR-1
Model	Partitioned Survival model
Assumption of proportional hazards between intervention and comparator	Yes, same distribution between epcoritamab and comparator, see section 7.1.2
Function with best AIC fit	Epcoritamab: Log-normal
Function with best BIC fit	Epcoritamab: Log-normal
Function with best visual fit	Epcoritamab: Log-Normal
Function with best fit according to evaluation of smoothed hazard assumptions	Log-normal
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Epcoritamab: Exponential
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	NA

8.2 Presentation of efficacy data from [additional documentation]

NA

8.3 Modelling effects of subsequent treatments

NA

8.4 Other assumptions regarding efficacy in the model

NA

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

Table 35 Estimates in the model

	Modelled average OS	Modelled median OS	Observed median from relevant study
Epcoritamab	54,9 months	17 months	EPCORE-NHL-1
R-CIT	9,1 months	3,2 months	SCHOLAR-1

Table 36 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	TTD	PFS	OS
Epcoritamab	12,2 month	26,3 month	54,9 month
R-CIT	4 cycles	4 month	9,1 month

9. Safety

9.1 Safety data from the clinical documentation

Safety data from the EPCORE-NHL-1 are analyzed both based on the entire LBCL population with the data cut from 31 January 2022 (published) and on the data cut from [redacted] on DLBCL patients (data on file).

Moreover, the LBCL population with the data cut from January 2022 has also been compared with R-CIT in SCHOLAR-1 in a naïve safety comparison and is reported in section 9.1.2 below.

Overall, evidence from the EPCORE-NHL-1 trial demonstrates that the safety profile of epcoritamab is manageable having a low rate of severe (grade ≥3) CRS, Immune effector cell-associated neurotoxicity syndrome (ICANS) and AE-related treatment discontinuation.

9.1.1 Safety data EPCORE-NHL-1 (data cut Jan 2022)

As of the data cutoff date of 31 Jan 2022, a total of 219 patients were screened and 157 patients received at least one dose of epcoritamab in the expansion cohort, including 139 with DLBCL.

As of the data cutoff date, 156 (99.4%) subjects with LBCL had experienced at least 1 treatment-emergent AE (TEAE). Of these, 130 (82.8%) subjects experienced TEAEs considered related to epcoritamab by the investigator. A total of 96 (61.1%) subjects experienced grade 3 or higher TEAEs and 42 (26.8%) subjects had grade 3 or higher TEAEs considered related to epcoritamab by the investigator (Table 37). Median follow-up time is 10.7 months.

Table 37 Overview of safety events. LBCL, (EPCORE-NHL-1, Jan 2022, full-analysis set)

	Epcoritamab (N=157)
Number of adverse events, n	NA
Number and proportion of patients with ≥1 adverse events, n (%)	156 (99.4%)
Number of serious adverse events*, n	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n	89 (56.7%)
Number of TEAE grade ≥ 3 events, n	NA
Number and proportion of patients with ≥ 1 TEAE grade ≥ 3 events§, n	96 (61.1%)
Number of adverse reactions, n	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	130 (82.8)
Number and proportion of patients with ≥ 1 serious adverse reaction*,	55 (35%)
Number and proportion of patients with ≥ 1 TEAE grade ≥ 3 adverse	42 (26.8%)
Number and proportion of patients who had a dose delay, n (%)	54 (34.4%)

	Epcoritamab (N=157)
Number and proportion of patients who discontinue treatment	106 (67,5%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	12 (7.6%)

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

Adverse events of special interest (AESIs) included cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and clinical Tumor Lysis Syndrome (CTLS). Table 38 shows the AESIs for epcoritamab in the full population and Figure 7 illustrates where CRS occurred during treatment in the EPCORE-NHL-1 study.

Table 38 AESI

Adverse events	Epcoritamab, LBCL (N = 157)				
	Number of patients with adverse events, N (%)	**Number of adverse events (n)**	**Grade 1 (n)**	**Grade 2 (n)**	**Grade ≥ 3 (n)**
CRS	78 (49.7%)	NA	50 (31.8%)	24(15.3%)	4 (2.5%)
ICANS	10 (6.4%)	NA	7(4.5%)	2(1.3%)	1(0.6%)
CTLS	2 (1.3%)	NA			2(1.3%)

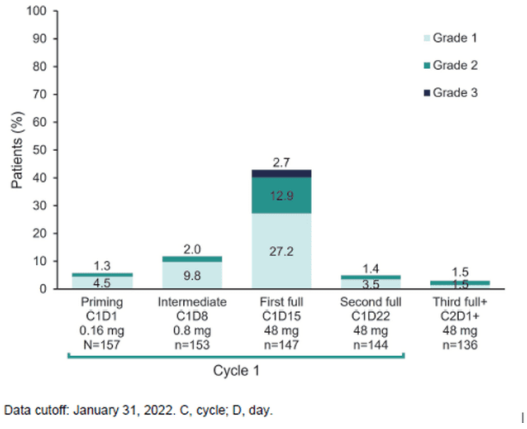


Figure 7 Frequency of CRS events by dosing period (supplement, (38))

In Table 39 most common (≥10%) treatment-emergent AEs of patients are stated.

Table 39 Treatment emergent AE's ≥10% by worst grade in patients with LBCL (data cut Jan 2022) (38)

Event,* No. (%)	All, Any grade N = 157 (%)	Grade ≥3 N = 157 (%)
CRS	78 (49,7)	4 (2,5)

Injection-site reaction	31 (19,7)	0
Neutropenia	34 (21.7)	23 (14.6)
Fatigue	36 (22.9)	3 (1.9)
Pyrexia	37 (23.6)	0
Trombocytopenia	21 (13,4)	9 (5,7)
Nausea	31 (19.7)	2 (1.3)
Anemia	28 (17.8)	16 (10.2)
Headache	21 (13.4)	1 (0.6)
Diarrhea	32 (20.4)	0
Abdominal pain	22 (14.0)	3 (1.9)
Constipation	20 (12.7)	0
Decreased appetite	19 (12.1)	1 (0.6)
Vomiting	19 (12.1)	1 (0.6)
Peripheral edema	17 (10.8)	0
Back pain	16 (10.2)	1 (0.6)

Data cutoff: January 31, 2022.
*Classified using Medical Dictionary for Regulatory Activities version 24.1. Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome weregraded per Lee et al 20194; all other events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
†One fatal case of immune effector cell–associated neurotoxicity syndrome

Serious adverse events are reported in Appendix E.

9.1.2 Safety data comparison between EPCORE-NHL-1 (data cut Jan 2022) and SCHOLAR-1

Safety data from the EPCORE-NHL-1 trial, with the data cut from January 2022 (data on full trial population, LBCL, N=157), has been compared with R-CIT in SCHOLAR-1 in a naïve safety comparison presented below. Further safety data on the April datacut for DLBCL can be found in section 9.1.3.

Overall, the LBCL population from the EPCORE-NHL-1 trial showed low rates of severe (grade ≥3) CRS (2.5%), ICANS (0.6%), CTLS (1.3%) and AE-related treatment discontinuation (7.6%).

Safety data from SCHOLAR-1 can be retrieved from the 4 sources that were used for the pooled analyses of the DLBCL population in SCHOLAR-1 and was the first patient-level analysis of outcomes of refractory DLBCL:

SCHOLAR-1 pooled data from 2 clinical trials:

- 1. **LY.12 study**, a follow-up of 2 large phase 3 randomized controlled trials, Canadian Cancer Trials Group study
- 2. **CORAL study**, the Lymphoma Academic Research Organization (LYSARC) Collaborative Trial in Relapsed Aggressive Lymphoma)

and 2 observational cohorts:

- 1. Observational cohorts from MD Anderson Cancer Center (**MDACC**)
- 2. The Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (**IA/MC**))

There was no reported safety information in the SCHOLAR-1, nor in the papers based on the observational cohorts. However, some safety information was reported in CORAL and the LY.12 study where the following safety information was described.

In the CORAL study grade 3 and 4 hematologic toxicities were found to be more severe in the R-DHAP arm compared to the R-ICE arm. In addition, more severe AEs occurred in the R-DHAP arm (120 SAEs in 68 patients) than in the R-ICE arm (90 SAEs in 58 patients). Infections were the most common SEA occurring with a similar rate across both arms (16%). Grade 3 and 4 non-hematologic toxicities were more severe in the R-DHAP arm including grade 4 renal toxicity in 11 patients (43).

In the LY.12 trial eight patient died due to protocol treatment related complications; two patients died during GDP treatment and 6 after receiving DHAP treatment. In those patients receiving GDP grade 3 and 4 AEs were observed significant less frequent in the two first cycles of chemotherapy (47 % vs. 61% P < 0.001) including febrile neutropenia (9% vs. 23%; P < 0.001).

A naïve safety data comparison between EPCORE-NHL-1 (data cut Jan 2022) and SCHOLAR-1 (from the LY.12 trial) has been presented below.

Table 40 Serious Adverse Events from EPCORE-NHL-1 (data cut Jan 2022) and the LY.12 trial

Adverse events	EPCORE-NHL-1 (data cut Jan 2022) N=157, n (%)*	GDP from LY.12 arm N = 306, n (%)	DHAP from LY.12 arm N = 304, n (%)
Thrombosis/embolism	9 (5.7)	18 (8)	18 (6)
Fatigue	3 (1.9)	30 (10)	28 (9)
Nausea	2 (1.3)	13 (4)	25 (8)
Vomiting	1 (0.6)	22 (7)	21 (7)
Infection with grade 3 to 4 neutropenia	23 (14.6)	18 (6)	28 (9)
Infection without neutropenia	Not reported	21 (7)	22 (7)

Febrile neutropenia	Only Neutropenia reported	28 (9)	70 (23)
Syncope	Not reported	7 (2)	16 (5)
Worst overall	Not reported	143 (47)	186 (61)
CRS	4 (2.5)	Not applicable	Not applicable
Anemia	16 (10.2)	Not reported	Not reported
Headache	1 (0.6)	Not reported	Not reported
Abdominal pain	3 (1.9)	Not reported	Not reported
Decreased appetite	1 (0.6)	Not reported	Not reported
Back pain	1 (0.6)	Not reported	Not reported

* Grade ≥3 Treatment emergent AE's in ≥10% of the patients with LBCL

As seen from above table many adverse events are not reported to be able to make a fair comparison between the study populations. Moreover, the severeness of the adverse event has not been clearly stated from the LY.12 trial on DHAP and GDP, and the definition of for instance neutropenia might differ between the trials. However, based on the information available, we can see that apart from CRS, which is only applicable to epcoritamab, the adverse events for epcoritamab are in general lower than for the conventional CIT from LY.12.

Same challenges in comparing safety data have been acknowledged from the UK and the other markets. For the NICE appraisal in the UK for instance, they have used a proxy for their R-CIT arm (TA895 Axi-cel and TA875 Pola-BR).

9.1.3 Safety data EPCORE-NHL-1, DLBCL ([redacted])

As of the data cutoff date[redacted] subjects with DLBCL had experienced at least 1 treatment-emergent AE (TEAE). Of these[redacted] subjects experienced TEAEs considered related to epcoritamab by the investigator (Table 41). A total of [redacted] subjects experienced grade 3 or 4 TEAEs by preferred term (≥5%) where the most common were [redacted].

Serious TEAEs were reported in [redacted](Table 41), where the most common (≥2%) were

[redacted]. Fatal TEAEs were reported [redacted] subjects (Table 41). A summary of most common (≥10%) treatment emergent AE's can be seen in Table 43.

Adverse events of special interest (AESIs) included CRS, ICANS, and CTLS. [redacted] experienced an AESI of CRS, [redacted] patients experienced an AESI of ICANS ([redacted] and [redacted] patients experienced an AESI of CTLS [redacted](Table 42).

Table 41 Overview of safety events. State the time period the table covers.

	Epcoritamab (N=139) (EPCORE-NHL-1, data cut [redacted])
Number of subjects with ≥1	
TEAE, n (%)	[redacted]
Related TEAE, n (%)	[redacted]
Grade 3 and higher TEAE, n (%)	[redacted]
Grade 3 and higher related TEAE, n (%)	[redacted]
TEAE by worst toxicity grade	
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
Serious TEAE	[redacted]
Serious related TEAE	[redacted]
TEAE leading to treatment discontinuation	[redacted]
TEAE leading to dose delay	[redacted]
Fatal TEAE	[redacted]
Fatal related TEAE	[redacted]

Table 42 AESI

Adverse events	Epcoritamab, DLBCL (N = 139)
	Number of patients with adverse events, N (%)
CRS	[redacted]

Adverse events	Epcoritamab, DLBCL (N = 139)
ICANS	[redacted]
CTLS	[redacted]

In Table 43 below, most common (10%) treatment emergent AEs are shown for patients with DLBCL. The data are based on the [redacted] data cut, and only available for the safety analysis set. The AEs are divided into all and those related to treatment.

Median follow-up time is [redacted] months.

Table 43 Most common (at least 10%) Treatment emergent AE's in patients with DLBCL (N=139, data cut [redacted]) (43)

Event, n (%)	All	All Drug-Related
Subjects with ≥1 TEAE	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]

All treatment emergent AE's Grade ≥3 in more than 5% of the patients with DLBCL and

AESI were included in the health economic analysis. See section 9.2 for AE's used in the health economic analysis for epcoritamab and comparator.

Serious adverse events are reported in Appendix E.

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

Adverse events applied in the health economic analysis for R-CIT are based on external literature, from a previous NICE evaluation (40), showing incidences for CIT in the disease DLBCL, and where the AEs found most plausible for the comparator R-CIT. Only adverse events including grade 3 or 4 that occurred in ≥5% of the patients in EPCORE-NHL-1 trial, or grade 1-2 AEs if those AEs were expected to lead to hospitalization and costly treatments were included.

Table 44 Adverse events used in the health economic model

	Intervention Epcoritamab (N=139) (EPCORE-NHL-1, [redacted] data cut, median follow-up = [redacted] months)	Comparator R-CIT (NICE TA 649)
The adverse events presented include grade 3 or 4 AEs that occurred in ≥5% of the patients of any of the studies (EPCORE-NHL-1 or comparator trials). Grade 1-2 AEs were included if those AEs were expected to lead to hospitalization and costly treatments.		
Anaemia	[redacted]	17.9%
CRS	[redacted]	0.0%
Febrile neutropenia	[redacted]	12.8%
ICAN	[redacted]	0.0%
Leukopenia	[redacted]	7.7%
Lymphopenia	[redacted]	0.0%
Neutropenia	[redacted]	33.3%
Rash	[redacted]	7.7%
Thrombocytopenia	[redacted]	23.1%

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

Table 45 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
Instrument EQ-5D-3L	EPCORE-NHL-1	Utilities
Instrument FACT-LYM	EPCORE-NHL-1	Effectiveness

10.1 Presentation of the health-related quality of life

Patients reported outcomes and improvements in the lymphoma related symptoms and in their general quality of life were measured using the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) and the 3-dimension level EuroQol questionnaire (EQ-5D-3L) which has 2 components: the EQ-5D descriptive system and the EQ VAS. The descriptive system consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 3 levels (no health problems, moderate health problems, and extreme health problems), which correspond to scores of 1, 2, and 3. The VAS records the subject's self-rated health on a vertical visual analogue scale from 0 to 100, where the endpoints are labelled as 100='Best imaginable health state' and 0='Worst imaginable health state'.

10.1.1 FACT-LYM

The FACT-LYM dataset is only available from January 2022 data cut.

10.1.1.1 Study design and measuring instrument.

For subjects with LBCL, steady and consistent improvements in FACT-Lym total scores were observed, with mean (standard deviation) scores improving from 118.4 (25.47) at baseline.

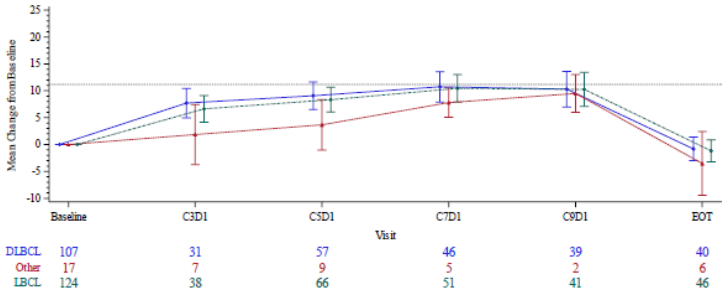
Cycle (C) 1, day (D) 1(C1D1, N=140) to 136.2 (19.35) at C9D1 (N=45), the final time point measured the consistency of improvement was reflected in the mean (standard deviation) change in FACT-Lym total scores from baseline ranging from 6.6 (15.11) by C3D1 to 10.3 (20.23) at C9D1. Among the subjects who later progressed and/or discontinued treatment (EOT) (N=50), mean (standard deviation) FACT-Lym total score at EOT remained comparable to the baseline at 118.1 (25.53).

Results for the DLBCL cohort were similar to those observed for the LBCL cohort.

10.1.2 HRQoL results

Figure 8 Mean Change from baseline Fact-Lym total score

Figure 11-17 Mean Change from Baseline in FACT-Lym Total Score - aNHL Cohort, Expansion Part (PRO-evaluable Set)



DLBCL	107	31	57	46	39	40
Other	17	7	9	5	2	6
LBCL	124	38	66	51	41	46

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; C = Cycle; D = Day; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; PRO = patient-reported outcome.
Note: Horizontal reference line indicates minimum important difference (MID=11.2).
Data cutoff date: 31 Jan 2022

10.1.3 EQ-5D-3L

10.1.3.1 Study design and measuring instrument

The relevant variables for the utility analysis were extracted from datasets collected in the [redacted] database lock of the single-arm trial EPCORE-NHL-1. The dataset provided subjects' HRQoL measurements. HRQoL was assessed using a validated self-reported questionnaire: the EuroQol group's EQ-5D-3L. The EQ-5D-3L is a generic preference-based measure of HRQoL, which has been validated in cancer populations to measure both utility and health status. Linear mixed models (LLM) for repeated measures were used to analyse the EQ-5D-3L data obtained in the trial.

To convert the EQ-5D-3L index scores into utility values for each health state, it is necessary to combine these scores with a country-specific value set that reflects the preferences of the general population for all possible EQ-5D-3L states (5 domains with 3 levels, 5 - 125 in total). The UK specific value set by Dolan(52) was used to derive UK utility values used in the utility analysis, the value set was applied in R statistical programming environment(53) using the eq5d package.

From the EPCORE-NHL-1 EQ-5D-3L individual item scores, utilities were estimated with a value range from 1 for state 11111 to -0.594 for state 33333.(52)

10.1.3.2 Data collection

The utility analysis was performed on a subset of the full analysis set, which comprised patients with DLBCL that received no prior CAR T included in the EPCORE-NHL-1 (GCT3013-01) trial of 86 subjects, all initiated treatment with epcoritamab. Of those participants, [redacted] provided at least one complete EQ-5D-3L measurements up to data cut-off (June 2022). This population is in alignment with the population that will be modelled in the cost-effectiveness model. Among the population, subjects were excluded from the utility analysis if they did not have any response assessment, or they did not have at least one complete EQ-5D-3L measurement.

EQ-5D-3L was assessed on day one of cycles 1, 3, 5, 7, and 9 (28-day cycle) and at the end of treatment (as soon as possible, but within 7 days after withdrawing from treatment).

All subjects ([redacted]) initiated treatment with epcoritamab. Of those participants [redacted] provided at least one complete EQ-5D-3L measurement up to the data cut-off. The four patients with missing EQ-5D-3L measurements at every measurement point were excluded from the analyses. A total of [redacted] complete EQ-5D-3L measurements from the [redacted] subjects were included in the utility analyses.

Table 46 provides an overview of the number of complete EQ-5D-3L responses received at each time point per health state.

[redacted]

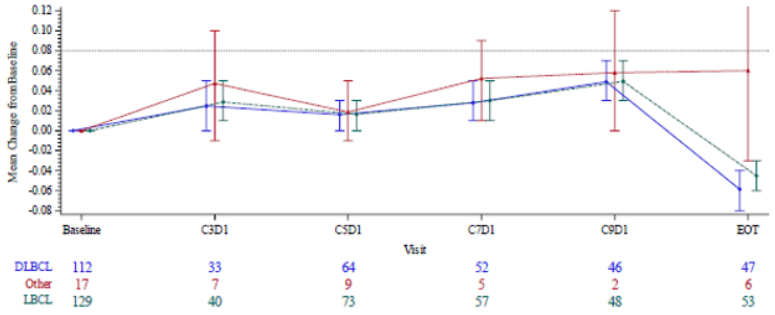
Table 46 Pattern of missing data and completion, june data cut 2022

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion PFS N (%)	Completion PD 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)	Number of patients who completed (% of patients expected to complete)
Baseline, day 1 Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 1 Cycle 3		[redacted]	[redacted]	[redacted]	[redacted]
Day 1 Cycle 5		[redacted]	[redacted]	[redacted]	[redacted]
Day 1 Cycle 7		[redacted]	[redacted]	[redacted]	[redacted]
Day 1 Cycle 9		[redacted]	[redacted]	[redacted]	[redacted]
End of treatment			[redacted]	[redacted]	[redacted]

10.1.4 HRQoL results

For the graph of mean change from baseline the EQ-5D-3L values, both EPCORE-NHL-1 published data, based on data cut January 2022 and later data cut [redacted] are presented. Graph of mean change for the EQ-5D-3L and the EQ VAS, is not used in the health economic analysis. See further below for the results on EQ-5D-3L, DLBCL, [redacted] data cut.

Figure 9 mean change from baseline in EQ-5D-3L Health Utility Score through the different data collection time points, Jan 2022 data cut



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; C = Cycle; D = Day; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; PRO = patient-reported outcome.
Note: Horizontal reference line indicates minimum important difference (MID=0.08).
Data cutoff date: 31 Jan 2022

Figure 10 mean change from baseline in EQ-5D-3L Health Utility Score through the different data collection time points, [redacted] data cut

[redacted]

Table 47 Descriptive statistics for utility values by health state

Intervention (epcoritamab)		
	Observations (N = subjects)	Mean (SE)
PFS (Baseline measurements)	78 (78)	0.735 (0.031)
PFS (all measurements)	215 (81)	0.813 (0.015)
PD (first measurement)	23 (23)	0.697 (0.06)
PD (last measurements)	23 (23)	0.643 (0.062)

PD (all measurements)	32 (23)	0.674 (0.052)

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

10.2.1 HSUV calculation

Health-related quality of life (HRQoL) data were collected from subjects in the EPCORE-NHL-1 trial using the EQ-5D-3L, database lock [redacted]. For the EPCORE-NHL-1 trial Diffuse large B-cell lymphoma (DLBCL) population with no prior CAR T, EQ-5D-3L data were available for [redacted] individual patients, [redacted] of the population, and a total of [redacted] complete EQ-5D-3L measurements from the [redacted] subjects were included in the utility analyses.

The EQ-5D-3L is a generic preference-based measure of HRQoL, which has been validated in cancer populations to measure both utility and health status. The EQ-5D-3L consists of two sections. First, subjects are asked to report their status "today" on the following five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension contains three response levels to reflect the degree of problems subjects are experiencing "today": no problems (level 1), some problems (level 2), and extreme problems (level 3). Second, participants are requested to rate their health today on a visual analogue scale (VAS), between 100 ("the best health you can imagine") and 0 ("the worst health you can imagine").

Responses to the five dimensions can be combined into a 5-digit number, the EQ-5D-3L index score. For instance, an EQ-5D-3L index score equal to 12231 indicates that, due to the disease, the subject has no problems in the first and fifth dimensions (i.e., mobility and anxiety/depression), has moderate problems in the second and third dimension (i.e., self-care and usual activity) and has extreme problems in the fourth dimension (i.e., pain/discomfort). Patients with completely missing EQ-5D-3L measurements (n=4), i.e. no complete EQ-5D-3L measurement up to the EPCORE-NHL-1 data cut-off, were excluded from the analyses, missing data was not imputed. Given the EQ-5D-3L measures were provided using the 5-digit code, missing values for a measurement were assumed all five digits were missing, missing individual digits were not imputed.

The Linear mixed model (LMM) approach were used to derive the EQ-5D-3L utility values utilizing fixed and random effects. In the LMM, the EQ-5D-3L utilities in EPCORE-NHL-1 (GCT3013-01) trial were the dependent variable.

The covariates that were investigated include:

- Health state (hs_{it})
  - PFS vs. PD
- Treatment status ($txstatus_{it}$)
  - On vs. off treatment

- A combination of health state and treatment status including an interaction term between both

Different models were fitted using health state, treatment status or both as covariates, and a summary is shown in Table 48. In the models, the term Y_{it} denotes the EQ-5D-3L utility value measured for subject *i* at time *t*, e_{it} is the random error term and u_i is the random intercept term. All models were conducted using the random intercept model, accounting for differences in utilities between subjects, see Appendix L. For each model, health state utilities and confidence intervals were calculated.

Table 48. LMMs estimated in the utility analyses

	Model specification	Coefficients	Use in cost-effectiveness model
Model 1	$Y_{it} = \beta_0 + \beta_1 hs_{it} + u_i + e_{it}$	Health state	Base case
Model 2	$Y_{it} = \beta_0 + \beta_1 hs_{it} + \beta_2 txstatus_{it} + u_i + e_{it}$	Health state + treatment status	allows health state and treatment status
Model 3	$Y_{it} = \beta_0 + \beta_1 hs_{it} + \beta_2 txstatus_{it} + \beta_3 txstatus_{it} * hs_{it} + u_i + e_{it}$	Health state + treatment status + interaction term	allows health state and treatment status

Abbreviations: CEM, cost-effectiveness model; e_{it}, random error term; hs_{it}, health state for subject *i* at time *t*; $txstatus_{it}$, treatment status for subject *i* at time *t*; u_i, random intercept term; Y_{it}, the EQ-5D-3L utility value measured for subject *i* at time *t*.

As conventional for HTA utility analysis, no individual level covariates were used such as age or clinical variables as based on the randomized trial assumptions, age and gender distributions between treatment arms should not differ. Additionally, adverse events (AEs) were not included as a covariate in the base case utility analysis, but were assumed to be captured through separate disutilities sourced from the literature.

All analyses were conducted in the R statistical programming environment. The "lmer" function from the lme4 package in R was used to estimate the models.(54,55) For each model, the specification tested was random intercept. This specification took account of the repeated measures in the data which might introduce non-independence of EQ-5D-3L reporting. The models were fitted with identical fixed effects structures and least square mean estimates of the EQ-5D-3L utility values and the related standard errors (SEs) were generated. For each model, the coefficients and related SEs, confidence intervals and fit statistics were reported, as well as the resulting health state utilities, see Appendix L.

The models were assessed using the Akaike's information criteria (AIC) and Bayesian information criteria (BIC) statistics and plausibility of results. The optimal model was defined as the model which best reflected reality, generated plausible results and was suitable for the cost-effectiveness model. This means that the optimal model was selected based on the direction, magnitude and significance of each estimated coefficient, the AIC and BIC statistics as well as whether it aligned with the capabilities of the cost-effectiveness model, see Appendix L. The results of the tree models, covariates of the

models tested and their AIC and BIC fit results are displayed in Appendix L. The best fit in terms of AIC and BIC was Model 1 with the most negative AIC and BIC i.e. the lowest values, including only the health state covariate. **Therefore, model 1 was selected as the most appropriate model.**

A total of [redacted] complete EQ-5D-3L measurements from the [redacted] subjects were included in the utility analyses.

A histogram displaying the distribution of these observations. [redacted] observations had the maximum utility of 1, for the EQ-5D-3L state 11111, [redacted] of these were measured in the PFS health state and [redacted] in the PD health state. Conversely, none of the observations was associated with the minimum utility of -0.594, for the EQ-5D-3L state 33333, the minimum observed utility was [redacted] and was observed in the PFS health state. The mean utility value across all time points was equal to [redacted] and the median utility value was [redacted].

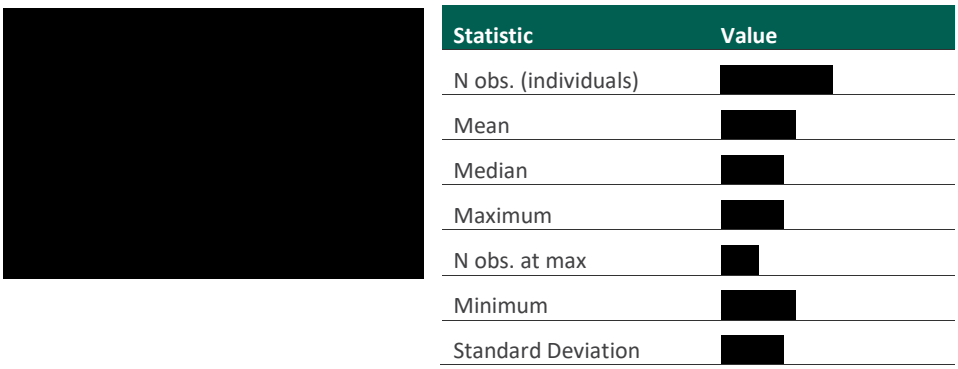
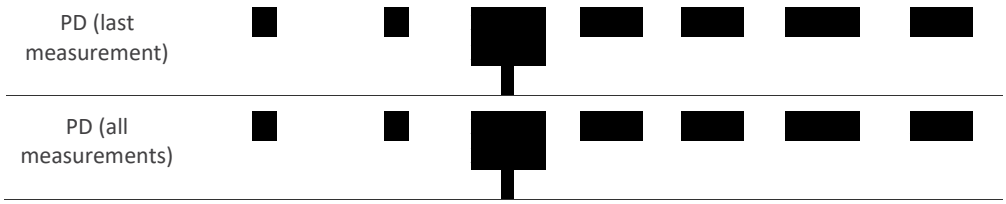


Figure 11. Distribution of the EQ-5D-3L utility data in the DLBCL population of EPCORE-NHL-1 trial using the [redacted] database lock

Only results on the descriptive utilities based on health state will be presented as model (model 1) will be used in the cost-effectiveness analysis. See results in Table 49.

Table 49. Descriptive statistics for utility values by health state

Health state	Total observations	Unique subjects	Mean utility (SD)	SE	Median utility	Minimum utility	Maximum utility
PFS (baseline measurement)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (all measurements)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD (first measurement)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



As expected, utility was higher in the PFS state than in PD [redacted]), as shown in Table 49. For PFS, the utility was higher when considering all observations compared to baseline observation, indicating that as patients remained progression free, the utility increased. For PD, this relationship was reversed as the utility was higher at the first vs. the last PD measurement, indicating that patients deteriorated after disease progression. However, there were only a small number of patients providing multiple PD measurements, as all PD measurements contained [redacted] observations from [redacted] unique subjects.

The sample size for both the first and last measurement in PD was also [redacted] since if a patient only had one observation, their first observation was also their last observation. The calculation for the first observation was taken from the earliest date when the PD utility estimate was taken, and the same applied to the last observation, where the last observation was taken from the latest date when the PD utility estimate was taken for each patient. This means that the data became the same if a patient only had one observation. See the table below.

Table 50. Descriptive statistics for utility values by health state

Health state	Timepoint	Total observations	Unique subjects	Mean utility (SD)	SE	Median utility	Minimum utility	Maximum utility
PFS	D1 C1	[redacted]						
	D1 C3	[redacted]						
	D1 C5	[redacted]						
	D1 C7	[redacted]						
	D1 C9	[redacted]						
	EoT	[redacted]						
PD	D1 C1	[redacted]						

The average difference between measurements was [redacted], and the median difference between measurements [redacted]

Results based on model 1 can be seen in Table 51.

Table 51. Utility model 1 utility values per health state

Parameters	Health state value (CI)	SE
PFS	[redacted]	[redacted]
PD*	[redacted]	[redacted]
PD	[redacted]	[redacted]

Abbreviations: PD, progressed disease; PFS, progression free survival.
* To retrieve the utility value for Health state PD, the utility value for PD* is subtracted from the utility value for Health state PFS

The descriptive analyses showed that utility scores for the progression free survival (PFS) health state are higher than the progressed disease (PD) health state and that progression had a negative impact on the utility scores.

The utilities estimated for the EPCORE-NHL-1 DLBCL population using a LMM including only health state as covariate of [redacted] in PFS and [redacted] in PD were considered appropriate for use. Estimates generated from the EPCORE-NHL-1 trial were preferred over estimates from other trials or submissions, as those might not be fully generalizable to the modelled population.

The EQ-5D-5L Danish preference weights were used in the health economic analysis using mapping from EQ-5D-3L, see section 10.2.1.1. The utility values has been age-adjusted to the Danish population, as per DMC guidelines. (35)

10.2.1.1 Mapping

Table 53 provides a summary of the utility values derived from the EPCORE-NHL-1 (GCT3013-01) trial, using the best performing model, and mapped to Danish EQ-5D-5L values using the reverse-cross-walk V2.2 method from EuroQol.(56,57)

10.2.2 Disutility calculation

Approach for capturing AEs as it is acknowledged that in clinical trials where HRQoL assessment is usually time-based rather than event-based and HRQoL is assessed infrequently (in this case every 4 to 8 weeks), it is unlikely that AEs are fully captured within the EQ-5D assessment visits, particularly given the EQ-5D recall period of "today". Additionally, any AEs that are captured are implicitly assumed to apply for the full duration of time between HRQoL assessments, regardless of the true duration of the AE in practice. Therefore, it tends to be preferred for AEs to be captured separately in literature based disutilities.(58)

Disutility for specific adverse events where not captured in the EPCORE-NHL-1 study. Disutilities for adverse events where applied to health economic model and where estimated from a previous NICE assessment (NICE TA 649(40) and NICE TA 306(59)).

Table 52 Input data used in the model:

AE	Disutility	Disutility duration (days)	Datasource
Anaemia	0.25	16	NICE TA 649 NICE TA 306
CRS	0.81	4	NICE TA 649 NICE TA 306
Febrile neutropenia	0.15	6	NICE TA 649 NICE TA 306
ICAN	0.81	17	NICE TA 649 NICE TA 306
Leukopenia	0.2	14	NICE TA 649 NICE TA 306
Neutropenia	0.09	15	NICE TA 649 NICE TA 649 NICE TA 306
Rash	0.25	16	NICE TA 649 NICE TA 306
Thrombocytopenia	0.11	23	NICE TA 649 NICE TA 306

10.2.3 HSUV results

Table 53 Overview of HSUV derived from EPCORE-NHL-1, Danish weights

	Results [95% CI]	From Instrument	Tariff	Comments
PFS				
EPCORE-NHL-1	[redacted]	EQ-5D-3L	EQ-5D-5L, DK	EQ-5D-3L data was collected in EPCORE-NHL-1 trial. Estimate is based on mapping to Danish utility

	Results [95% CI]	From Instrument	Tariff	Comments
				weights and the EQ-5D-5L value set using the reverse cross walk method.
PD				
EPCORE-NHL-1	[redacted]	EQ-5D-3L	EQ-5D-5L, DK	EQ-5D-3L data was collected in EPCORE-NHL-1 trial. Estimate is based on mapping to Danish utility weights and the EQ-5D-5L value set using the reverse cross walk method

The utility values obtained from the EPCORE-NHL-1 trial analysis will be used in the base case setting.

Based on the literature research, see Appendix J, a scenario analyses will be performed based on utility values adjusted to the values from Axi-cel's ZUMA-1 trial and previous NICE and oncology submissions within DLBCL. However, not based on Danish utility weights. Below table provides an overview of the utility values used in a scenario analysis.

Table 54 Utilities used in scenario analyses, derived from ZUMA-1(41)

Health state	Utility	SE
DLBCL		
Pre-progression	0.72	0.030
Post progression	0.65	0.060

These utility values were used in the model irrespective of population and comparator.

10.3 Presentation of utility values measured in other trials

NA

11. Resource use and costs

The model includes several cost categories to reflect the key cost components related to treatments, disease management, and monitoring of DLBCL. The cost categories include initial treatment costs (drug acquisition and administration costs), disease management costs associated with health states (hospital visits, blood tests and other non-drug related monitoring costs), adverse event costs associated with initial treatments, subsequent treatment costs (pharmacological treatment, drug costs and administration) and indirect costs (patient time and transportation costs). The categories are explained more detail in below sections.

11.1 Pharmaceutical costs for Epcoritamab and R-CIT

For drugs with more than one formulation and prices, the least expensive option was used in the economic evaluation. The drug acquisition costs were calculated by multiplying the costs per milligram with the required amount per dose. The required amount per dose also included the drug wastage.
Se Appendix N for all the current prices per compound and Table 55-Table 58 for those used in health economic model.

Table 55 Pharmaceutical cost used in the model for epcoritamab

Treatment	Admin route	frequence	Dose intensity	Vial sharing	Refrence	Package	Price	Reference drug cost
Epcoritamab	SC	Cycle 1: 0.16 mg day 1, 0.8 mg day 8, 48 mg day 15 and 22	96,5 %	No	EPCORE-NHL-1 CSR[53]	4 mg	4.105,38	Internal
		Cycle 2 and 3: 48 mg day 1, 8, 15, and 22						
		Cycle 6-9: 48 mg day 1 and 15				48 mg	49.264,51	
		Cycle 10+: 48 mg day 1	98.6 %					

Table 56 Pharmaceutical cost used in the model for R-GemOx

Treatment	Admin route	Admin frequency	Dose intensity	Vial Sharing	Reference	Package dose used in model	Price per package used in model	Reference drug cost
Rituximab	IV	375 mg/m^2 day 1, up to 4 cycles	100%	No	SmpC and clinical inputs	2x 500 mg	6687 kr.	Medicinpriser.dk
						2x 100 mg	2676 kr.	
Gemcitabine	IV	1.000 mg/m^2 day 1 and 8, up to 4 cycles	100%	No	SmPC and clinical input	220x 10 mg	420 kr.	Medicinpriser.dk
Oxaliplantine	IV	100 mg day 1, up to 4 cycles	100%	No	SmpC and clinical input	40x 5 mg	127,82	Medicinpriser.dk

Table 57 Pharmaceutical cost used in the model for R-GDP

Treatment	Admin	Admin frequency	Dose intensity	Vial Sharing	Reference	Package dose	Price per packa	Reference drug cost

	route					used in model	ge used in model	
Rituximab	IV	375 mg/m² day 1, up to 4 cycles	100%	No	SmpC and clinical inputs	2x 500 mg	6687 kr.	Medicinpriser.dk
						2x 100 mg	2676 kr.	
Gemcitabine	IV	1.000 mg/m² day 1 and 8, up to 4 cycles	100%	No	SmPC and clinical input	220x 10 mg	420 kr.	Medicinpriser.dk
Dexamethasone	Oral	40 mg day 1-4, up to 4 cycles	100%	No	SmPC and clinical inputs	10x 40 mg	1490 kr.	Medicinpriser.dk
Cisplatin	IV	100 mg/m² day 1, up to 4 cycles	100%	No	SmpC and clinical inputs	50x 1mg	100 kr.	

Table 58 Pharmaceutical cost used in the model for R-DHAP

Treatment	Admin route	Admin frequency	Dose intensity	Vial Sharing	Reference	Package dose used in model	Price per package used in model	Reference drug cost
Rituximab	IV	375 mg/m² day 1, up to 4 cycles	100 %	No	SmpC and clinical inputs	2x 500 mg	6687 kr.	Medicinpriser.dk
						2x 100 mg	2676 kr.	
Dexamethasone	Oral	40 mg day 1-4, up to 4 cycles	100 %	No	SmPC and clinical inputs	10x 40 mg	1490 kr.	
Cytarabine	IV	2000 mg/m² day 1 and 2, for up to 4 cycles	100 %	No	SmpC and clinical inputs	20x 100mg	150 kr.	
Cisplatin	IV	100 mg/m² day 1, up to 4 cycles	100 %	No	SmpC and clinical inputs	50x 1mg	100 kr.	

11.2 Pharmaceutical costs – co-administration

Co-medication are excluded after communication with Danish clinicians, that stated no difference will be seen in co-medication. Co-medication for both Epcoritamab and comparators exist of paracetamol and prednisolone, where higher use will be seen for the comparator, chemotherapy, thus excluding co-medication is a conservative estimation.

11.3 Administration costs

The Epcoritamab and comparator are administered at the hospital, and require an outpatient visit per administration. For the administration of subcutaneous and intravenous, the cost are the same, and are in general a conservative estimation. For oral administration the cost are set to zero, as no visit are expected separately with oral medication.

Se unit cost in table, and administration cost per cycle for each treatment in Table 59.

Table 59 Cost for administration type

Administration type	Unit cost	Reference
IV administration	2.005 kr.	DRG tariff 2023: 17MA98: Diagnose: DC833 Diffust storcellet B-celle lymfom. P (BWAA62) Medicingivning ved intravenøs infusion
SC administration	2.005 kr.	DRG tariff 2023: 17MA98: Diagnose: DC833 Diffust storcellet B-celle lymfom. P (BWAA3) Medicingivning ved ved subkutan injektion
Oral administration	0 kr.	N/A

11.4 Disease management costs

The disease monitoring and disease management are captured by routine monitoring visits related to the health states “PFS” and “PD”. However, clinical inputs suggest reduced resource use in the PFS state after 3 years. A multiplication factor has been included for the resource use in PFS state after 3 years to be reduced with 75% and the multiplication factor has been set to 25% of the original resource use in this state, based on clinical inputs.

The list of disease monitoring resource items and frequencies was selected based on clinical guidelines and Danish clinical experts.

The unit cost of disease monitoring inputs are shown in Table 60. The unit costs were sourced from Danish DRG-tariffs and the RH labportal. The selection of unit costs was based on the description of the DRG-code that matched the particular type of resource best.

Table 60 Hospital costs used in the model

Resource	Cost per event (DKK)		Resource use per year, by health state		
	Value	***Reference***	***PF ≤ 3 years***	***PD***	***Reference***
Oncologist	2.005 kr.	DRG-tariff 2023: 17MA98: MDC17 1-dagsgruppe, pat. Mindst 7 år Diagnose: DC833 Diffust storcellet B-celle lymfom. P (DZ087) Kontrolundersøgelse efter kombineret behandling af kræft	4	2	Clinical input
Radiologist	1.713 kr.	DRG-tariff 2023: 30PR18: Røntgenundersøgelse (alm), ukompliceret. Diagnose: DC833 Diffust storcellet B-celle lymfom. P (UXRC00) Røntgenundersøgelse	4	2	Clinical input
PET-CT scan	2.440 kr.	DRG-tariff 2023: 30PR06: CT-scanning, kompliceret Diagnose: DC833 Diffust storcellet B-celle lymfom. P (UXCF00) CT-skanning	2	4	Clinical input
GP visit	155,24 kr.	Laeger.dk Honorar table 2023, Konsultation	2	4	Clinical input
Full blood count	674 kr.	Labportal.rh.dk	4	4	Clinical input
LDH					
Liver function					
Renal function					
Immunoglobulin					
Calcium phosphate					

Resource use cost per cycle, per health state is shown in Table 61. See results from the Excel sheet.

Table 61 Cost per cycle, per Health state

Health state	Cost per cycle

PFS < 3 year	1.807,83 kr.
PFS > 3 year	451,96 kr.
PD	1.635,69 kr.

Besides the routine monitoring costs per model cycle from above table, patients who progress will incur one-time costs for various tests upon progression, which are shown in Table 62.

Table 62 Disease progression-related resource use and cost inputs applied as one-time costs in the cost-effectiveness model

Resource	Cost per patient	Reference	Used in % of patients	Reference	Total cost
ECG	206 kr.	Labportal.rh.dk	67%	Clinical input	10.546,81 kr.
MUGA	3.549 kr.	DRG-tariff 2023: 05PR03: Diagnose: DC833 Diffust storcellet B-celle lymfom. P (UXUC80C) Transtorakal ekkokardiografi med kontrast	33%	Clinical input	
PET-CT-scan	2.440 kr.	DRG-tariff 2023: 30PR06: CT-scanning, kompliceret: Diagnose: DC833 Diffust storcellet B-celle lymfom. P (UXCF00) CT-skanning	100%	Clinical input	
MRI	2.447 kr.	DRG-tariff 2023: 30PR02: MR-scanning, kompliceret Diagnose: DC833 Diffust storcellet B-celle lymfom. P (UXMH00) MR-skanning af hele kroppen1	10%	Clinical input	
Bone marrow biopsy	12.925 kr.	DRG-tariff 2023: 17PR01: Udtagning af knoglemarv til diagnostisk undersøgelse: Diagnose: DC833 Diffust storcellet B-celle lymfom. P (KTNE25A)	50%	Clinical input	

knoglemarvsbiopsi
fra crista iliaca

11.5 Costs associated with management of adverse events

Treatment-emergent adverse events (AEs) of grade 3 or above that occurred in ≥5% of the patients in any of the studies (either GCT-3013-01 or any comparator trials) were included in terms of their impact on costs and effects, as commonly adopted in oncology economic models.

The AEs of grade 1-2 were considered if those AEs are expected to lead to hospitalization and costly treatments. Only cytokine release syndrome (CRS), ICANS and febrile neutropenia where included from these. Adverse events inputs have already been presented in section 9.2.1 above.

Total costs due to AEs were applied during the first model cycle. The total costs were calculated by multiplying the incidence of the AE's with the associated costs, after which the sum over all AE's was taken.

Unit costs for AE are presented in the below table.

Table 63 Adverse event cost inputs applied in the cost-effectiveness model

Adverse event	Cost per event (DKK)	Reference
Anaemia	2.240 kr.	DRG-Tariff 2023: 16MA98: MDC16 1-dagsgruppe, pat. Mindst 7 år: Diagnose: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel. P (DT887) lægemiddelbivirkning UNS
CRS	2.089 kr.	DRG-Tariff 2023: 05MA08: Diagnose D1952 Hypotension forårsaget af lægemiddel. Lang. P (DT887) lægemiddelbivirkning
Febrile neutropenia	38.209 kr.	DRG-Tariff 2023: 16MA03: Diagnose DD709A Neutropeni og agranulocytose forårsaget af lægemiddel lang. P (DT789) Bivirknin UNS
ICAN	12.043 kr.	DRG-Tariff 2023: 21MA05: Forgiftning og toksis virkning af lægemiddel, øvrige: Diagnose DT509A Forgiftning med lægemiddel UNS. P (DT887) Lægemiddelbivirkning UNS
Leukopenia	2.240 kr.	DRG-Tariff 2023: 16MA98: MDC16 1-dagsgruppe, pat. Mindst 7 år: Diagnose DD728H Leukopeni. P (DT887) lægemiddelbivirkning
Neutropenia	38.209 kr.	DRG-Tariff 2023: 16MA03: Diagnose DD709A Neutropeni og agranulocytose forårsaget af lægemiddel lang. P (DT789) Bivirknin UNS
Rash	2.005 kr.	DRG-Tariff 2023: 17MA98: MDC17 1-dagsgruppe, pat. Mindst 7 år. Diagnose DR219 Hududslæt UNS. P (APA4) Sygehuslæge

Thrombocytopenia	38.209 kr.	DRG-Tariff 2023: 16MA03: Diagnose DD696 Trombocytopeni UNS lang. P (DT789) Bivirkning UNS

11.6 Subsequent treatment costs

Subsequent treatment costs are applied each cycle to patients who enter the PD health state. Subsequent treatment costs were calculated by multiplying the percentage of patients on a certain subsequent treatment, with the number of administrations of that treatment per cycle, the mean number of cycles a patient is on that treatment, and the costs of that treatment. Treatment costs of the subsequent treatment and proportion of receiving each treatment are presented in the table below. All subsequent treatments are calculated based on DRG tariffs, as these were found to be the most representative for procedures in the following lines, except for chemotherapy. For chemotherapy, the cost of the drug per cycle for R-GemOx was multiplied by the number of cycles used. 4 cycles of Chemotherapy were included. Only the administration cost for chemotherapy was added to the subsequent treatment, as the administration costs for other procedures were expected to be covered within the DRG tariff. The subsequent treatment distributions are based on clinical inputs.

Table 64 Subsequent treatment use in the health economic model

Treatment at entry	Subsequent drug use (%)					Reference
	R-Chemo	**CAR T**	**Radiotherapy**	**ASCT**	**Allogenic SCT**	
Epcoritamab	61,0%	0,5%	25,0%	0,5%	3,0%	DCI
R-GemOx	30,4%	5,0%	20,0%	17,0%	7,6%	DCI
R-DHAP	30,4%	5,0%	20,0%	17,0%	7,6%	DCI
R-GDP	30,4%	5,0%	20,0%	17,0%	7,6%	DCI

Table 65 Subsequent treatment cost inputs applied in the cost-effectiveness model

Subsequent treatment	Cost per admin	Number of admins per model cycle	Reference
R-Chemo	7.463	1.00	DRG-Tariff 2023: 17MA98: Diagnose DC833 Diffust storcellet B-celle lymfom. P (BWHA1) Basis cytostatisk behandling)
Terminal care	2.005	1.00	DRG-Tariff 2023: 17MA98: Diagnose DC833 Diffust storcellet B-celle lymfom. P (BXBA0) Specialiseret palliativ indsats med lægelig intervention

Radiotherapy	2.230	6.00	DRG-Tariff 2023: 27MP08: konventionel strålebehandling Diagnose: DC833 Diffust storcellet B-celle lymfom. Procedure (BWGC1) konventionel ekstern strålebehandling
ASCT	44.770	1.00	DRG-Tariff 2023: 17MA01: Diagnose DC833 Diffust storcellet B-celle lymfom. P (BOQE1) Beh. M stamcellekonc. Fra autolog knoglemarv:
Allogenic SCT	44.770 kr.	1.00	DRG-Tariff 2023: 17MA01: Diagnose DC833 Diffust storcellet B-celle lymfom. P (BOQE3) Beh. M stamcellekonc. Fra allogen knoglemarv fra familiedonor. lang
CAR-T	3.398.337	1.00	DRG-Tariff 2023: 26MP21: Behandling med CAR-T celleterapi: Diagnose DC833 Diffust storcellet B-celle lymfom. P (BOQX1) Beh. Med genetisk modificerede autologe blodceller

11.7 Patient costs

Patient time and transport costs are included in the model and are counted for each drug administration, resource use, subsequent treatment and AE's. See table for transportation cost per round trip to the hospital and hourly wage. The cost are based on the Danish guidelines.

Table 66 patient time and transport cost

	Cost (DKK)
Transportation per round trip	149,2 kr.
Hourly wage (patient time)	203 kr.

Number of hours patient spent per activity are based on clinical input. One transportation is anticipated per activity. For patient time spent on transport 40 kilometers per round trip to the hospital with 60 km/hour are used for estimation.

For first dosing of epcoritamab it was described in the EPCORE NHL-1 study that patients were hospitalized for 24 hours after the first full dose of epcoritamab (this planned hospitalization was not to be reported as an serious adverse events (SAE)). However, input from Danish clinicians stated that this would not be common practice, as they will not admit patients if they don't see a risk in serious adverse events due to epcoritamab. CRS and ICANS as adverse events for this type of cancer therapy has been handled commonly in Danish clinical practice. 24 hour hospitalization is included in the model but is a conservative estimate.

See Table 67.

Table 67 patient time per activity

Activity	Number of hours patient spent
Drug admin	
Ritxumab	1,5
Gemcitabine	1,66
Oxaliplatin	2,0
Dexamethasone	0
Cisplatine	1,0
Cytarabine	2,0
Epcoritamab 1st dose	24
Epcoritamab following dose	0,25
AEs	
Anaemia	1,0
CRS	1,0
Febrile neutropenia	48
ICAN	4,0
Leukopenia	1,0
Neutropenia	5,0
Rash	1,0
Trombocytopenia	1,0
Resources	
Oncologist	1,5
Radiologist	2,0
GP	1,0
PET-CT scan	2,0
Full blood count	0,25

ECG	0,5
MUGA	1,0
CT scan	1,0
MRI	4,0
PET-CT scan	2,0
Bone Marrow biopsy	4,0
Subsequent treatment	
Terminal care	48
CIT	5,0
Radiotherapy	2,0
Autologous stem cell transplant	72
Allogenic stem cell transplant	168
CAR-T	240

11.8 Other costs

NA

12. Results

12.1 Base case overview

Table 68 Base case overview

Setting	Base case
Comparators	R-GemOX, R-DHAP, R-GDP (all R-CIT)
Type of model	Partitioned survival model, piece-wise model
Perspective	Limited societal
Time horizon	30 years (life time)
Patient and treatment line	R/R DLBCL, 3L +.
Baseline age	65,67 years
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in EPCORE-NHL-1 mapped to Danish EQ-5D-5L weights.
Included costs	Pharmaceutical costs, no waste included Hospital costs Costs of adverse events Subsequent treatment cost Patient costs
Average time on treatment, TTD	Epcoritamab: Time to treatment discontinuation, R-CIT: 4 cycles of chemotherapy, fixed duration
Parametric function for PFS	Epcoritamab: Log-normal (same for comparator) HR value vs CIT: [redacted]
Parametric function TTD	Epcoritamab: Exponential (no TTD curve for comparator)

Parametric function for OS	Epcoritamab: Log-normal (same for comparator) HR value vs. CIT: [redacted]
Average time on treatment	Epcoritamab: Mean Time to treatment discontinuation, 12,2 month R-CIT: 4 cycles of chemotherapy, fixed duration
Average time in PFS state	Epcoritamab: 26,3 month R-CIT: 4 month
Average time in PD state	Epcoritamab: 28,6 month R-CIT: 5,1 month
Average in OS state	Epcoritamab: 54,9 month R-CIT: 9,1 month

12.1.1 Base case results

All outcomes in the model are presented below.

Table 69 Base case results

Per patient	Epcoritamab	R-GemOX (1)	R-DHAP (2)	R-GDP (3)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Administrative costs	[redacted]	[redacted]	[redacted]	[redacted]
Disease management progression free	[redacted]	[redacted]	[redacted]	[redacted]
Disease management progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
One-time disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Adverse reactions costs	[redacted]	[redacted]	[redacted]	[redacted]
Patient time and transport costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Difference		[redacted]	[redacted]	[redacted]
Life years gained (progression free)	[redacted]	[redacted]	[redacted]	[redacted]
Life years gained (Progression)	[redacted]	[redacted]	[redacted]	[redacted]
Total life years gained	[redacted]	[redacted]	[redacted]	[redacted]
Difference		[redacted]	[redacted]	[redacted]
QALYs (progression free)	[redacted]	[redacted]	[redacted]	[redacted]
QALYs (progression)	[redacted]	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Difference		[redacted]	[redacted]	[redacted]

Per patient	Epcoritamab	R-GemOX (1)	R-DHAP (2)	R-GDP (3)
Incremental results				
ICER (per Life year)		[redacted]	[redacted]	[redacted]
ICER (per QALY)		[redacted]	[redacted]	[redacted]

12.2 Sensitivity analyses

12.2.1 Scenario analyses

Below scenario analyses are presented. Comparison against R-GemOx are used as show case, as the cost differs minimally, and efficacy difference are the same.

Table 70 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
HR value based on unadjusted analysis	[redacted]	HR Unadjusted analysis of Epco and R-CIT	[redacted]	[redacted]	[redacted]
HR based on relative efficacy analysis from CORAL extended studies	[redacted]	Adjusted HR analysis, investigating other resources for relative fficacy	[redacted]	[redacted]	[redacted]
Long-term remission assumption after 3 years, based on clinical input	OS as background mortality HR 1,4 after 3 years, and stopping treatment	Based on clinical input, clinicians expect patient to be in long term remission when not progressed after 3 years	[redacted]	[redacted]	[redacted]
Utility values from ZUMA-1	PD: 0.65 PFS: 0.72	Utilities from the ZUMA-1 trial has	[redacted]	[redacted]	[redacted]
OS distribution: Generalized gamma	OS curve: Generalized gamma	Based on statistical fit	[redacted]	[redacted]	[redacted]
OS distribution: log-logistic	OS curve: Log-logistic	Based on statistical fit	[redacted]	[redacted]	[redacted]
PFS distribution: Generalized gamma	PFS curve: Generalized gamma	Based on statistical fit	[redacted]	[redacted]	[redacted]

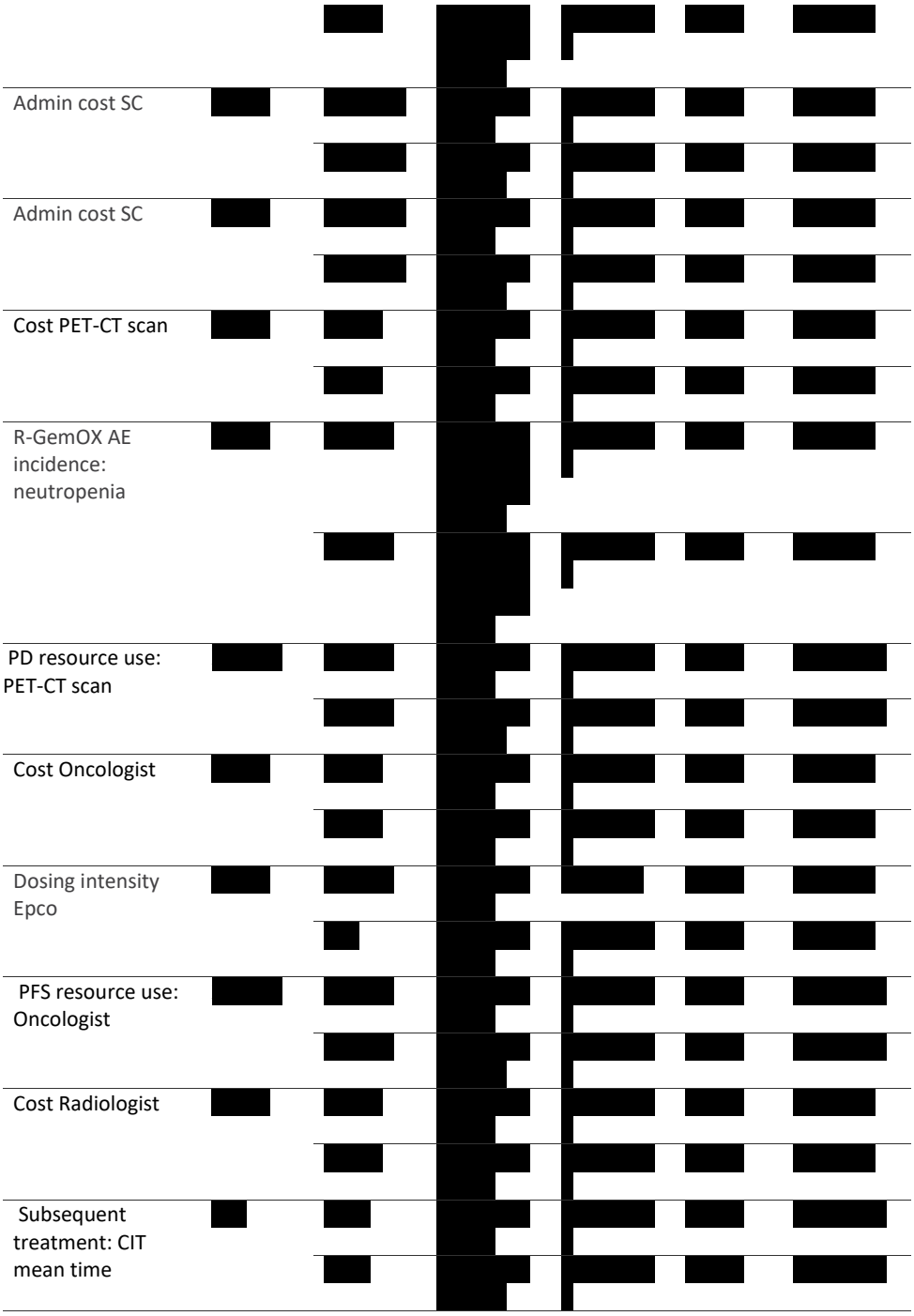
PFS distribution: Log-logistic	PFS curve: Log-logistic	Based statistical fit	[redacted]	[redacted]	[redacted]
TTD distribution EPCO: Log-normal	TTD curve: Log-normal	Based on statistical fit	[redacted]	[redacted]	[redacted]

12.2.2 Deterministic sensitivity analyses

Table 71 Show all changes and values for the deterministic sensitivity analyses for R-CIT. This will be based on One-away sensitivity analyses, and with the example for R-GemOX as all differences in QALY will be the same between the three comparators, and cost will vary minimally, with no impact on the results. Tornado diagram are presented below for each comparator. All lower and upper bound where based on CI intervals where possible or SE from analysis or studies. When this was not possible (e.g all cost) 10% SE where used +/- 1.96 for the 95% credibility interval.

Table 71 One-way sensitivity analyses results

	Value in the base case	Change Values	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratio (HR) Overall Survival (OS) First OS HR:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility value in the PD state (Epco trial)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility Value in the PFS state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



Abbreviation: CI; confidence interval, SE: Standard Error

Below is presented tornado diagrams of one-way sensitivity analyses on all comparators, with a number of 15 parameter values.

Figure 12 One-Way sensitivity analysis Epco vs. R-GemOX

Figure 13 One-Way sensitivity analysis Epco vs. R-GDP

Figure 14 One-Way sensitivity analysis Epco vs. R-DHAP

12.2.3 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses, including scatter plots of 5.000 model simulations on the cost-effectiveness plane (CEP)were performed.

See Probabilistic sensitivity analysis has been conducted using 5,000 iterations and is presented in the model spreadsheet “PSA”. All the model parameters that were varied in PSA and their associated distributions are presented in the model, on sheet “Inputs” and in Table 79 below. Point estimates and lower/upper bounds are presented. Whenever available, the standard error of the model input was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a parameter, the standard error for each parameter was assumed to be equal to the mean value divided by four. For survival estimates, uncertainty has been captured in the variance-covariance matrix of the parameter estimates and applied through Cholesky decomposition. Also, time horizon, cycle length, discount rates etc. are considered structural assumptions, and are fixed setting, and, as such, are not included in the PSA.

The choice of probability distribution follows standard practice. Resource use, costs, disutility and duration of treatment are following gamma distribution. Gamma distribution is used for non-negative parameters, having continuous probability distributions. Gamma distribution is therefore used for cost parameters. Age, bodyweight, BSA and HR to adjust BGM for long term remission are following normal distribution. A normal distribution is a type of continuous probability distribution in which most data points cluster toward the middle of the range, while the rest taper off symmetrically toward either extreme. Normal distribution is therefore used for parameters where you usually have a mean value in the middle. Gender, resource use parameters, and adverse events are following Beta distribution. The beta distribution is appropriate for describing the distribution of a

probability or proportion. Beta distribution is therefore used for incidence rates and number of visits per resource use parameter.

Parameters on survival distributions have been excluded from the PSA due to standard practice and the tests already performed in the DSA.

Table 79 in Appendix G for parameters including standard error. See below the PSA for all comparators.

Figure 15 PSA Total discounted Costs and QALYs

Figure 16 PSA Incremental costs and QALYs of Epcoritamab and comparators

Figure 17 Multi-way cost-effectiveness acceptability curves (CEAC) for Epcoritamab and comparators

13. Budget impact analysis

Number of patients (including assumptions of market share)
Around 41 patients are expected to be eligible for treatment with Epcoritamab each year. The expected market share will be 10% in year 1 and increased to 70% in year 5.

The current market share is divided equal between the chosen comparator, R-CIT. Number of patients are adjusted to market share and death.

Table 72 Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Epcoritamab					
R-CIT					
			Non-recommendation		
Epcoritamab					
R-CIT					

Budget impact

Table 73 Expected budget impact of recommending the pharmaceutical for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Epcoritamab is recommended					
Epcoritamab is NOT recommended					
Budget impact of the recommendation					

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 74 Main characteristic of studies included

Trial name: EPCORE NHL-1 – expansion part	**NCT number: 03625037**
Objective	To evaluate clinical efficacy of epcoritamab (as determined by Lugano criteria)
Publications – title, author, journal, year	Thieblemont C, Phillips T, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, Do YR, Feldman T, Gasiorowski R, Jurczak W, Kim TM, Lewis DJ, van der Poel M, Poon ML, Cota Stirner M, Kilavuz N, Chiu C, Chen M, Sacchi M, Elliott B, Ahmadi T, Hutchings M, Lugtenburg PJ. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol. 2022 Dec 22:JCO2201725.
Study type and design	Phase 1/2, single-arm, multicenter, open-label, dose-escalation/**dose-expansion** study. Status: ongoing.
Sample size (n)	157 patients; 139 with DLBCL – 18 subjects with other LBCL

Main inclusion and exclusion criteria	*<u>Inclusion criteria</u>* • *Documented CD20 positive mature B cell neoplasm or CD20+ MCL* • *Diffuse large B cell lymphoma, de novo or transformed (including double hit or triple hit)* • *Primary mediastinal large B cell lymphoma* • *Follicular lymphoma grade 3B* • *Histologic confirmed follicular lymphoma* • *Marginal zone lymphomas* • *Small lymphocytic lymphoma* • *Mantle Cell Lymphoma (prior BTKi or intolerant to BTKi)* • *At least 2 therapies including an anti CD20 monoclonal antibody containing chemotherapy combination regimen* • *Either failed prior autologous hematopoietic stem cell transplantation or ineligible for autologous stem cell transplantation due to age or comorbidities* • *At least 1 measurable site of disease based on CT, MRI or PET-CT scan with involvement of 2 or more clearly demarcated lesions and or nodes* *<u>Exclusion criteria</u>* • *Primary central nervous system (CNS) lymphoma or CNS involvement by lymphoma at screening* • *Known past or current malignancy other than inclusion diagnosis.* • *AST, and/or ALT >3 × upper limit of normal* • *Total bilirubin >1.5 × upper limit of normal, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin.* • *Estimated CrCl <45 mL/min.* • *Known clinically significant cardiovascular disease.* • *Ongoing active bacterial, viral, fungal, mycobacterial, parasitic, or other infection requiring systemic treatment (excluding prophylactic treatment). Past COVID-19 infection may be a risk factor.* • *Confirmed history or current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy* • *Seizure disorder requiring therapy (such as steroids or anti-epileptics)* • *Any prior therapy with an investigational bispecific antibody targeting CD3 and CD20*

Trial name: EPCORE NHL-1 – expansion part	NCT number: 03625037
	• *Prior treatment with chimeric antigen receptor T-cell (CAR-T) therapy within 30 days prior to first epcoritamab administration* • *Eligible for curative intensive salvage therapy followed by high dose chemotherapy with HSCT rescue.* • *Autologous HSCT within 100 days prior to first epcoritamab administration, or any prior allogeneic HSCT or solid organ transplantation* • *Active hepatitis B (DNA PCR-positive) or hepatitis C (RNA PCR-positive infection). Subjects with evidence of prior HBV but who are PCR-negative are permitted in* • *Known human immunodeficiency virus (HIV) infection* • *Exposed to live or live attenuated vaccine within 4 weeks prior to signing ICF* • *Pregnancy or breast feeding* • *Patient is known or suspected of not being able to comply with the study protocol or has any condition for which, participation would not be in the best interest of the patient.* • *Contraindication to all uric acid lowering agents*
Intervention	Epcoritamab (monotherapy) was supplied as a concentrate for solution for injection in 2 concentrations: 5 mg/mL and 60 mg/mL. The epcoritamab dosing regimen consisted of an initial priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg at C1D15, C1D22, and thereafter once every 4 weeks from cycle 10.. The route of administration was by SC injection.
Comparator(s)	N/A single arm study
Follow-up time	Median follow-up of 10.7 months (range 0.3, 17.9)
Is the study used in the health economic model?	Yes

Trial name: EPCORE NHL-1 – expansion part	NCT number: 03625037
Primary, secondary and exploratory endpoints	***Primary endpoint*** was overall response rate (ORR) – determined by Lugano criteria and assessed by Independent Review Committee. ***Secondary endpoints*** • DOR, CR, DOCR, PFS, TTR all determined by Lugano criteria as assessed by IRC. • ORR, CR rate, PFS, DOR, DOCR and TTR all determined by LYRIC as assessed by IRC. • Overall survival (OS). • Time to next (anti-lymphoma) therapy (TTNT). • Rate of MRD negativity. • Safety (ie, adverse events [AEs], laboratory parameters [biochemistry, hematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers], hospitalizations, and cytokine measures). • PK parameters and incidence of anti-drug antibodies (ADAs) to epcoritamab. • Changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym). ***Exploratory endpoints*** *were expression of CD3, CD20, and other molecular and genetic markers in tumor biopsies pretreatment and during treatment, and immune subpopulations in tumors and blood. Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy). Changes in well-being and general health status as evaluated by the FACT-Lym and EQ-5D-3L, respectively and through qualitative interview.*

Trial name: EPCORE NHL-1 – expansion part	NCT number: 03625037
Method of analysis	No formal hypothesis testing was performed on the aNHL expansion cohort. Analyses of trial participants and efficacy were performed using the Full Analysis Set (FAS), defined as all subjects who had been exposed to epcoritamab. Analysis of safety was performed using the Safety Analysis Set (SAF), which was identical to the FAS. Sensitivity analyses were performed using additional predefined analysis populations. ORR was defined as the proportions of patients who achieved best overall response of CR or partial response (PR). ORR was assessed as described above in the full analysis population (all patients who received at least on dose of epcoritamab). PFS defined as time from day 1 of cycle 1 to first documented disease progression or death because of any cause, whichever occurred first. DOR, PFS and OS were analysed using Kaplan-Meier estimates. Furthermore, MRD was assessed by circulating tumor DNA using the clonoSEQ MRD assay. Safety endpoints included adverse events and laboratory abnormalities. Relatedness of the AEs to the treatment was designated by the investigator. *State the method of analysis, i.e. intention-to-treat or per-protocol.* *E.g.: All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons. Hazard ratios adjusted for XX and YY were estimated with Cox proportional hazards regression. The proportional hazards assumption was assessed by looking for trends in the scaled Schoenfeld residuals.*
Subgroup analyses	*For each analysis, provide the following information:* *- characteristics of included population* *- method of analysis* *Subgroup analysis were prespecified.* *- assessment of validity, including statistical power of the analysis.*
Other relevant information	

Trial name: SCHOLAR-1	NCT number:
Objective	To evaluate responses and OS in patients with refractory NHL, including DLBCL-transformed follicular lymphoma and primary mediastinal B-cell lymphoma
Publications – title, author, journal, year	Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C. Blood. 2017
Study type and design	International, multicohort retrospective non-Hodgkin lymphoma research study, retrospectively evaluated outcomes in patients with refractory DLBCL. Data was pooled from 2 phase 3 clinical trials (LY.12 and CORAL) and 2 observational cohorts (from the MD Anderson Cancer Center [MDACC] and the Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence [IA/MC]).
Sample size (n)	636 patients with RR DLBCL.
Main inclusion and exclusion criteria	All patients from each data source who met criteria for refractory DLBCL, including TFL and PMBCL, who received subsequent therapy were considered for analysis. Refractory DLBCL (including subtypes PMBCL and TFL) was defined as progressive disease (received ≥4 cycles of first-line therapy) or stable disease (received 2 cycles of later-line therapy) as best response to chemotherapy or relapse ≤12 months after ASCT. TFL and PMBCL were included because they are histologically similar and are clinically treated as large-cell lymphoma. Patients must have received an anti-CD20 monoclonal antibody and an anthracycline as 1 of their qualifying regimens. For IA/MC, LY.12, and CORAL, patients were included at first instance of meeting refractory criteria, whereas for MDACC, patients who first met refractory criteria from second-line therapy onward were included. Patients with primary central nervous system lymphoma were excluded.
Intervention	Salvage Chemotherapy MDACC database study: Second line rituximab-containing salvage therapies included: HyperCVAD (17%), ICE (15%), DHAP (14%), ESHAP (12%), Gem-Ox (9%) and methotrexate-cytarabine (4%), other chemotherapies (14%) and therapies on clinical trials (15%) IA/MC database study: anthracycline-based immunotherapy as initial treatment LY.12 study: GDP or DHAP as second line treatment CORAL study: ICE or DHAP in addition to rituximab, mesna and G-CS
Comparator(s)	N/A

Trial name: SCHOLAR-1	NCT number:
Follow-up time	In the clinical trials, patients determined to be refractory were assessed for survival approximately every 3 months for 1 year and then every 6 months for 3 years in CORAL and at least annually for LY.12 per protocol. For the observational studies, patients were followed up for disease response and survival per institution standard procedures. Patients who were alive at the time of data extraction were censored at the date of last contact.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary endpoints: Response rates and Overall Survival **Other endpoints:** Response rate by refractory category; Primary, second-line/later-line Relapse ≤12 mo post-ASCT
Method of analysis	Patient-level data were collected for patients with refractory DLBCL from 4 sources. The extracted Patient-level data were submitted to a central database from which a pooled analysis was performed. For the randomized studies, responses were prospectively evaluated per the study schedule of assessments. For the observational cohorts, responses were determined at the time of patient treatment or management. Responses were obtained from an electronic medical record or patient medical record. Higgin's Q statistic was used to assess the heterogeneity of response rate between the source databases. Covariates for response were evaluated with a Cochran-Mantel-Haenszel test stratified by institution. Survival was estimated, and covariates were assessed by a Cox proportional hazards model stratified by data source.
Subgroup analyses	*For each analysis, provide the following information:* *- characteristics of included population* *- method of analysis* *Subgroup analysis were prespecified.* *- assessment of validity, including statistical power of the analysis.*
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 75 Results per study

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Referenc es
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS (months)	Epcoritamab	139	NR (11.3-NR)	N/A	N/A	N/A	N/A	N/A	N/A	OS was defined as the time from C1D1 to death from any cause. If a subject was not known to have died, then OS was censored at the latest date the subject was known to be alive.	
ORR	Epcoritamab	139	61.9% (53.3%-70.0%)	N/A	N/A	N/A	N/A	N/A	N/A	IRC-assessed ORR determined by Lugano criteria in the FAS.	
PFS	Epcoritamab	139	4.4 (3.0-8.2)	N/A	N/A	N/A	N/A	N/A	N/A	PFS was defined as the time from C1D1 to date of PD or death due to any cause, whichever occurred earlier. Date of	

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
										PD was defined as the earliest date of documented progression after which there was no more PR or CR assessment. PFS was derived for all subjects. Clinical progression without documented radiographical progression per Lugano or LYRIC was not considered progression for determination of PFS.
CR	Epcoritamab	139	38.8% (30.7%-47.5%)	N/A	N/A	N/A	N/A	N/A	N/A	CR was defined as the proportion of subjects with BOR of CR
Median DOR (months)	Epcoritamab	139	12.0(6.6 - NR)	N/A	N/A	N/A	N/A	N/A	N/A	DOR was defined as the time from the first documentation of response (CR or PR) to the date of PD or death among all responders. Main analysis for DOR was based on disease assessment per IRC by

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
										Lugano or LYRIC in the FAS.
Median TTNT (months)	Epcoritamab	139	8.2 (6.0-13.9)	N/A	N/A	N/A	N/A	N/A	N/A	TTNT was defined as the time from C1D1 to first recorded administration of subsequent anti-lymphoma therapy with curative intent or death, whichever occurred earlier. The expection is censoring subject without disease progression while receiving subsequent stem cell transplant after responding to epcoritamab to be consistent with the intent to measure duration of clinical benefit using TTNT.
Proportion of subjects with at	Epcoritamab	139	138 (99.3%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
least one TEAE										
Proportion of subjects with at least one TEAE related to epcoritamab	Epcoritamab	139	115 (82.7%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one Grade 3 or higher TEAE	Epcoritamab	139	86 (61.9%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one Grade 3 or higher TEAE related to epcoritamab	Epcoritamab	139	38 (27.3%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
Proportion of subjects with at least one SAE	Epcoritamab	139	80 (57.6%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one SAE related to epcoritamab	Epcoritamab	139	49 (35.3%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one Grade 3 or higher SAE	Epcoritamab	139	38 (27.3%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with CRS	Epcoritamab	139	68 (48.9%)	N/A	N/A	N/A	N/A	N/A	N/A	CRS were graded according to the ASTCT criteria
Proportion of subjects	Epcoritamab	139	4 (2.9%)	N/A	N/A	N/A	N/A	N/A	N/A	CRS were graded according to the ASTCT criteria

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
with CRS grade 3+										
Proportion of subjects with ICANS	Epcoritamab	139	9 (6.5%)	N/A	N/A	N/A	N/A	N/A	N/A	ICANS Overall, the ICANS grade was determined by the most severe event of the neurotoxicity domains (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause.
Proportions of subjects with CTLS	Epcoritamab	139	2 (1.4%)	N/A	N/A	N/A	N/A	N/A	N/A	CTLS were graded according to Cairo-Bishop
Proportion of subjects discontinued due to AEs	Epcoritamab	139	11/139 (7.9%)	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
			[redacted]							

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS (months)	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	OS was defined as the time from C1D1 to death from any cause. If a subject was not known to have died, then OS was censored at the latest date the subject was known to be alive.	
ORR	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	IRC-assessed ORR determined by Lugano criteria in the FAS.	
PFS	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	PFS was defined as the time from C1D1 to date of PD or death due to any cause, whichever occurred earlier. Date of PD was defined as the earliest date of documented progression after which there was no more PR or CR assessment. PFS was	

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
										derived for all subjects. Clinical progression without documented radiographical progression per Lugano or LYRIC was not considered progression for determination of PFS.
CR	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	CR was defined as the proportion of subjects with BOR of CR
Median DOR (months)	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	DOR was defined as the time from the first documentation of response (CR or PR) to the date of PD or death among all responders. Main analysis for DOR was based on disease assessment per IRC by Lugano or LYRIC in the FAS.

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
Median TTNT (months)	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	TTNT was defined as the time from C1D1 to first recorded administration of subsequent anti-lymphoma therapy with curative intent or death, whichever occurred earlier. The expection is censoring subject without disease progression while receiving subsequent stem cell transplant after responding to epcoritamab to be consistent with the intent to measure duration of clinical benefit using TTNT.
Proportion of subjects with at least one TEAE	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
Proportion of subjects with at least one TEAE related to epcoritamab	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one Grade 3 or higher TEAE	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one SAE	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0
Proportion of subjects with at least one SAE related to	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
epcoritamab										
Proportion of subjects with CRS	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	CRS were graded according to the ASTCT criteria
Proportion of subjects with CRS grade 3+	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	CRS were graded according to the ASTCT criteria
Proportion of subjects with ICANS	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	ICANS Overall, the ICANS grade was determined by the most severe event of the neurotoxicity domains (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause.
Proportions of subjects with CTLS	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	CTLS were graded according to Cairo-Bishop

Results of EPCORE-NHL-1 (NCT03625037) – Jan datacut										
Proportion of subjects discontinued due to AEs	Epcoritamab	139	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	All AEs were graded by investigators according to NCI-CTCAE v5.0

Table 76 Results per study

Results of SCHOLAR-1											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS (months)	N/A	523	6.3 (5.9-7.0)	N/A	N/A	N/A	N/A	N/A	N/A	N/A.	
ORR	N/A	523	26% (21%-31%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

Appendix C. Comparative analysis of efficacy

[redacted]

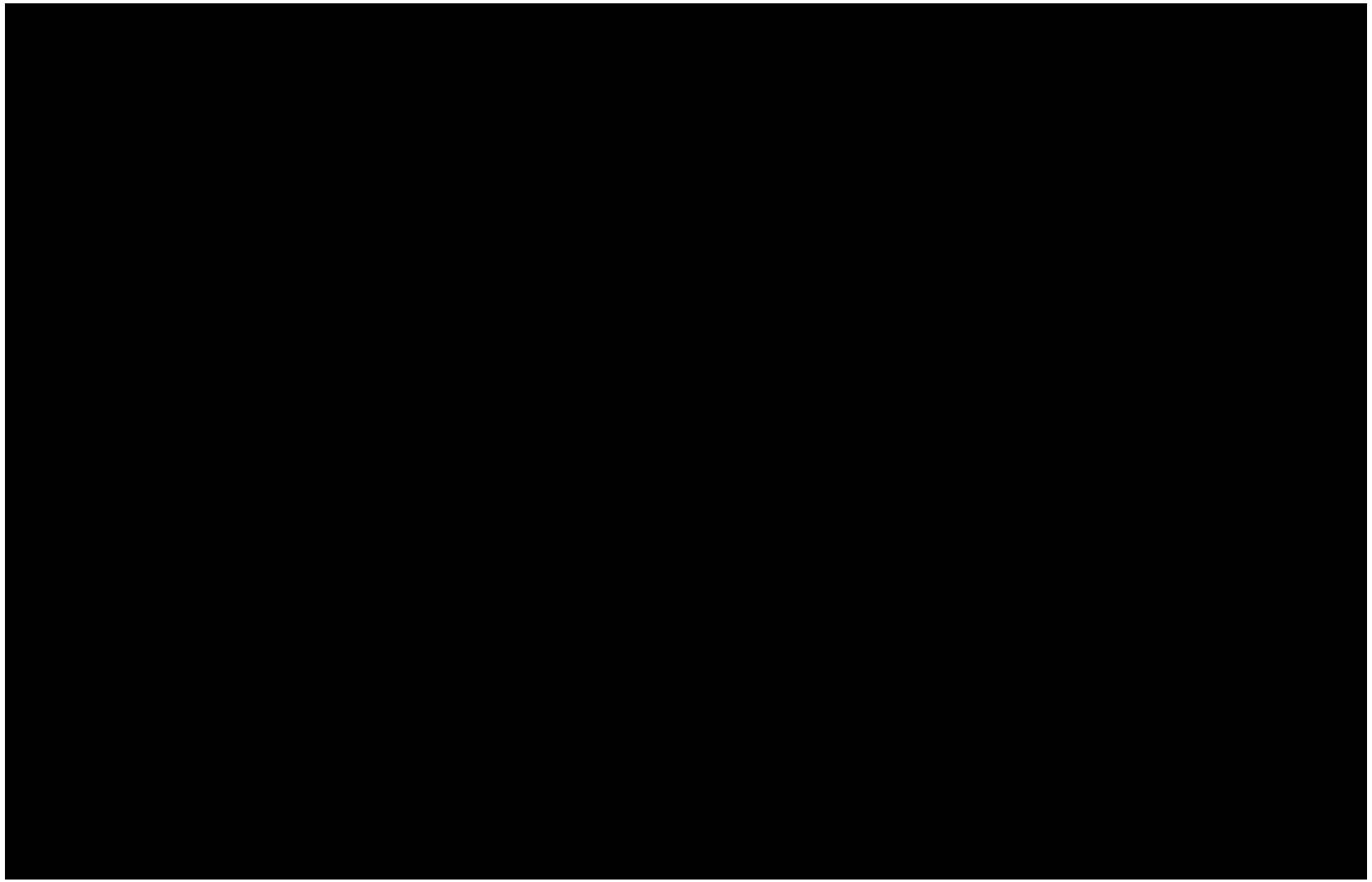
Epcoritamab vs SCHOLAR-1 CIT

		Unadjusted Epcoritamab [redacted]	Adjusted Epcoritamab [redacted]
Survival, HR [95% CI]			
	Overall survival (OS)	[redacted]	[redacted]
	Progression-free survival (PFS)	Na	**Na**
Response rates, %			

Complete response (CR)	[redacted]	[redacted]
Difference, % [95% CI]	[redacted]	[redacted]
Overall response (OR)	[redacted]	[redacted]
Difference, % [95% CI]	[redacted]	[redacted]

Abbreviations:; CI, confidence interval; CIT, chemoimmunotherapy; HR, hazard ratio; na, not applicable; N_{eff}, effective sample size;

[redacted]



Appendix D. Extrapolation

Based on DMC recommendation on extrapolation of time-to-event data the following criteria was tested/conducted to document adequate adaption of the study's observed data.

- Assessment of the plausibility of PH based statistical test and graphical presentations (log-cumulative hazard plot and Schoenfeld-risiduals)
- Log-cumulative hazard plot of the different parametric functions
- Test of Akaike's information criteria (AIC) and Bayesian information Criteria (BIC)
- Clinical and biological validity based on external data and clinical inputs

D.1 Extrapolation of OS

D.1.1 Data input

[redacted]

[redacted]

[redacted]

D.1.2 Model

[redacted]

D.1.3 Proportional hazards

[redacted]

Test of parametric distributions

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

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

D.1.5 Evaluation of visual fit

[redacted]

[redacted]

D.1.6 Evaluation of hazard functions

[redacted]

[redacted]

D.1.7 Validation and discussion of extrapolated curves

[redacted]

[redacted]

[redacted]

[redacted]

D.1.8 Adjustment of background mortality

[redacted]

D.2 Extrapolation of PFS

D.2.1 Data input

[redacted]

D.2.2 Evaluation of statistical fit (AIC and BIC)

Distribution	AIC	BIC
Log-normal		
Generalized gamma		
Log-logistic		
Gompertz		
Weibull		

Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

D.2.3 Evaluation of visual fit

[redacted]

[redacted]

D.2.4 Evaluation of hazard functions

[redacted]

only the log-normal (best fitting curve in terms of BIC), generalized gamma (best fitting curve in terms of AIC), and log-logistic distributions follow the observed smoothed hazard relatively well.

[redacted]

[redacted]

D.2.5 Validation and discussion of extrapolated curves

[redacted]

[redacted]

D.2.6 Adjustment of background mortality

[redacted]

D.3 Extrapolation of TTD

D.3.1 Data input

[redacted]

[redacted]

[redacted]

D.3.2 Evaluation of statistical fit (AIC and BIC)

[redacted]

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

Generalized gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

D.3.3 Evaluation of visual fit

[redacted]

[redacted]

D.3.4 Evaluation of hazard functions

[redacted]

[redacted]

[redacted]

[redacted]

D.3.5 Validation and discussion of extrapolated curves

[redacted]

D.3.6 Adjustment of background mortality

Appendix E. Serious adverse events

E.1 EPCORE-NHL-1 LBCL (Jan datacut 2022)

All serious adverse events from the January data cut are based on full analysis set divided in all and those related to treatment.

Table 77 Most common (2% or higher in any group) Serious TEAEs, Jan Data cut

System Organ Class/Preferred Term	DLBCL (N=139)		Other Subtypes[a] (N=18)		LBCL (N=157)	
	All	Related	All	Related	All	Related
Subjects with ≥1 serious TEAE	**80 (57.6%)**	**49 (35.3%)**	**9 (50.0%)**	**6 (33.3%)**	**89 (56.7%)**	**55 (35.0%)**
Immune system disorders	**40 (28.8%)**	**40 (28.8%)**	**6 (33.3%)**	**6 (33.3%)**	**46 (29.3%)**	**46 (29.3%)**
Cytokine release syndrome	40 (28.8%)	40 (28.8%)	6 (33.3%)	6 (33.3%)	46 (29.3%)	46 (29.3%)
Infections and infestations	**22 (15.8%)**	**2 (1.4%)**	**3 (16.7%)**	**0**	**25 (15.9%)**	**2 (1.3%)**
Sepsis	4 (2.9%)	1 (0.7%)	0	0	4 (2.5%)	1 (0.6%)
COVID-19	3 (2.2%)	0	0	0	3 (1.9%)	0
Pneumonia	3 (2.2%)	0	0	0	3 (1.9%)	0
Nervous system disorders	**11 (7.9%)**	**5 (3.6%)**	**0**	**0**	**11 (7.0%)**	**5 (3.2%)**
Immune effector cell-associated neurotoxicity syndrome	4 (2.9%)	4 (2.9%)	0	0	4 (2.5%)	4 (2.5%)
Respiratory, thoracic and mediastinal disorders	**8 (5.8%)**	**1 (0.7%)**	**2 (11.1%)**	**0**	**10 (6.4%)**	**1 (0.6%)**
Pleural effusion	5 (3.6%)	1 (0.7%)	2 (11.1%)	0	7 (4.5%)	1 (0.6%)

Blood and lymphatic system disorders	**8 (5.8%)**	**3 (2.2%)**	**0**	**0**	**8 (5.1%)**	**3 (1.9%)**
Febrile neutropenia	4 (2.9%)	1 (0.7%)	0	0	4 (2.5%)	1 (0.6%)
General disorders and administration site conditions	**7 (5.0%)**	**1 (0.7%)**	**0**	**0**	**7 (4.5%)**	**1 (0.6%)**
Pyrexia	4 (2.9%)	0	0	0	4 (2.5%)	0

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; LBCL = large Bcell lymphoma; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: Adverse events are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per SOC and only once per PT.
[a] Other includes 9 subjects with high-grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
Data cutoff date: 31 Jan 2022

E.2 EPCORE-NHL-1 DLBCL ([redacted])

[redacted]

[redacted]

Event, No. (%)	All N = 139 (%)	Related N = 139 (%)
Subjects with at least one Most Common (at least 2%) Serious TEAE	[redacted]	[redacted]
CRS	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Immune effector cell-associated neurotoxicity syndrome	[redacted]	[redacted]

Febrile neutropenia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

[redacted]

Table 78 Summary of AESI: Cytokine Release Syndrome

Summary of AESI: Cytokine Release Syndrome (CRS)	DLBCL (N=139)
Subjects with at least one CRS event	[redacted]
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	[redacted]
Leading to treatment discontinuation	[redacted]
Time to first CRS onset median, (days)	[redacted]
Time to CRS resolution, median, (days)	[redacted]
Subjects with CRS resolution	[redacted]

Appendix F. Health-related quality of life

[If specific domains from the assessment instrument need to be highlighted, data should be presented here. Argue for the relevance of the domain-specific data.]

NA

Appendix G. Probabilistic sensitivity analyses

Probabilistic sensitivity analysis has been conducted using 5,000 iterations and is presented in the model spreadsheet "PSA". All the model parameters that were varied in PSA and their associated distributions are presented in the model, on sheet "Inputs" and in Table 79 below. Point estimates and lower/upper bounds are presented. Whenever available, the standard error of the model input was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a parameter, the standard error for each parameter was assumed to be equal to the mean value divided by four. For survival estimates, uncertainty has been captured in the variance-covariance matrix of the parameter estimates and applied through Cholesky decomposition. Also, time horizon, cycle length, discount rates etc. are considered structural assumptions, and are fixed setting, and, as such, are not included in the PSA.

The choice of probability distribution follows standard practice. Resource use, costs, disutility and duration of treatment are following gamma distribution. Gamma distribution is used for non-negative parameters, having continuous probability distributions. Gamma distribution is therefore used for cost parameters. Age, bodyweight, BSA and HR to adjust BGM for long term remission are following normal distribution. A normal distribution is a type of continuous probability distribution in which most data points cluster toward the middle of the range, while the rest taper off symmetrically toward either extreme. Normal distribution is therefore used for parameters where you usually have a mean value in the middle. Gender, resource use parameters, and adverse events are following Beta distribution. The beta distribution is appropriate for describing the distribution of a probability or proportion. Beta distribution is therefore used for incidence rates and number of visits per resource use parameter.

Parameters on survival distributions have been excluded from the PSA due to standard practice and the tests already performed in the DSA.

Table 79. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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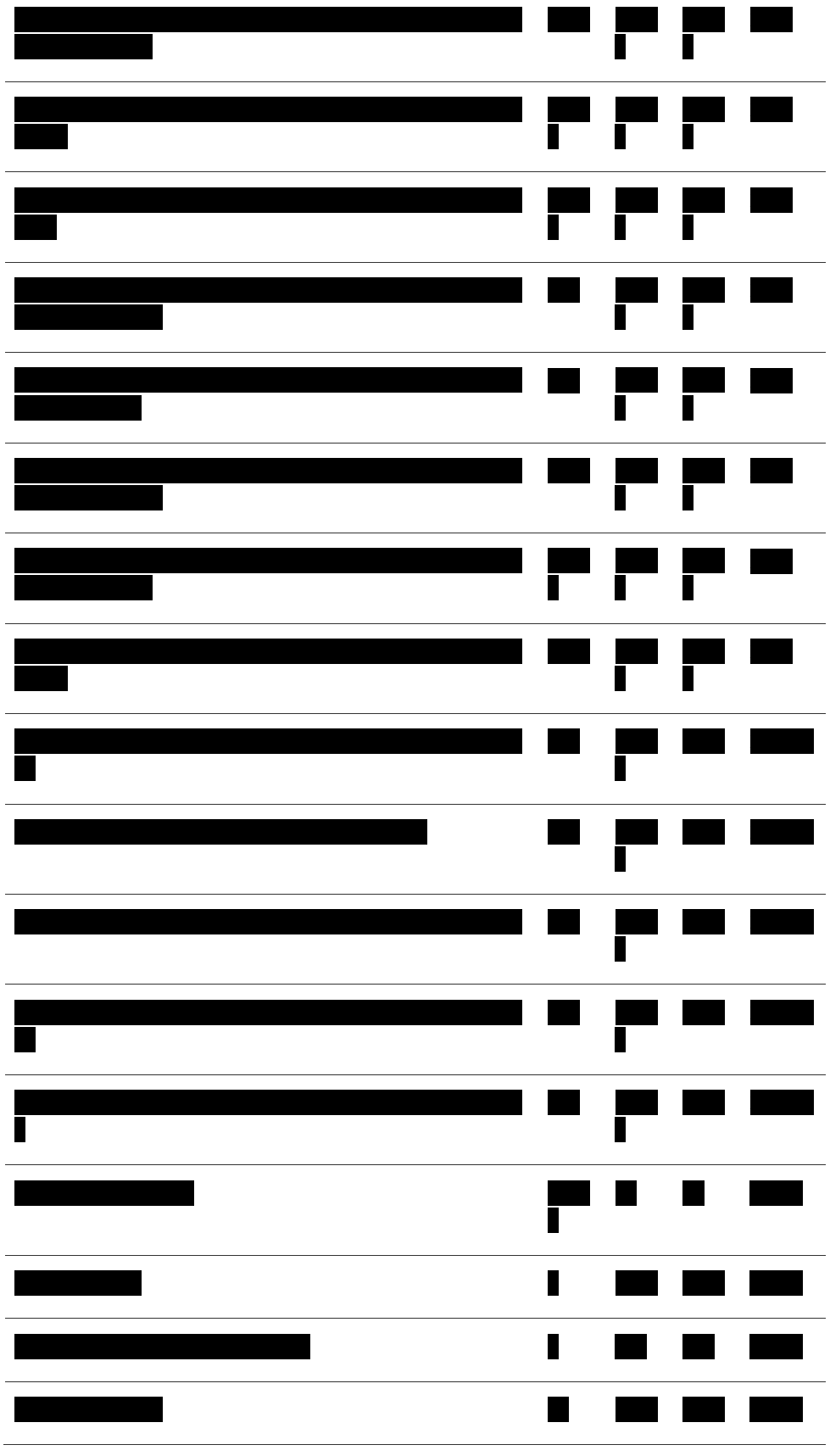
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

Appendix H. Literature searches for the clinical assessment

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

Table 80 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Medline	Pubmed	No limit	13.06.2024
CENTRAL	Cochrane Library	No limit	13.06.2024

H.1.1 Search strategies

Table 81 of search strategy table for CENTRAL (Via Cochrane Library) 13.06.2024

#ID	Search terms	Hits	Comments
1	("diffuse large B cell lymphoma" OR DLBCL OR "large B cell diffuse lymphoma" OR "diffuse large cell lymphoma" OR "large b cell lymphoma"):ti,ab	1930	Search criteria for population
2	("no response" OR refractor* OR relaps* OR "refractory/relapse" OR "relapse/refractory"):ti,ab	64412	
3	#1 AND #2	943	
4	(epcoritamab OR gen3013 OR "DuoBody-CD3xCD20" OR "DuoBodyCD3xCD20" OR Epco):ti,ab,kw	57	Search criteria for intervention and comparator
5	(R-DHAP OR RDHAP OR R-GDP OR GDP-R OR RGDP OR R-GemOX OR RGemOX OR R-ICE OR RICE OR ICE-R OR R-DHAOX OR RDHAOX):ti,ab,kw	2956	
6	(salvage chemotherapy OR "systemic chemotherapy" OR chemotherap* OR "systemic chemotherapeutics" OR "salvage treatment" OR "chemoimmunotherapy" OR "salvage therapy"):ti,ab,kw	98322	
7	#4 OR #5 OR #6	101160	

8	#3 AND #7	554	Search terms for exclusion of publications
9	(clinicaltrials.gov or trialsearch):so	506654	
10	(NCT*):au	259695	
11	(animal* OR murine OR mouse OR mice OR rat OR rats OR rodent):ti,ab	28235	
12	"conference proceeding":pt	244130	
13	#9 OR #10 OR #11 OR #12	768602	
14	(Journal article OR Trial registry record):pt	2138272	
15	#8 AND #14 NOT #13	149	
16	#15 NOT "PubMed":an	15	Final search

Feltkoder: ti = title, ab = abstract, kw = keywords, pt = publication type, so = source, an = accession number.

H.1.2 Search strategies

Table 82 of search strategy table for Medline (Via Pubmed) 13.06.2024

#	Searchterms	Hits	Comments
1	diffuse large B cell lymphoma[tiab] OR DLBCL[tiab] OR "large B cell diffuse lymphoma"[tiab] OR "diffuse large cell lymphoma"[tiab] OR "large B cell lymphoma"[tiab]	22280	Search criteria for population
2	"no response"[tiab] OR refractor*[tiab] OR relaps*[tiab] OR refractory/relapse[tiab] OR relapse/refractory[tiab]	391295	
3	#1 AND #2	4328	
4	epcoritamab OR gen3013 OR "DuoBody-CD3xCD20" OR "DuoBodyCD3xCD20" OR Epco	128	Search criteria for intervention and comparator
5	R-DHAP OR RDHAP OR R-GDP OR GDP-R OR RGDP OR R-GemOX OR RGemOX OR R-ICE OR RICE OR ICE-R OR R-DHAOX OR RDHAOX	121359	
6	Rituximab AND (dexamethasone OR cisplatin OR cytarabine OR gemcitabine OR oxaliplatin OR ifosfamide OR carboplatin OR etoposide)	1959	

7	salvage therapy [MeSH] OR "salvage chemotherapy" OR "systemic chemotherapy" OR "chemotherap*" OR "systemic chemotherapeutics" OR "salvage treatment" OR ((system* OR salvage) N/5 (treat* OR treatment* OR chemotherap* OR chemotherapeutics OR therap*)) OR "chemoimmunotherapy"	646056	
8	#4 OR #5 OR #6 OR #7	767162	
9	#3 AND #8	2472	
10	randomized controlled trial [pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial [ti] OR "Randomized Controlled Trials as Topic"[Mesh] OR “Observational Study” [pt] OR “Observational Studies as Topic” [Mesh] OR observation* [tiab]	2738170	Filter for Identification of RCTs and observational studies
11	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	7668155	Search terms for exclusion of publications
12	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	1695199	
13	#11 OR #12	9303179	
14	#9 AND #10 NOT #13	265	Final search

Feltkoder: Mesh = MeSH Term, tiab = title/abstract, incl. writerkeywords pt = publication type

Systematic selection of studies

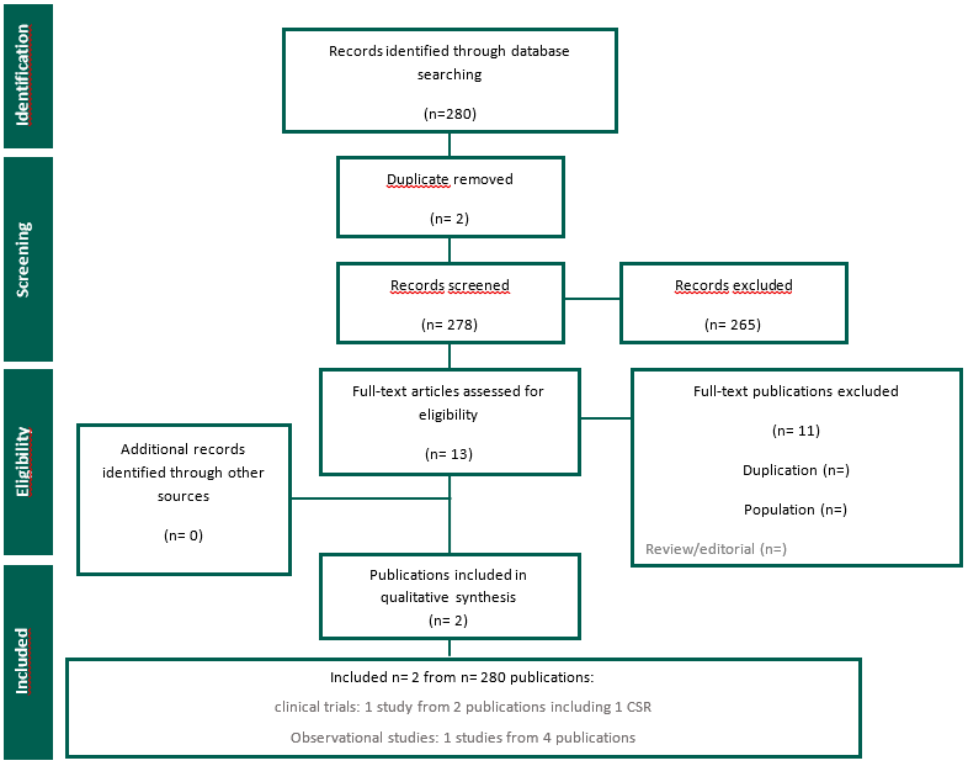
Inclusion and exclusion criteria were selected based on the clinical question to assess. Two reviewers were included in the search strategy and selection process.

Table 83 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult (> 18 years) patients with refractory or relapsed DLBCL treated with at least 2 lines of systematic therapy	• Studies with patients that had no or only 1 prior treatment • Patients < 18 years • Animal studies
Intervention	Epcoritamab	

Comparators	R-chemotherapy (GDP, DHAP, GemOX, DHAOX, ICE)	Other comparators
Outcomes	OS, PFS FACT-Lym, AE	
Study design/publication type	RCT, observational studies, single or multiple arm studies	
Language restrictions	English	

Figure 18 PRISMA flow for literature search of clinical assessment



H.1.3 Ful text articles assessed for eligibility

Excluded		
Titel	Author, journal, year	Reason
Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A	Mounier N, Gnaoui TE, Tilly H, Canioni D, Sebban C, Casasnovas RO, et al.	Wrong population.

phase II Lymphoma Study Association trial.	Haematologica. 2013;98:1726–31.	
Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study.	Hagberg H, Gisselbrecht C. Ann Oncol. 2006;17 Suppl 4:iv31-2.	Symposium article. Wrong population.
Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study.	Neste EVD, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Bone Marrow Transplant. 2016;51:51–7.	Patients in EPCORE-NHL-1 had a high number of refractoriness, which is an important prognostic factor/effect modifier, therefor an important factor to adjust for, in which was not stated in the CORAL extended studies
Efficacy, Prognosis and Safety of Rituximab Combined with GDP Regime for Patients with Relapsed Diffuse Large B-cell Lymphoma.	Muhebaier, Aziguli A, Liu ;, Guzailinuer H, Mao ;, M. Anti-tumor pharmacy, 2018, 8(6), 0897-902.	Foreign language (Chinese).
Efficacy of rituximab combined with CHOP for treating patients with diffuse large B-cell lymphoma.	Hu, Zeng X, Yang M, Liang SE, Ding X, Guo SS, et al. Medicine (united states), 2017, 96(45)	Wrong population (untreated adults)
Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study.	Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, et al. Lancet. 2021;398:1157–69	Publication for the dose-escalation phase of epcoritamab. The Dose-expansion part were used for assessment
R-ICE Versus R-DHAP in Relapsed Patients with CD20 Diffuse Large B-Cell Lymphoma (DLBCL) Followed by Stem Cell Transplantation and Maintenance Treatment with Rituximab or Not: First Interim Analysis on 200 Patients. CORAL Study.	Gisselbrecht C, Schmitz N, Mounier N, Ma D, Trneny M, Hagberg H, et al. Blood. 2007;110(11):517.	Conference Abstract.

R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplatation: CORAL study.	Gisselbrecht C, Glass B, Mounier N, Gill D, Linch D, Trneny M, et al. Journal of clinical oncology. 2009;27:436.	Meeting Abstract.
Treatment Outcomes with Standard of Care in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Real-World Data Analysis.	Ip A, Mutebi A, Wang T, Jun M, Kalsekar A, Navarro FR, et al. Adv Ther. 2024;41:1226–44.	Wrong intervention.
Survival Outcomes for Patients with Relapsed/ Refractory Aggressive B Cell Lymphomas Following Receipt of High-Dose Chemotherapy/Autologous Stem Transplantation and/or Chimeric Antigen Receptor-Modified T Cells	Landsburg DJ, Nasta SD, Svoboda J, Gerson JN, Schuster SJ, Barta SK, et al. Transplant Cell Ther. 2023;29:495–503.	Wrong intervention.
Comparative study of R-GemOx and RICE regimens as second-line treatments for refractory or relapsed DLBCL.	Zhang H, Wang H, Fu K, Hou Y, Li W, Zhou S, et al. Chinese journal of clinical oncology. 2011;38:1107-1110.	Foreign language (Chinese)

Included	
Titel	Author, journal, year
Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study.	Crump M, Neelapu SS, Farooq U, Neste EVD, Kuruvilla J, Westin J, et al. Blood. 2017;130:1800–8.
Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial.	Thieblemont C, Phillips T, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, et al. J Clin Oncol. 2023;41:2238–47.

Table 84 Overview of study design for studies included in the technology assessment

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
EPCORE NHL-1; GCT3013-01 Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial.	*To evaluate clinical efficacy of epcoritamab (as determined by Lugano criteria)*	*Phase 1/2, single-arm, multicenter, open-label, dose-escalation/* ***dose-expansion*** *study.* *Status: ongoing*	*157 patients; 139 with DLBCL – 18 subjects with other LBCL*	Epcoritamab (157)	***Primary endpoint*** *was overall response rate (ORR) – determined by Lugano criteria and assessed by Independent Review Committee* [redacted]	***Secondary endpoints*** • DOR [redacted], CR, DOCR [redacted] PFS [redacted] TTR all determined by Lugano criteria as assessed by IRC. • ORR, CR rate, PFS, DOR DOCR and TTR all determined by

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
						LYRIC as assessed by IRC. • Overall survival (OS). [redacted] • Time to next (anti-lymphoma) therapy (TTNT). [redacted] • Rate of MRD negativity. [redacted] • Safety (ie, adverse events [AEs], labora

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
						tory parameters [biochemistry, hematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers], hospitalizations, and cytokine measures). • PK parameters and incidence of anti-drug antibodies (ADAs) to epcori

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
						tamab. • Changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym).
SCHOLAR-1	Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR1 study	Data collection from 4 studies	DLBCL	635	OS	NA

H.1.4 Quality assessment

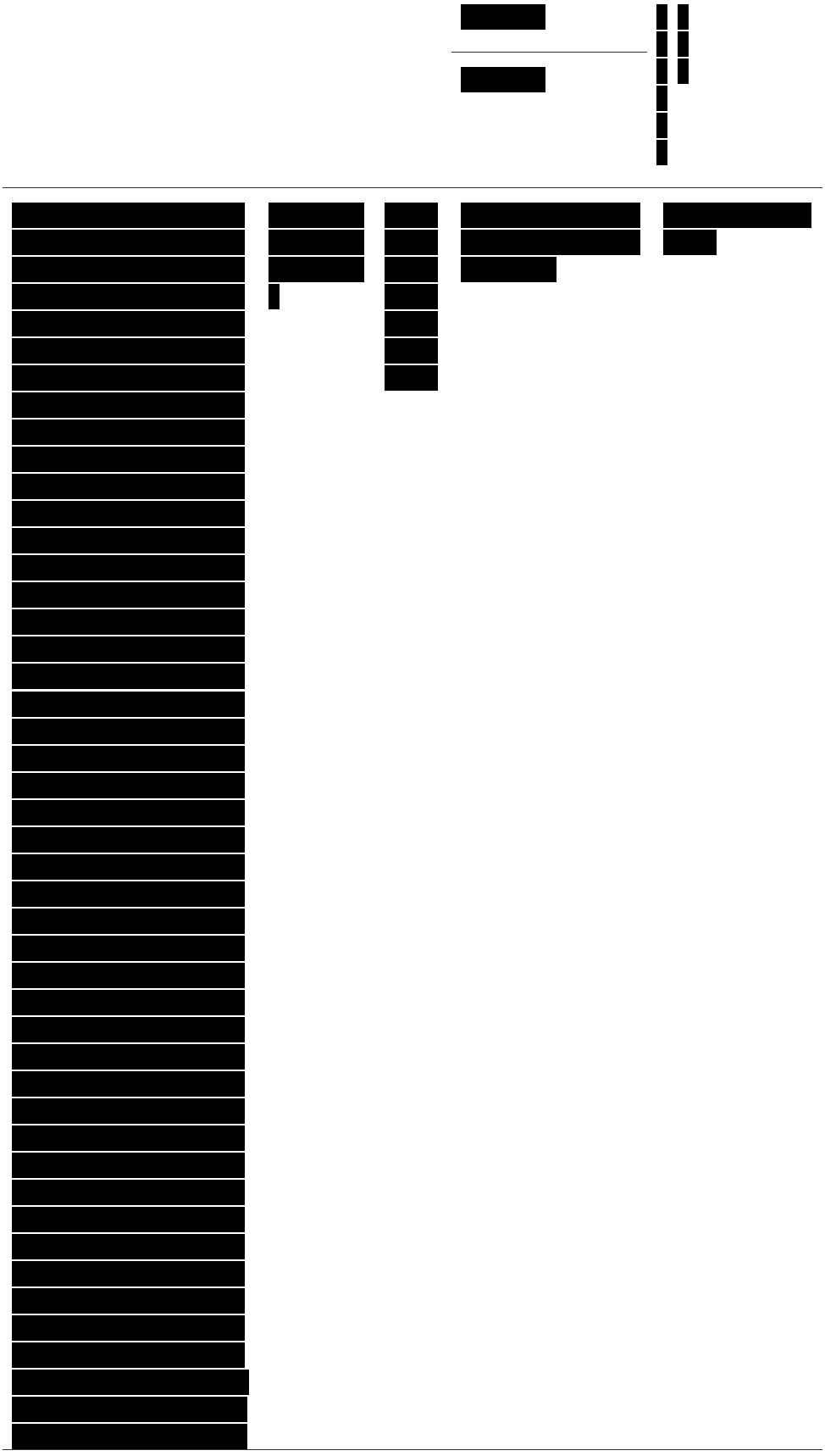
NA

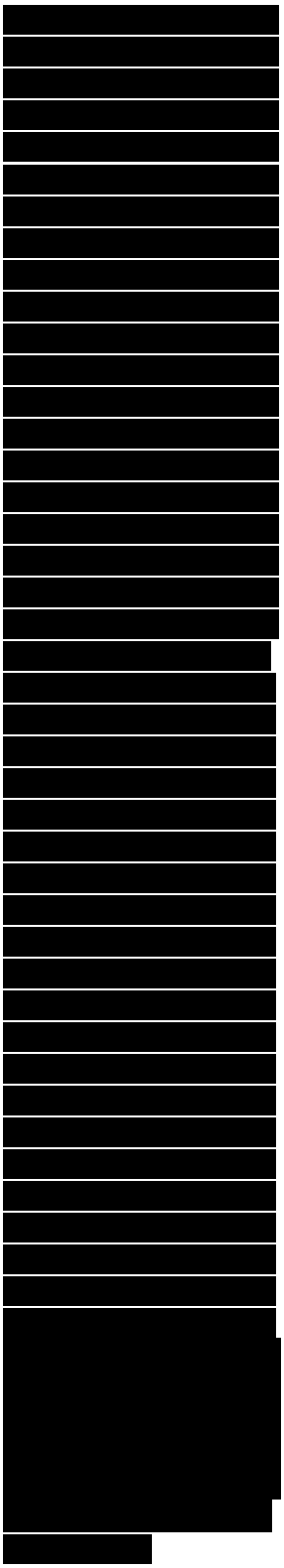
H.1.5 Unpublished data

Unpublished data was included on a later data cut ([redacted]) on initial publication (Jan 2022) for the phase I/II trial of epcoritamab for R/R DLBCL who receive ≥2 prior lines of systematic treatment.

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

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





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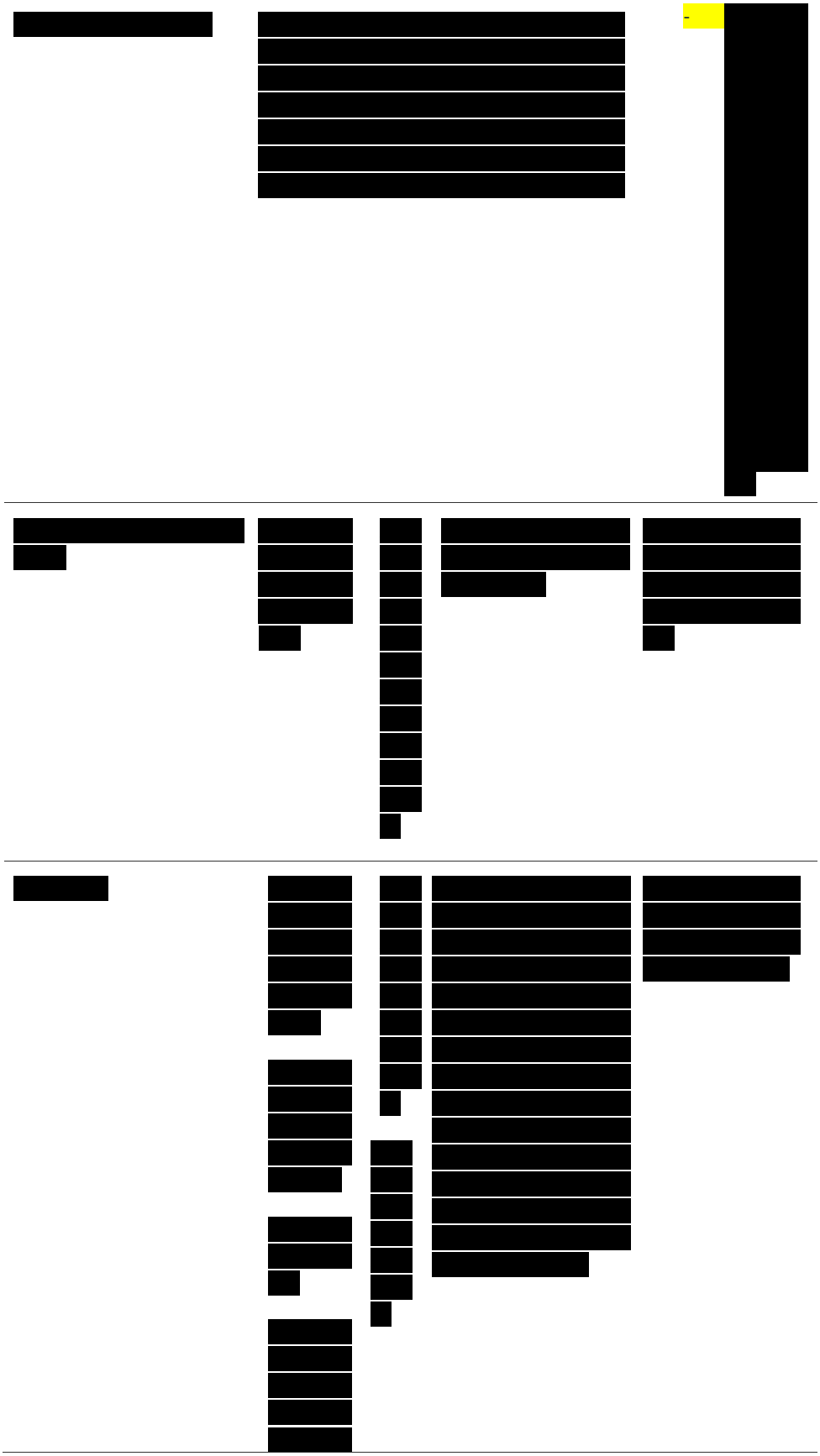

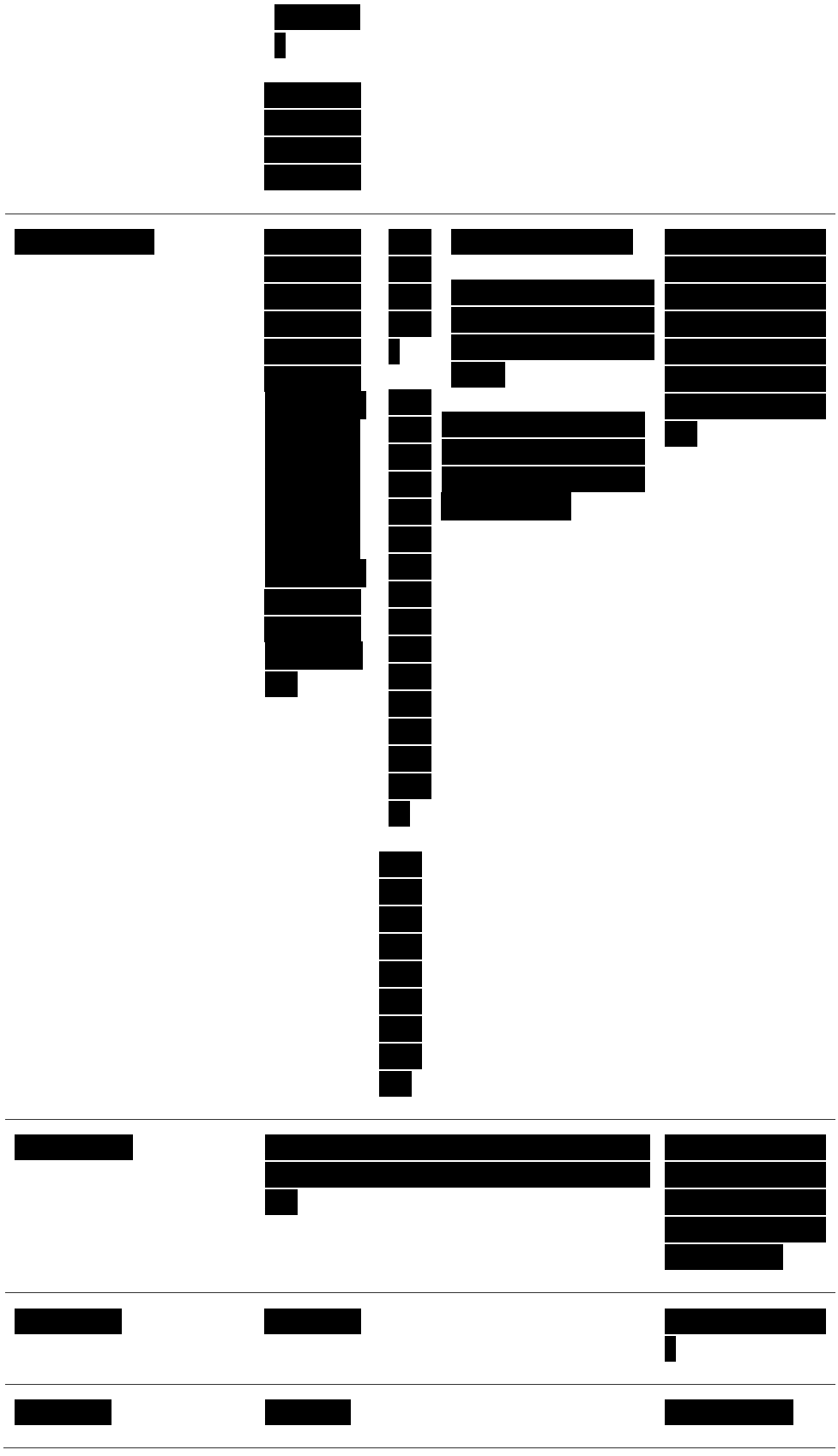

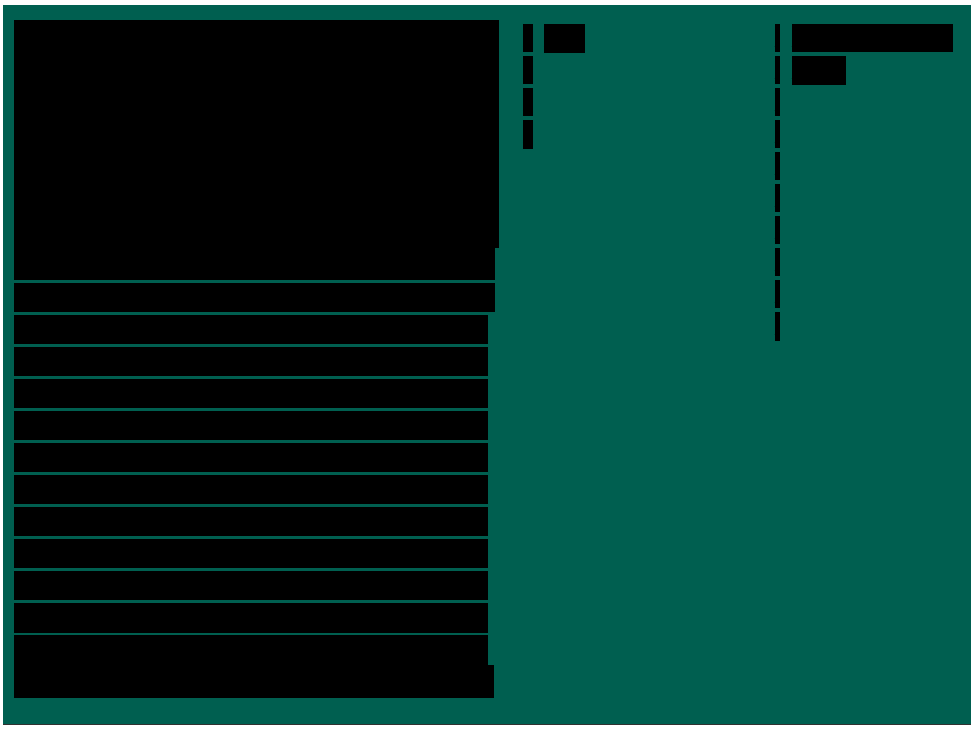

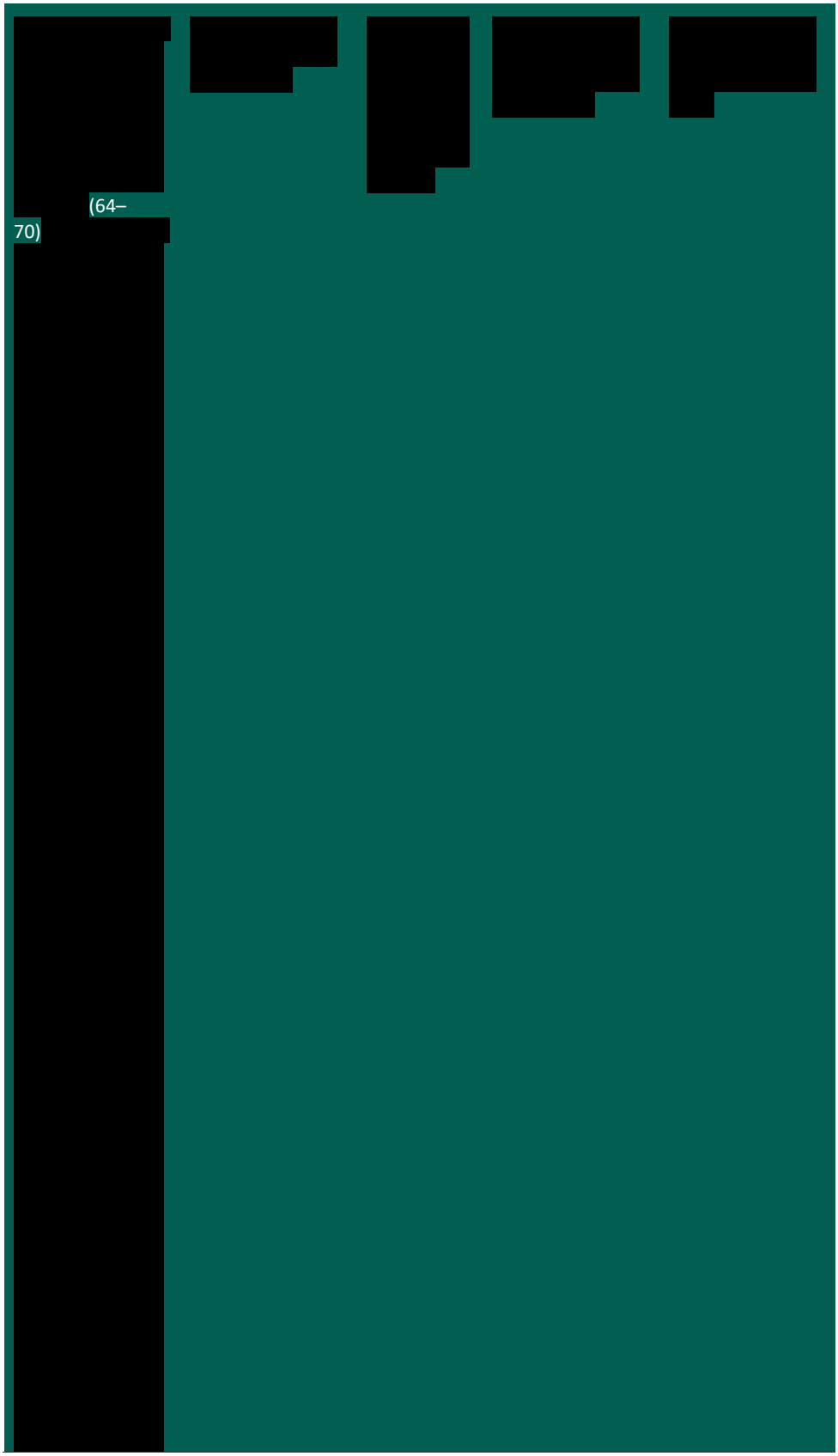

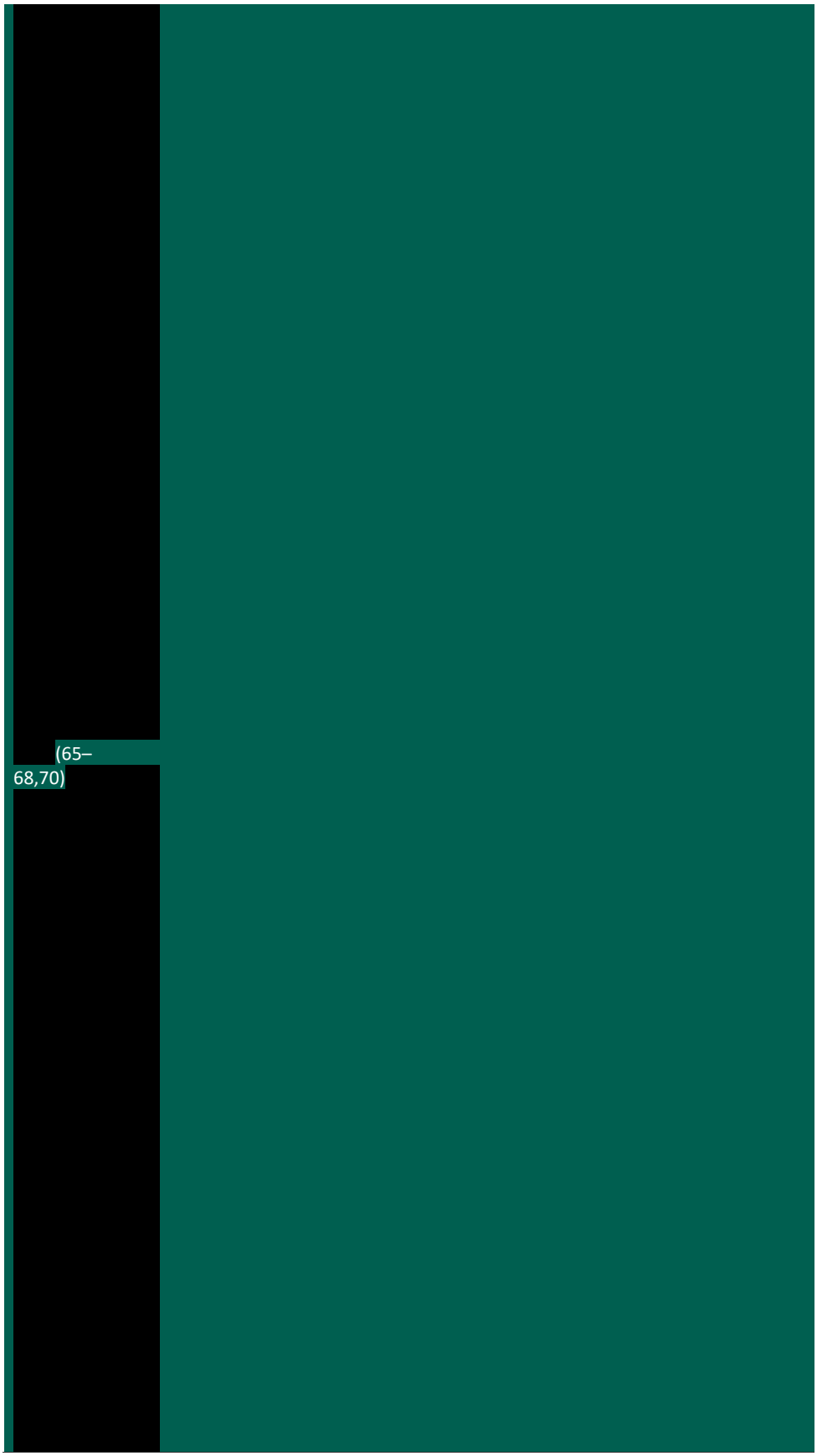

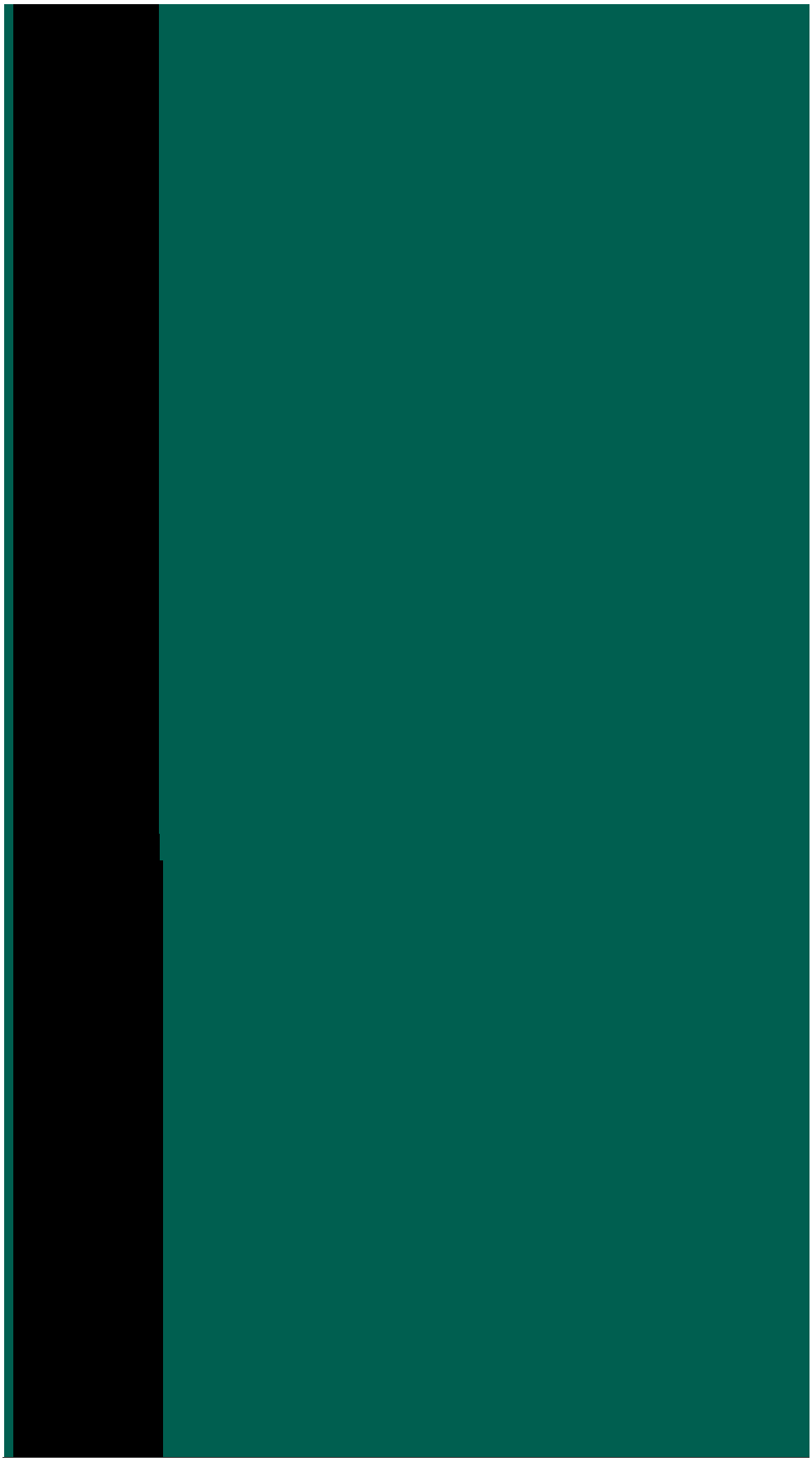

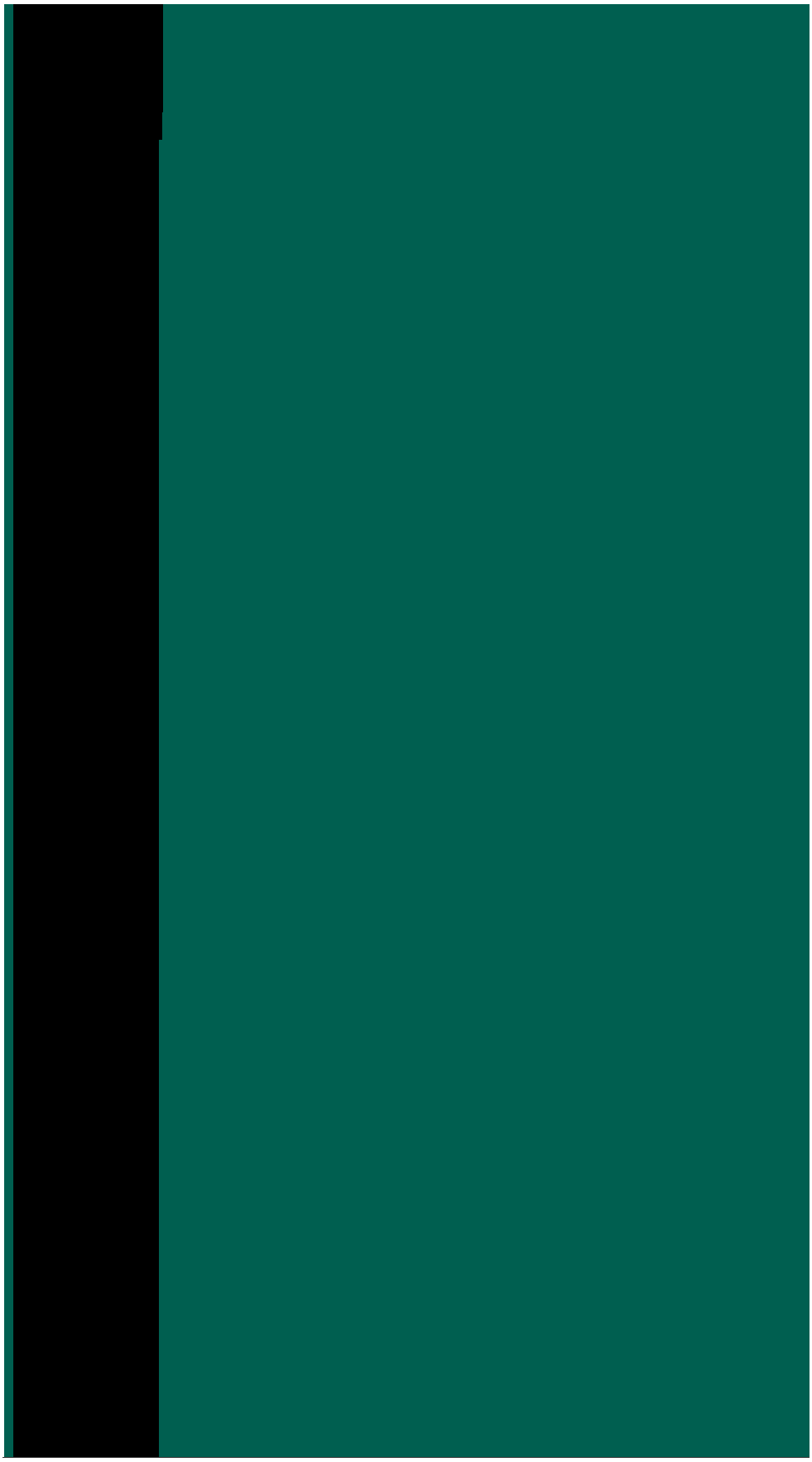

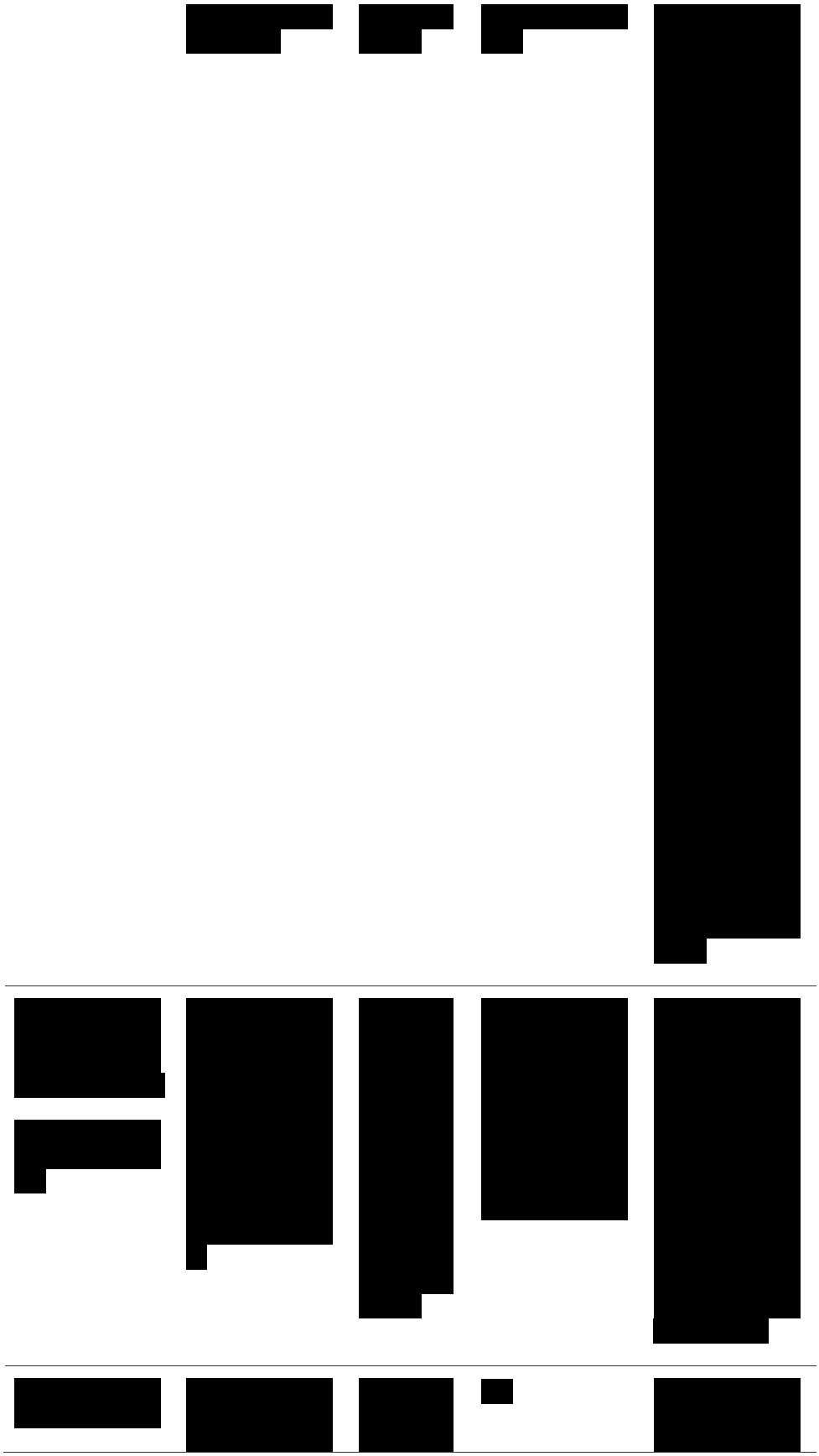

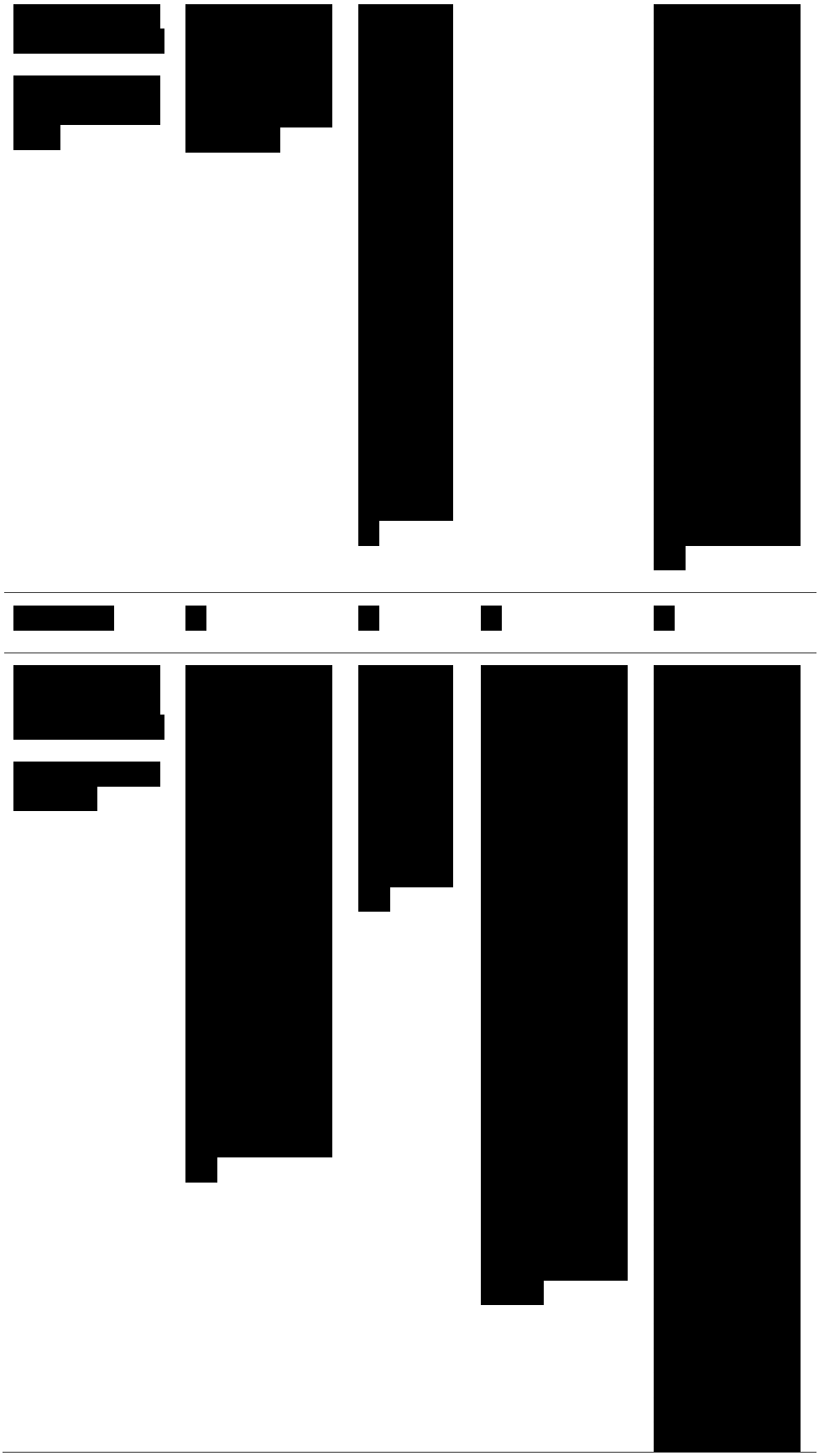

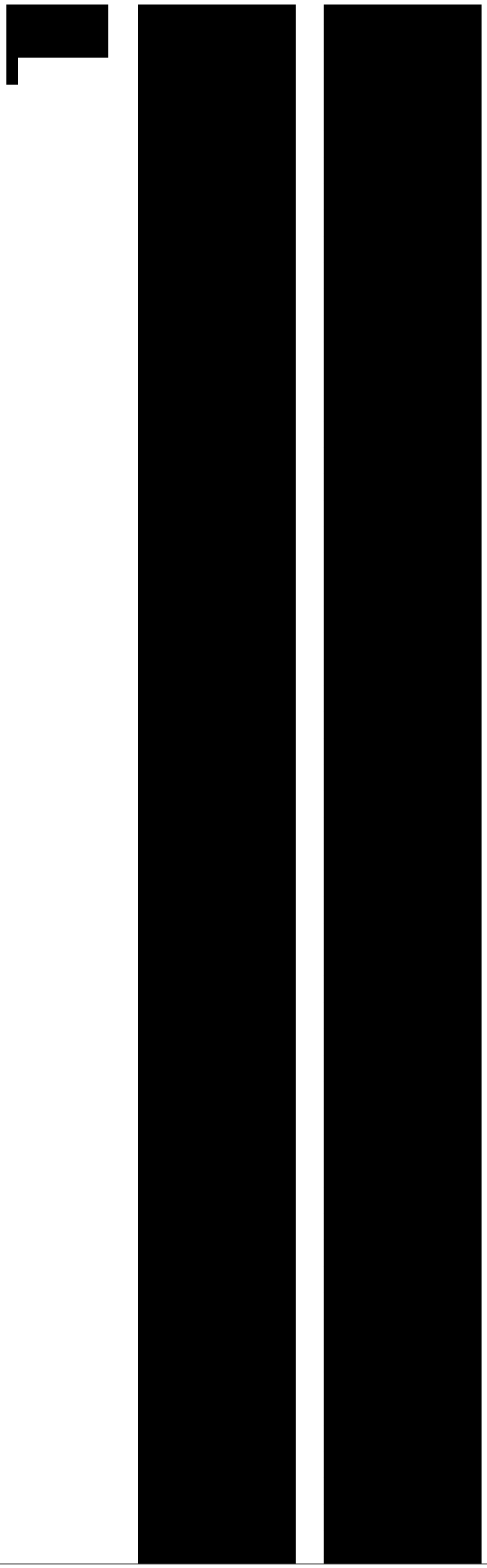

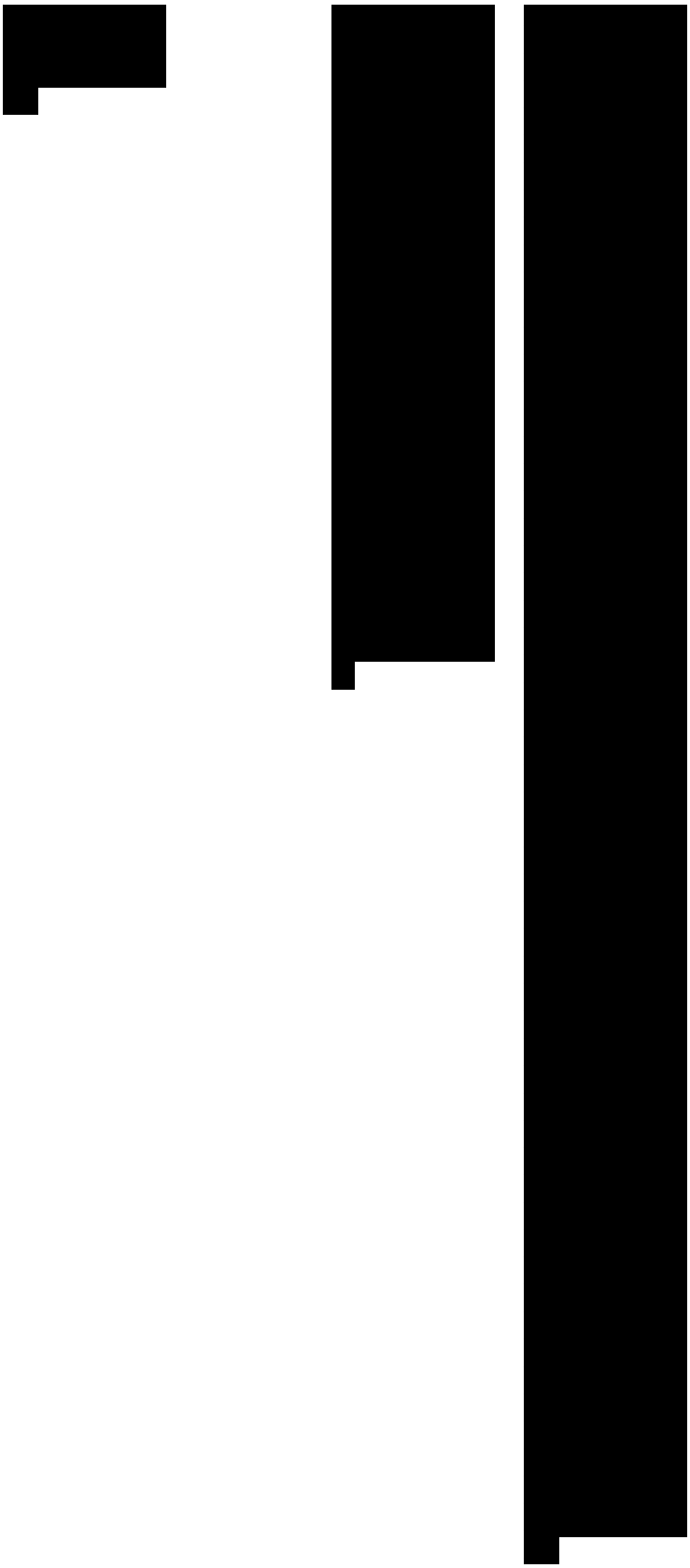

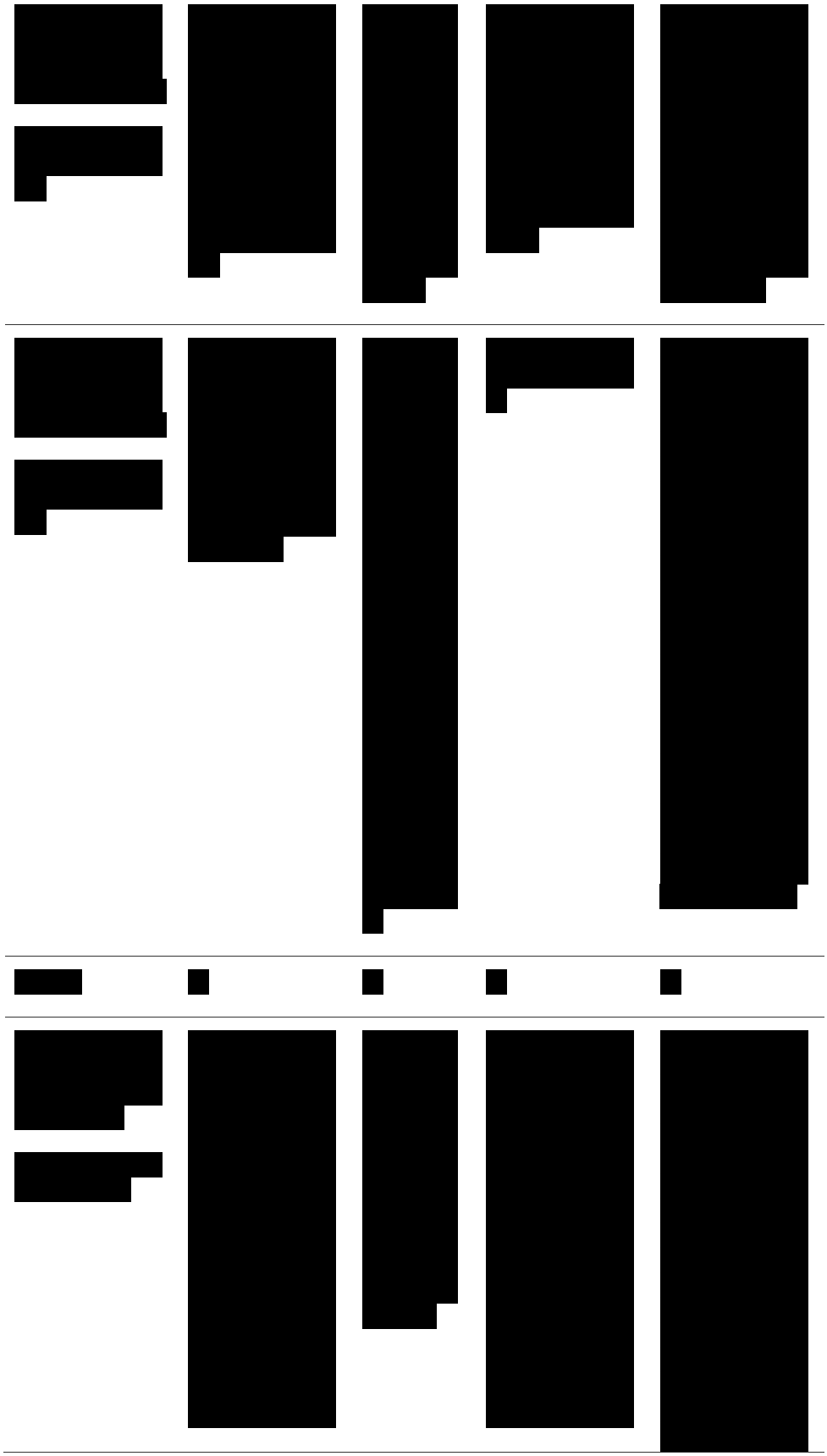

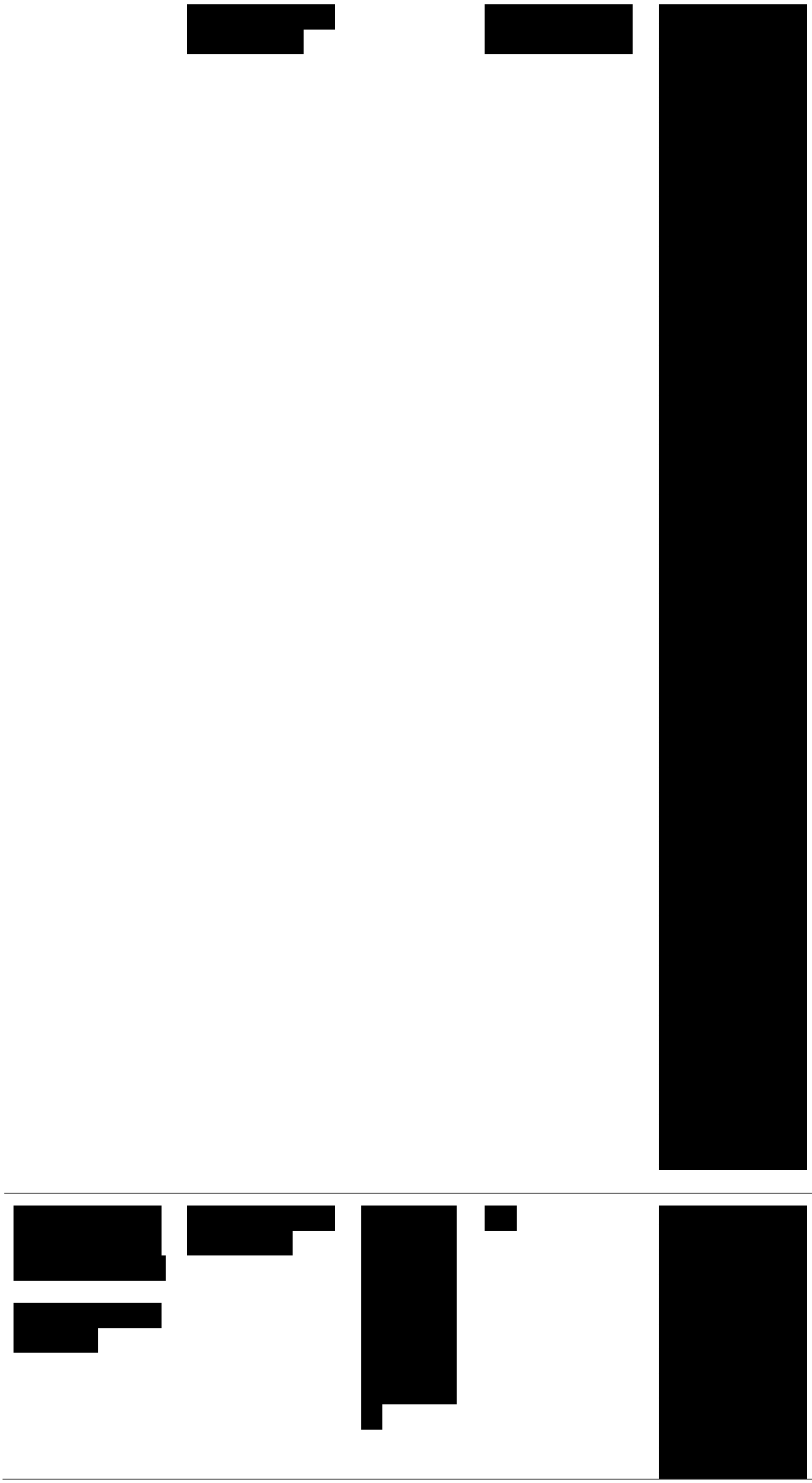

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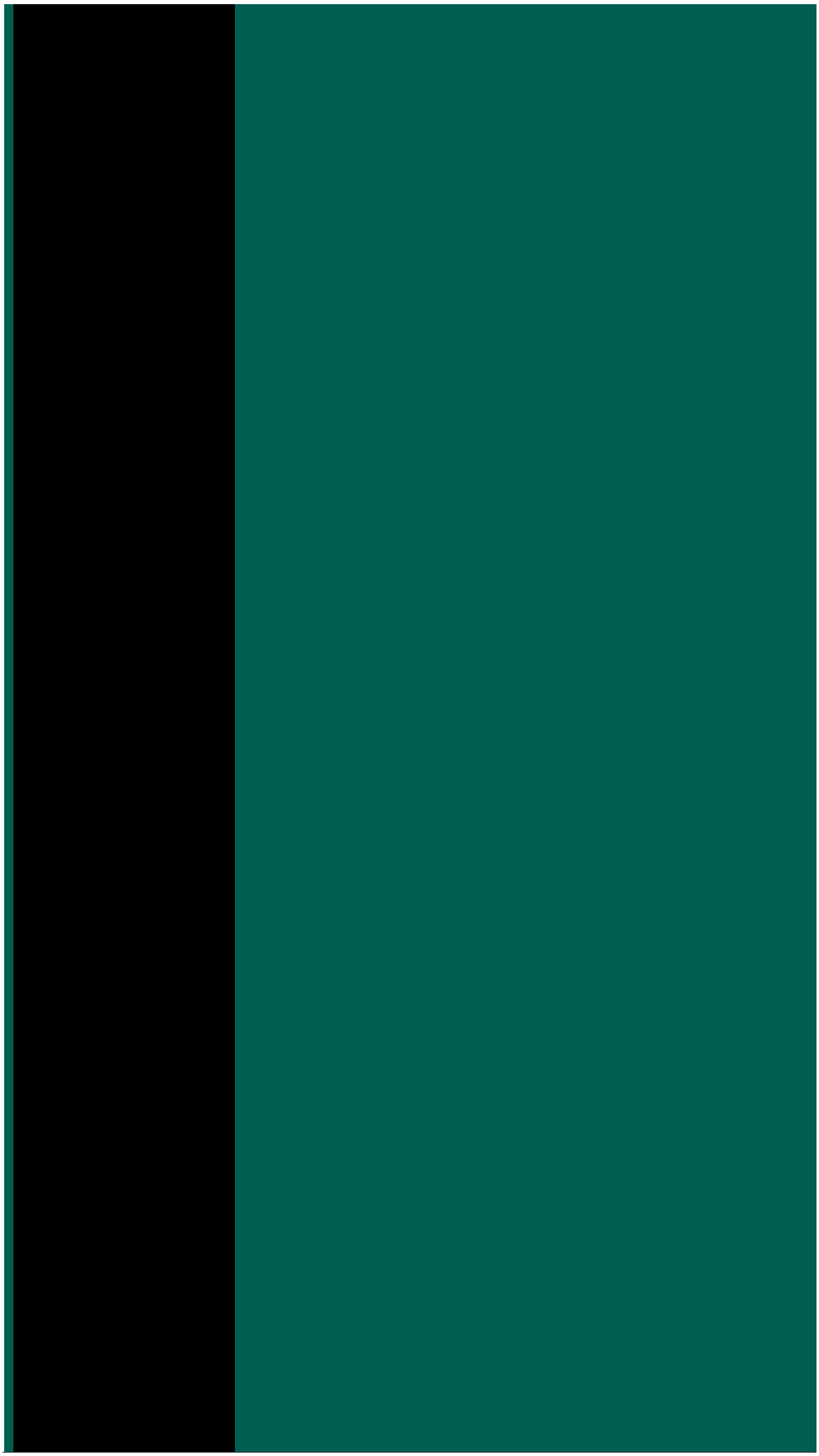
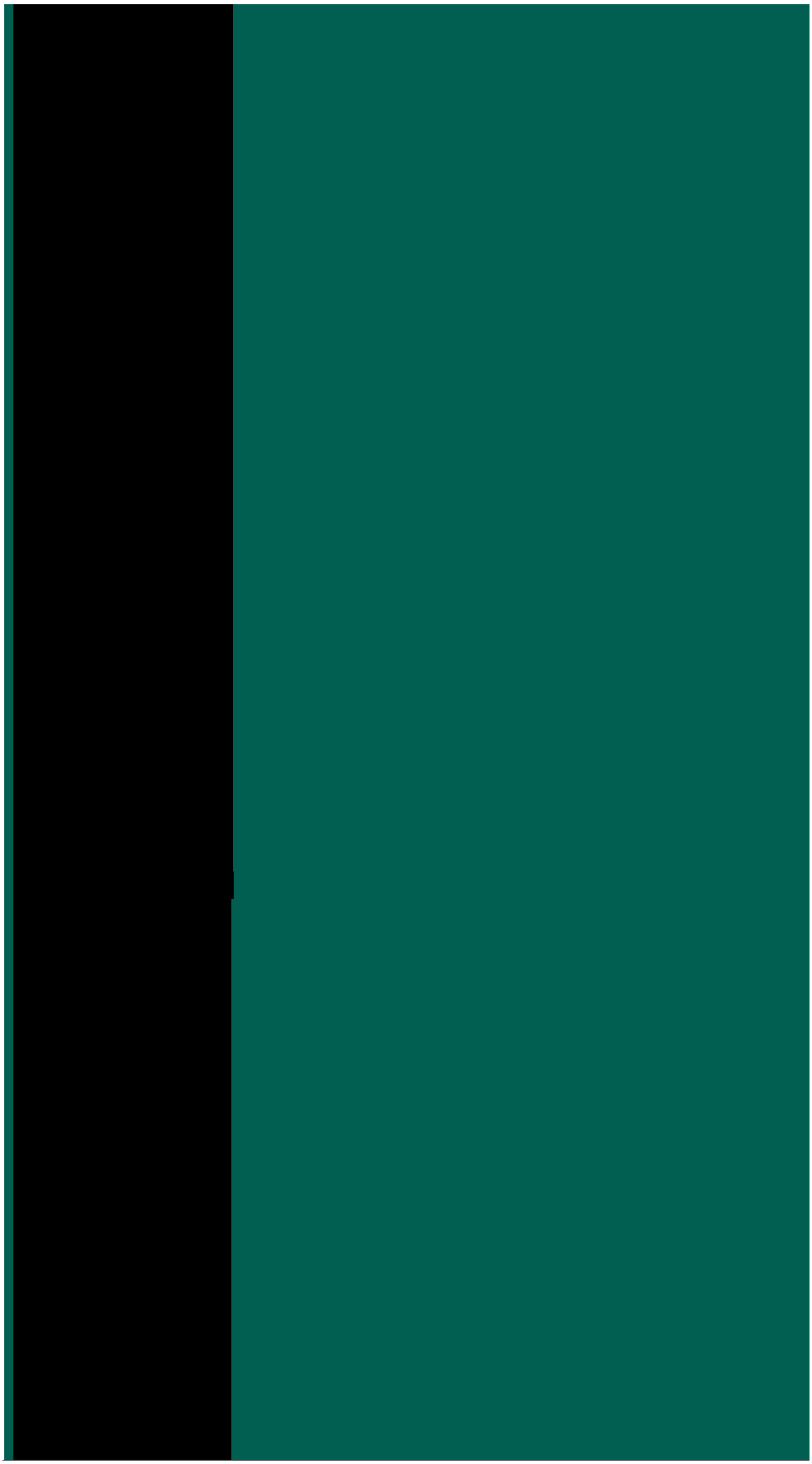
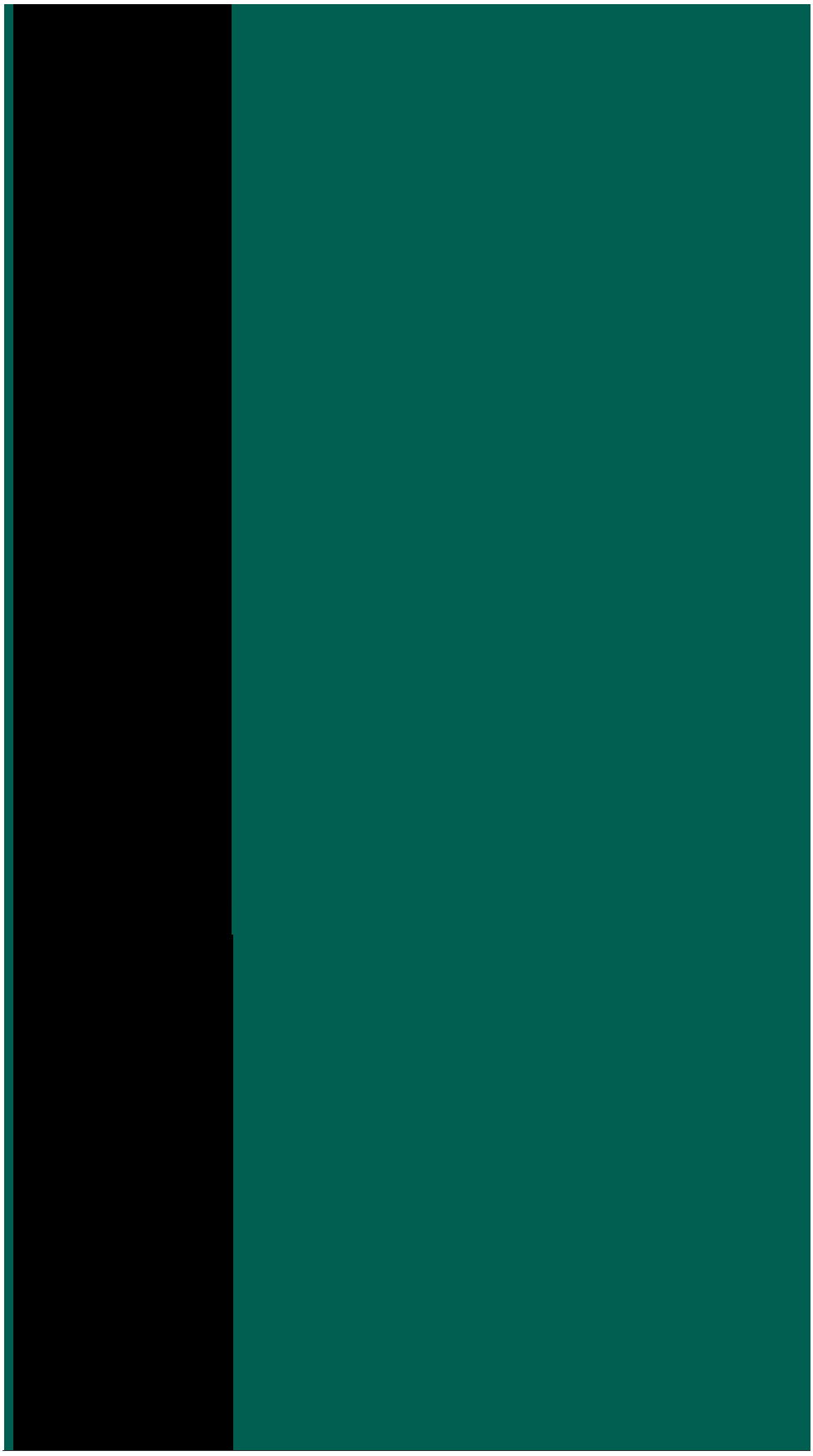
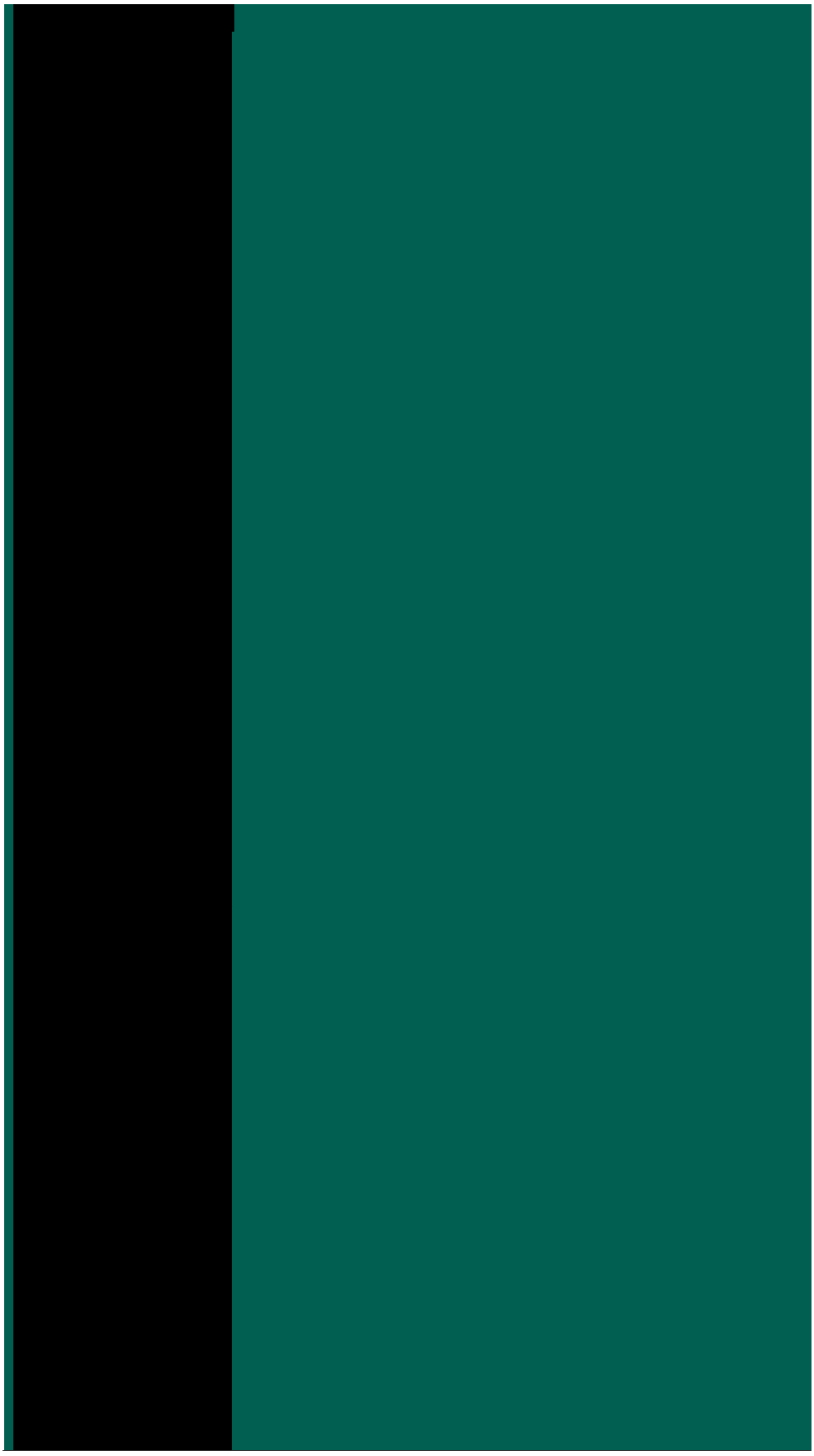
Appendix J. Literature searches for input to the health economic model

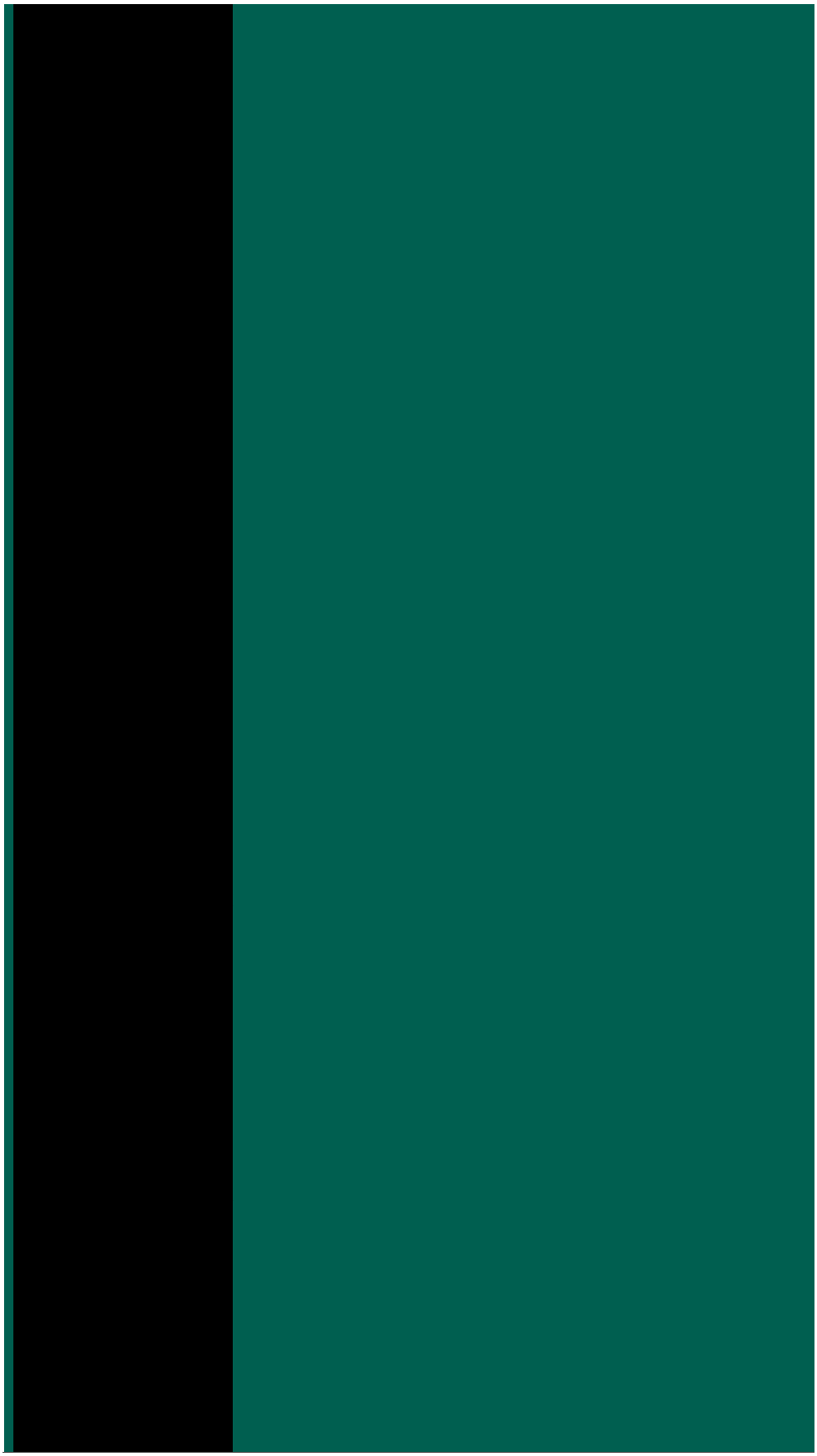
J.1 External literature for input to the health economic model

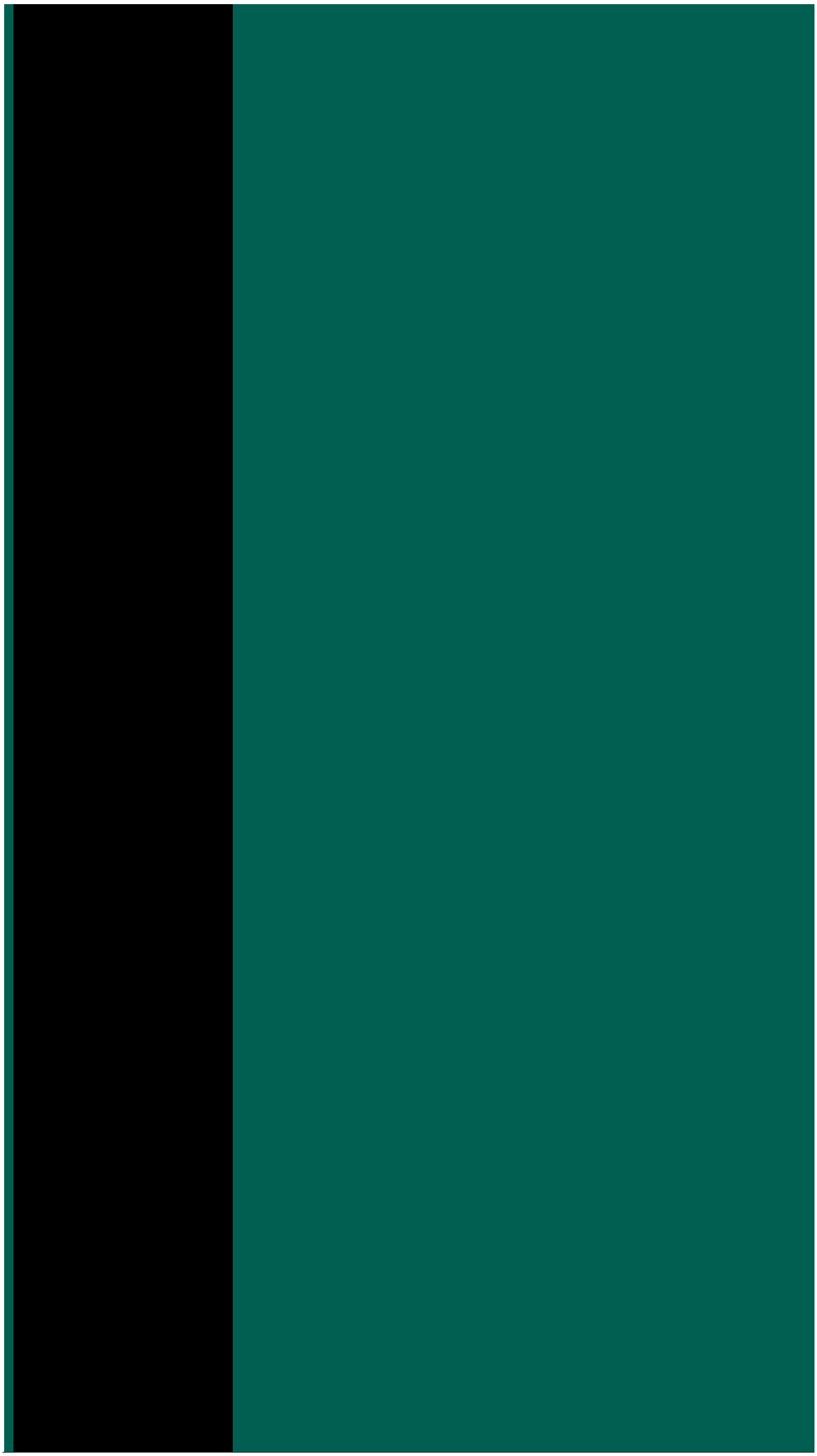


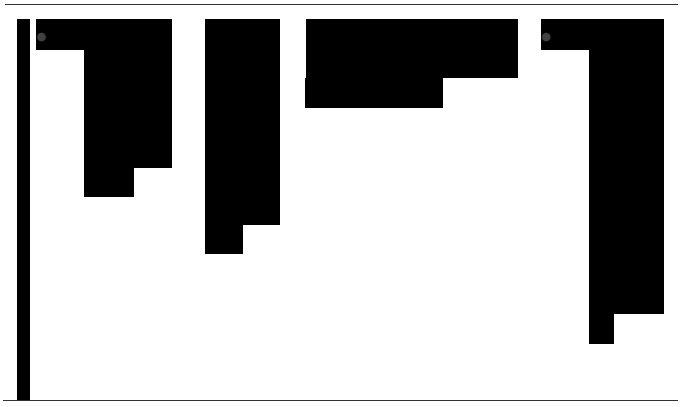


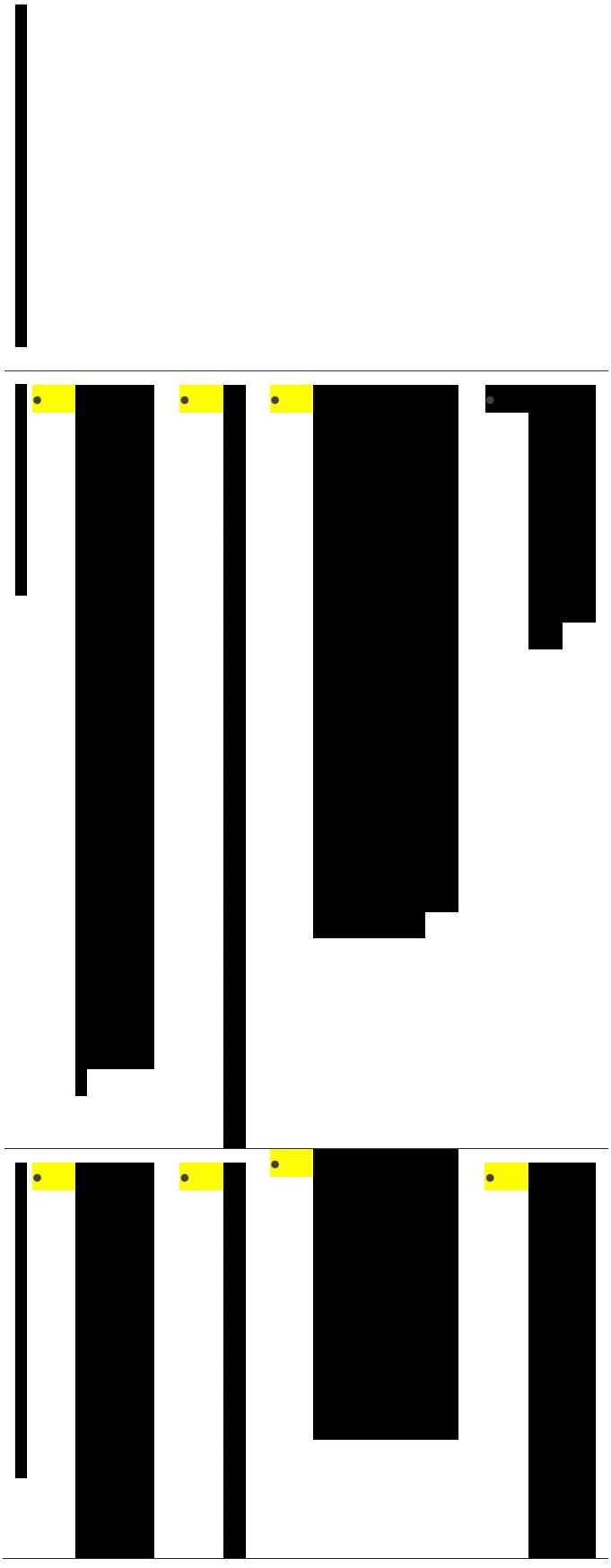


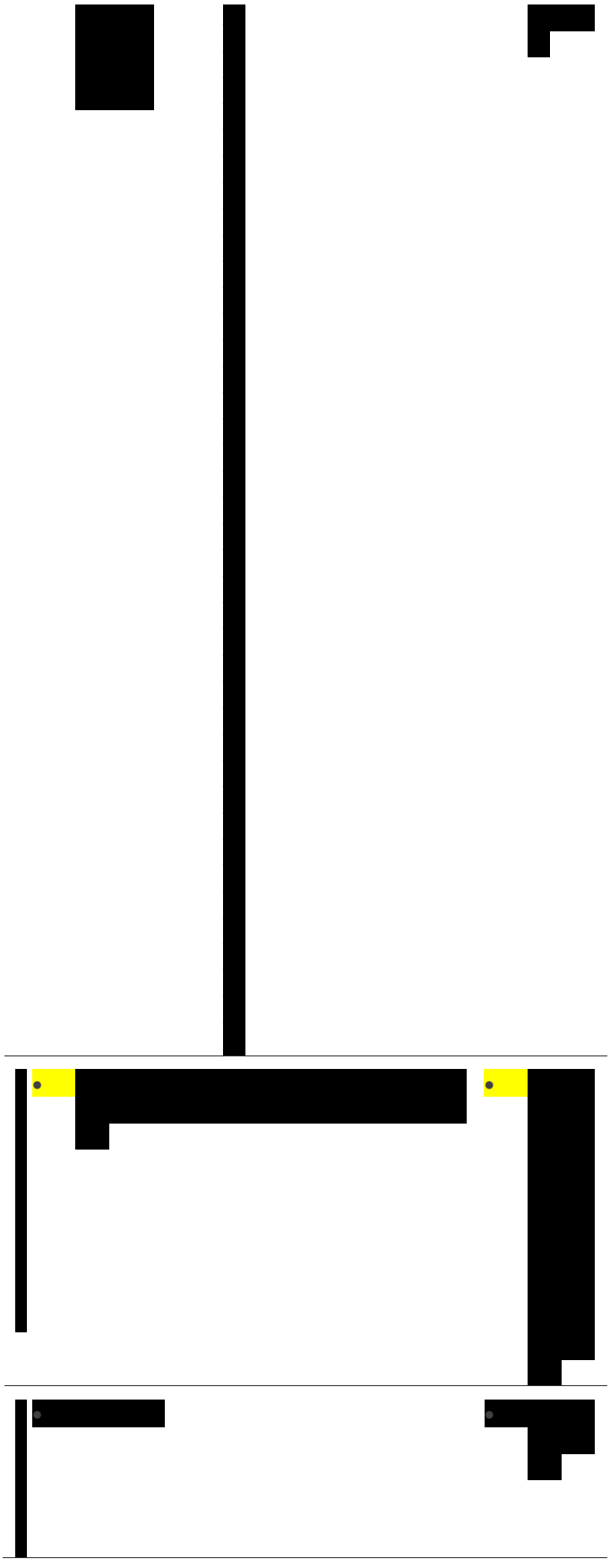


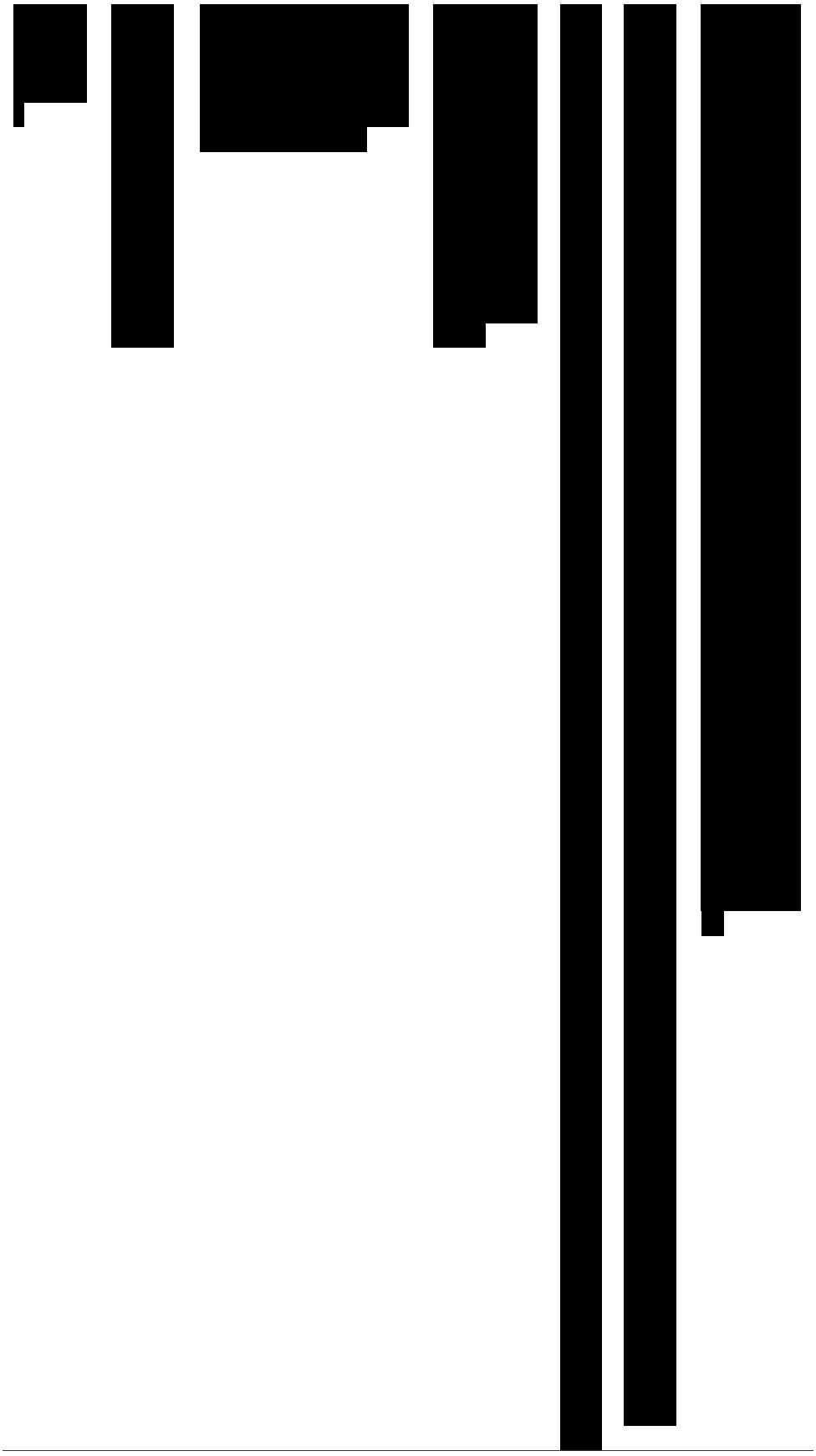


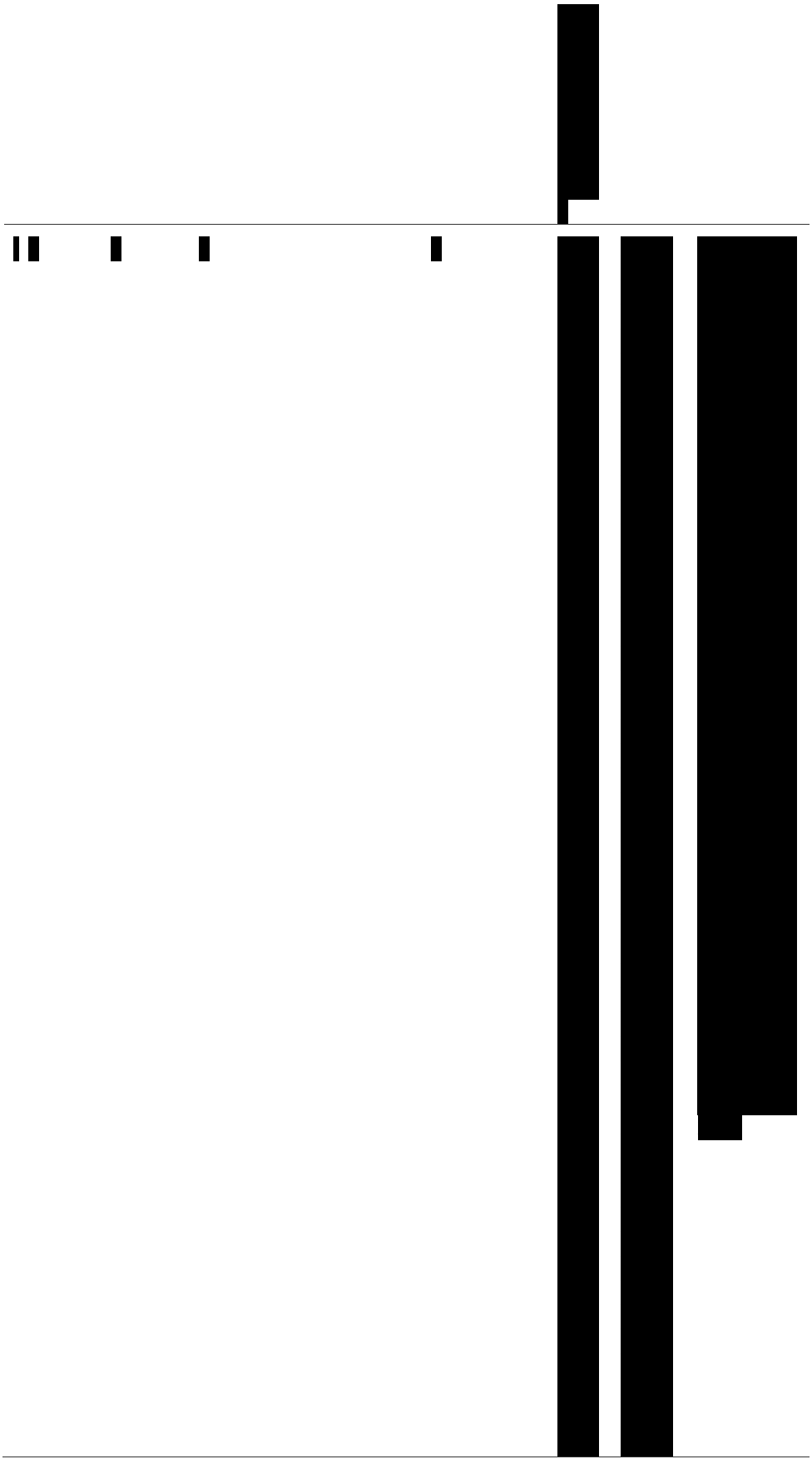


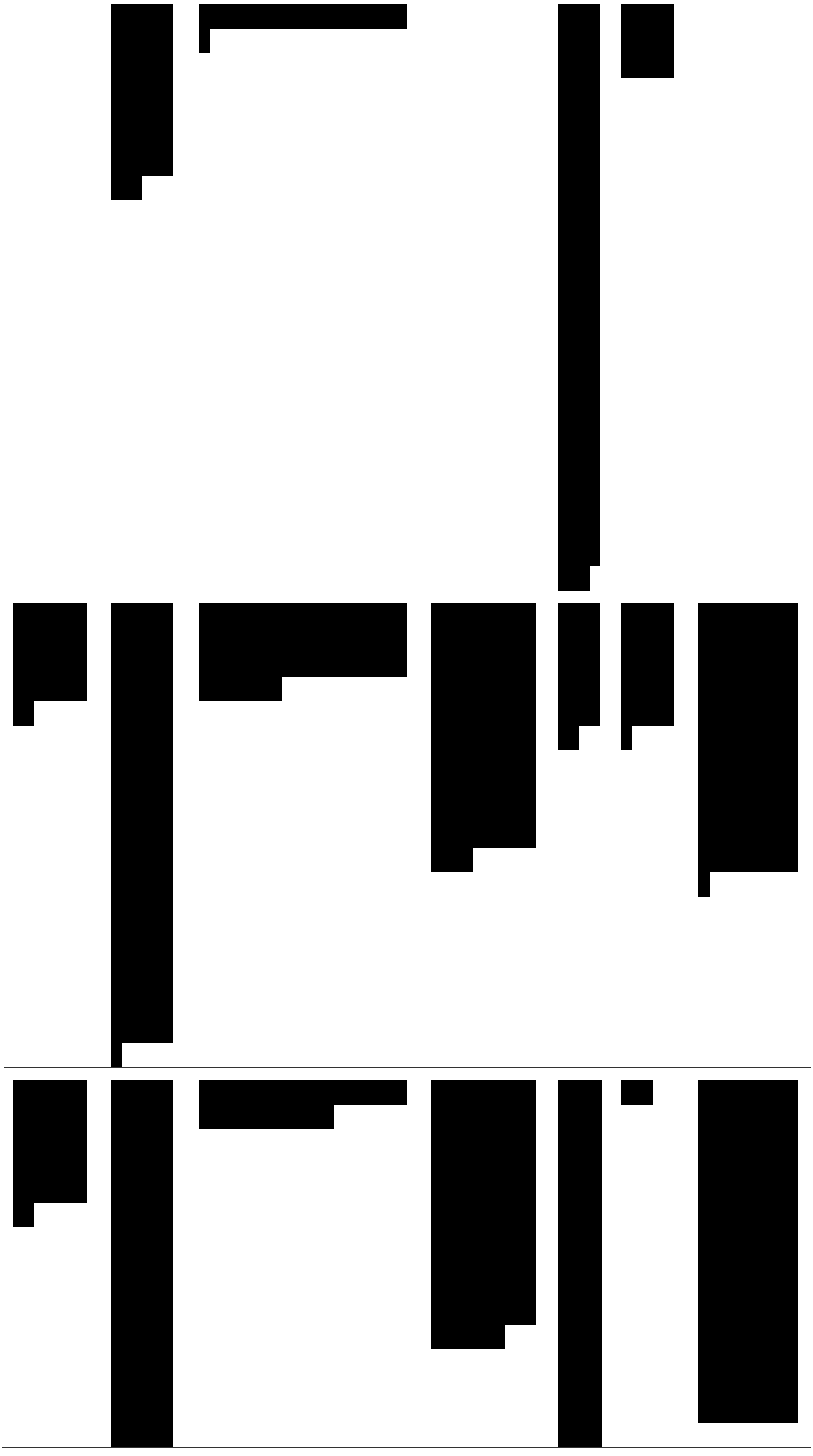


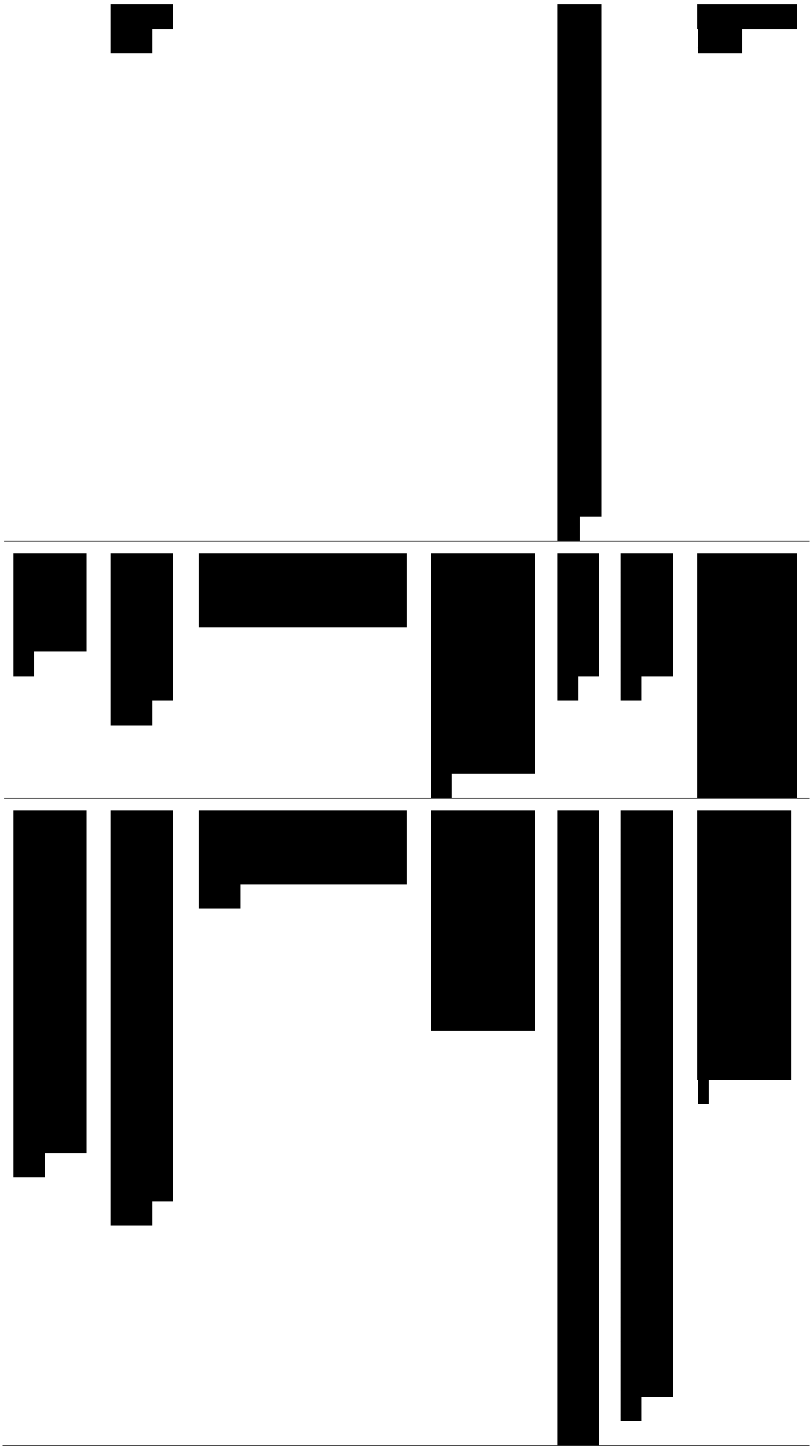


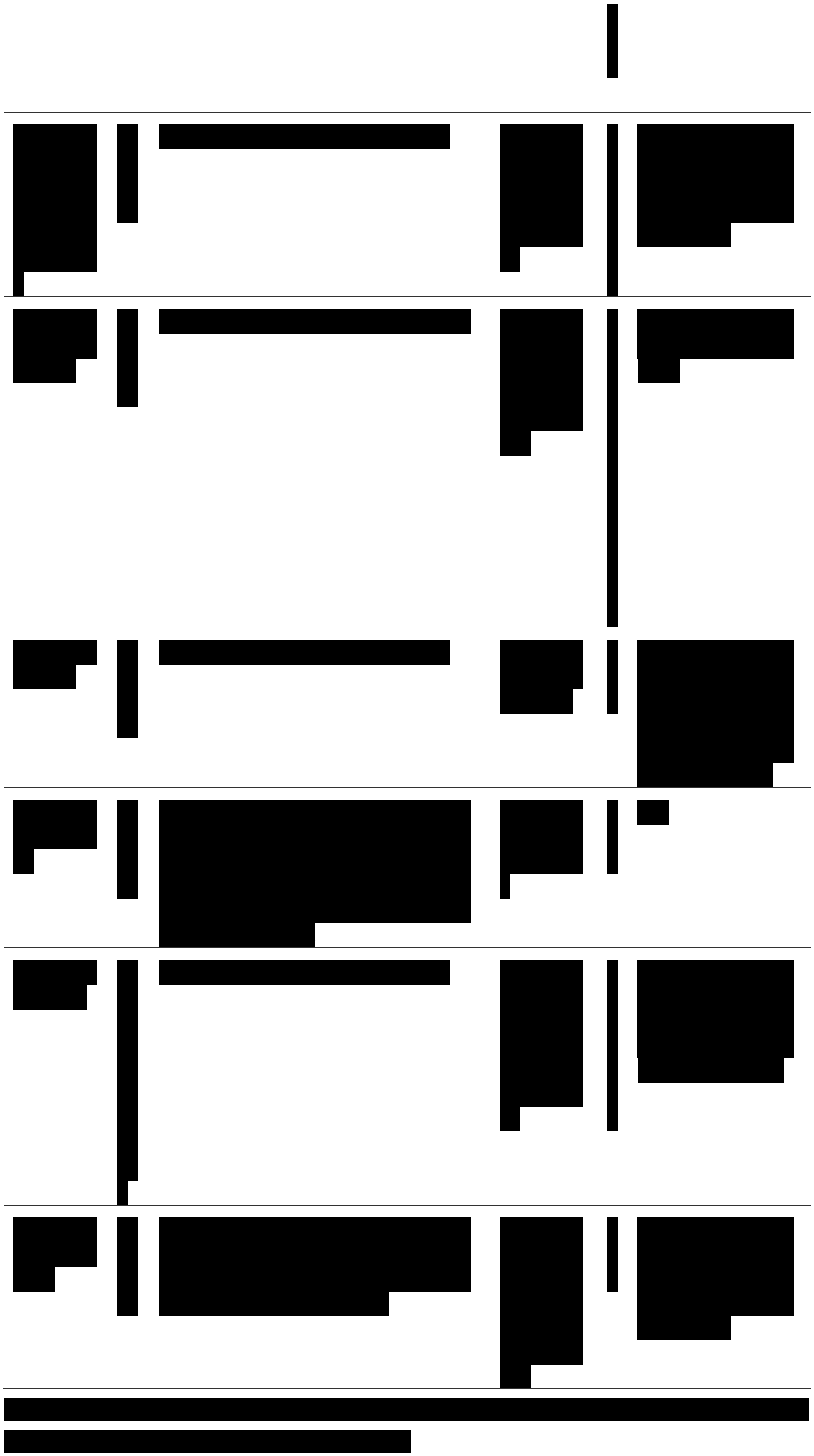


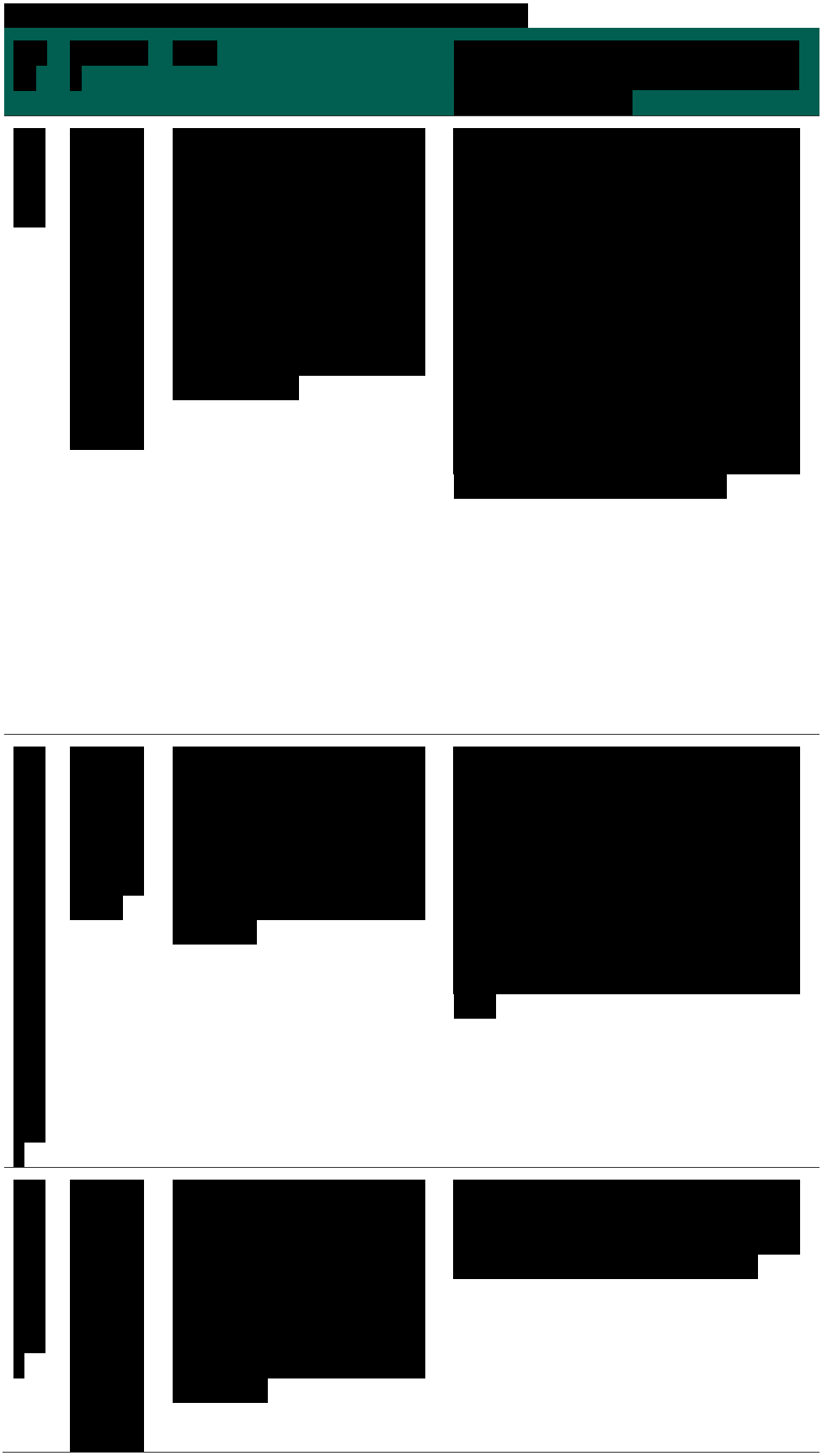










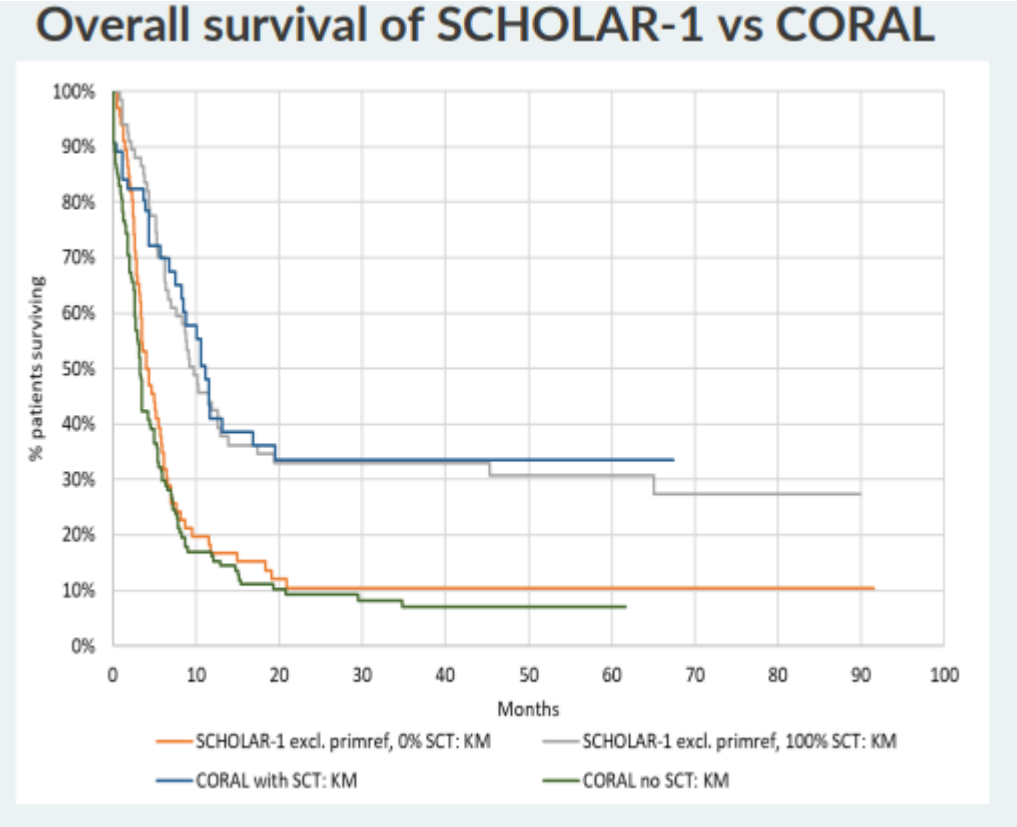


Appendix K. Relative efficacy of epcoritamab vs R-CIT based on CORAL studies

This section present the results of the ITC for epcoritamab compared to R-CIT using the extended CORAL studies from the study Hamadani et al.(42) This analysis is only represented as a scenario analysis, and not relevant for the clinical assessment. The results are based on a MAIC. Epcoritamab demonstrated statistical significant improvement in overall survival. However, the populations are not likely to be adequately adjusted given the sparse demographic data reported for CORAL. One of the key patient characteristics and prognostic factors notified by the clinicians was refractoriness. The CORAL studies did not report on refractoriness in the baseline criteria which is a major prognostic factor and difference between the EPCORE-NHL-1 trial.

Also, in the base case where SCHOLAR-1 was included in the relative efficacy assessment this information where included. Both SCHOLAR-1 and extended CORAL studies has been discussed in other HTA submissions. In NICE This has led to an comparison of overall survival between SCHOLAR-1 and CORAL between those patients that received stem cell transplantation (SCT), see Figure 19.The figure shows very similar efficacy in OS between the two studies. Also, here the primary refractoriness was excluded in the population for SCHOLAR-1. It was concluded that the SCHOLAR-1was the most representative study to compare efficacy in the R/R DLBCL patients that have received several lines of therapy. SCHOLAR-1 were also accepted in several other countries (Norway, Sweden and Canada). It is reasonable to believe, when looking at the differences in the adjusted results of the comparison between epcoritamab and SCHOLAR-1 and the results of epcoritamab and CORAL is due to the adjustment for refractoriness in the patient population.

Figure 19 OS comparison between SCHOLAR-1 and CORAL (84)



Adjusted baseline characteristics and the results can be seen in the tables below.

Table 85 Unadjusted and adjusted patient characteristics from the EPCORE-NHL-1

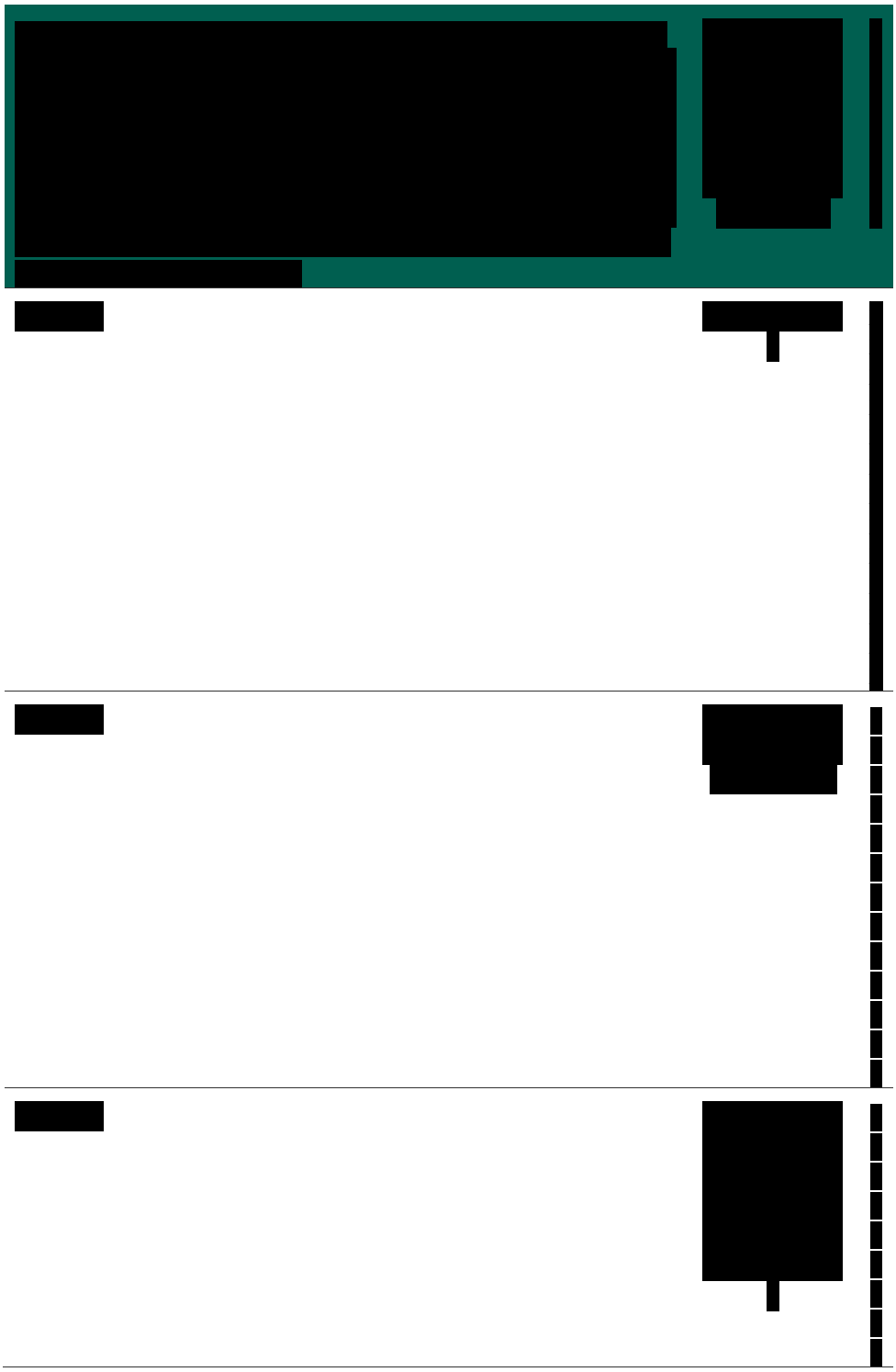
Baseline	Unadjusted	Adjusted to CORAL	CORAL
Age	[redacted]	[redacted]	[redacted]
median			
Male	[redacted]	[redacted]	[redacted]
Mean			

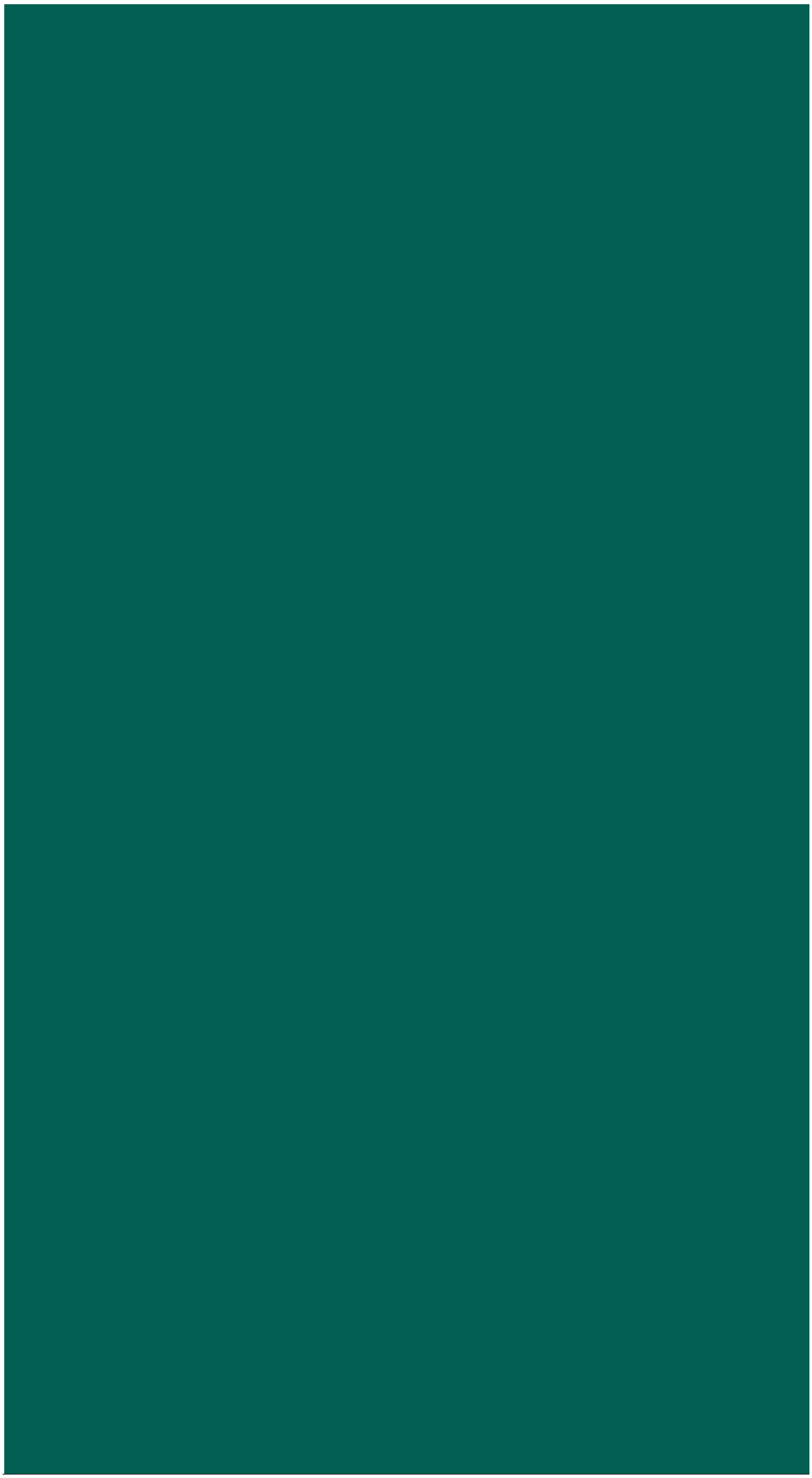
IPI 0-2 vs 3-5	[redacted]	[redacted]	[redacted]
Prior ASCT	[redacted]	[redacted]	[redacted]

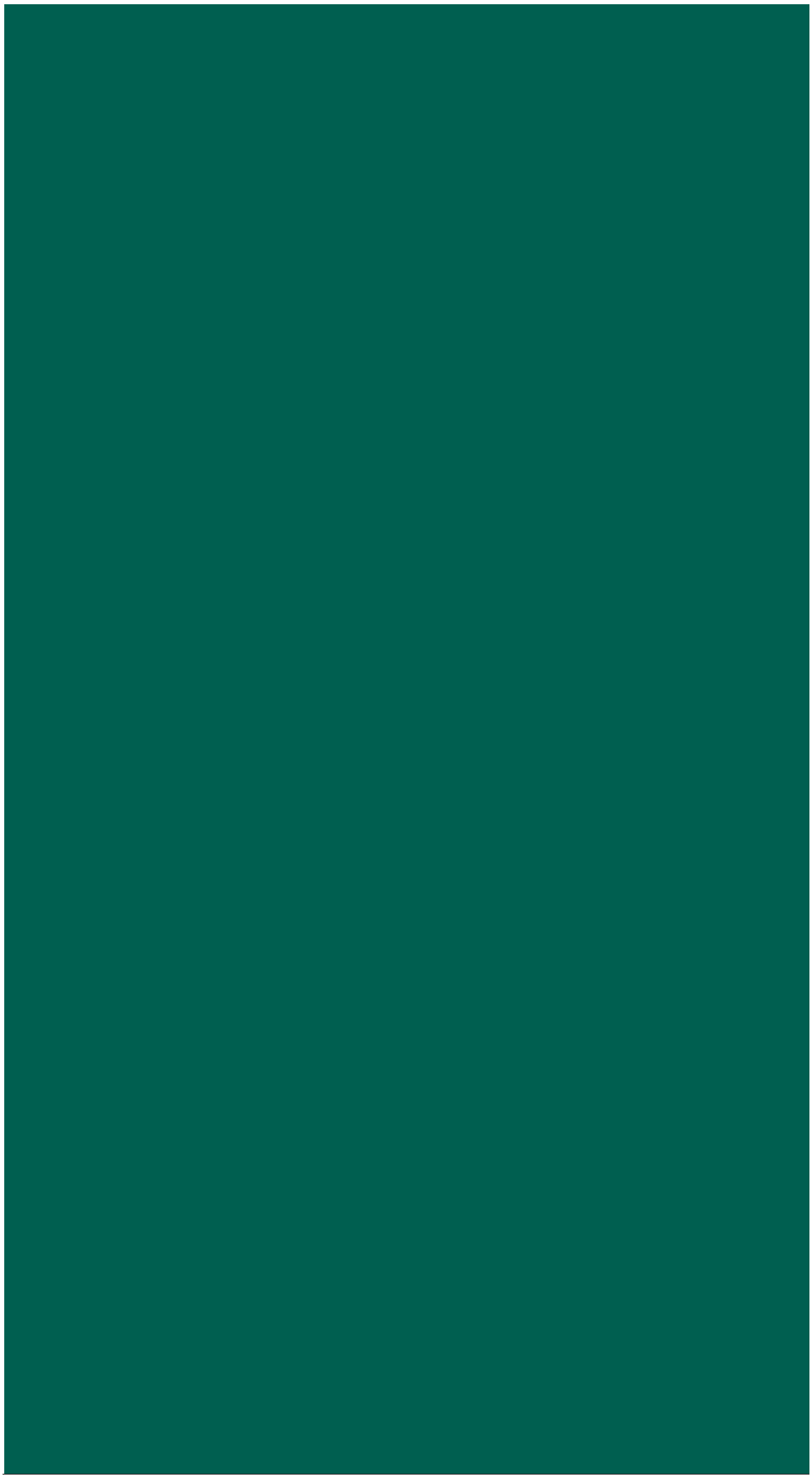
Table 86 Unadjusted and adjusted results of the comparison between EPCORE-NHL-1 and CORAL

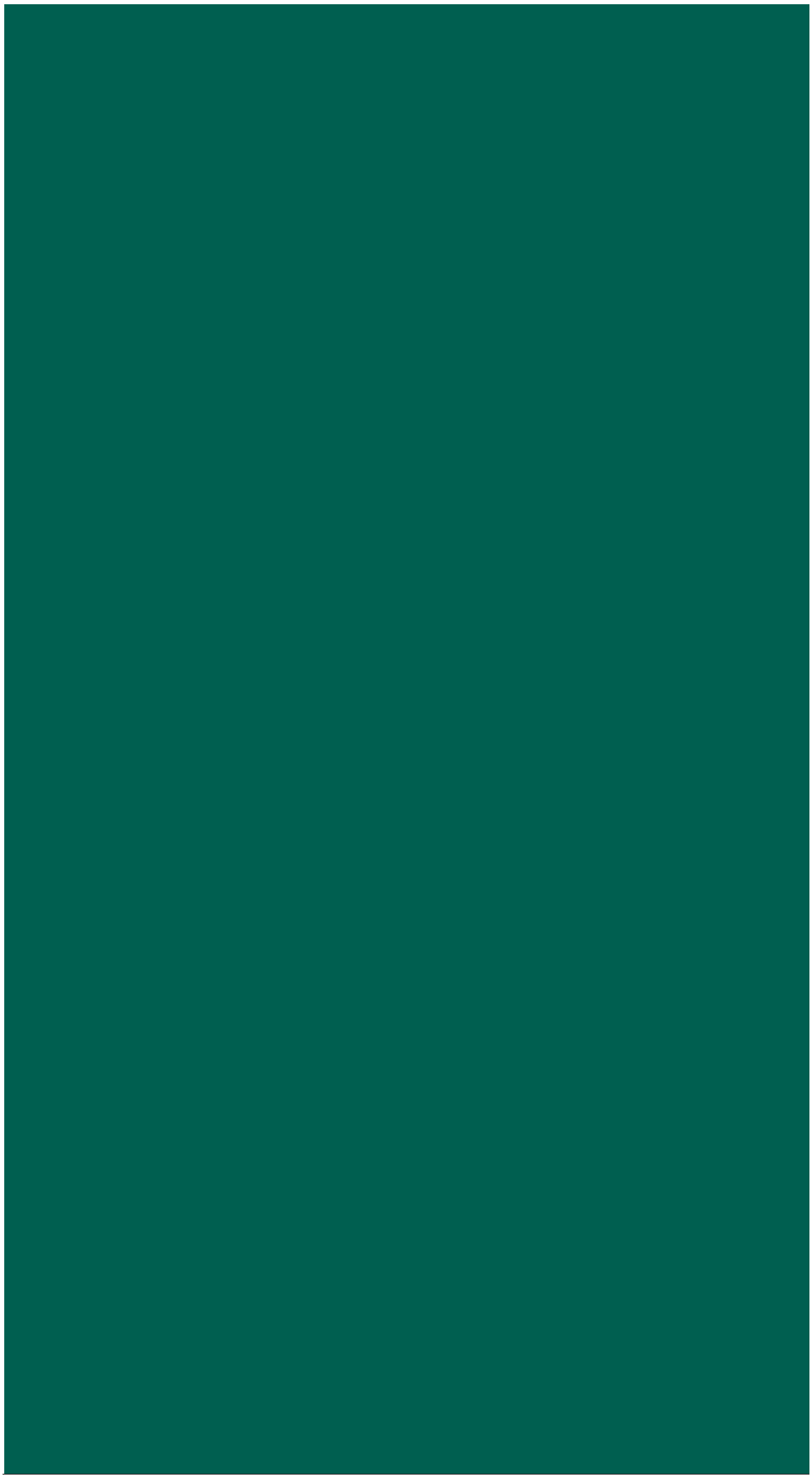
Unadjusted	Adjusted
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

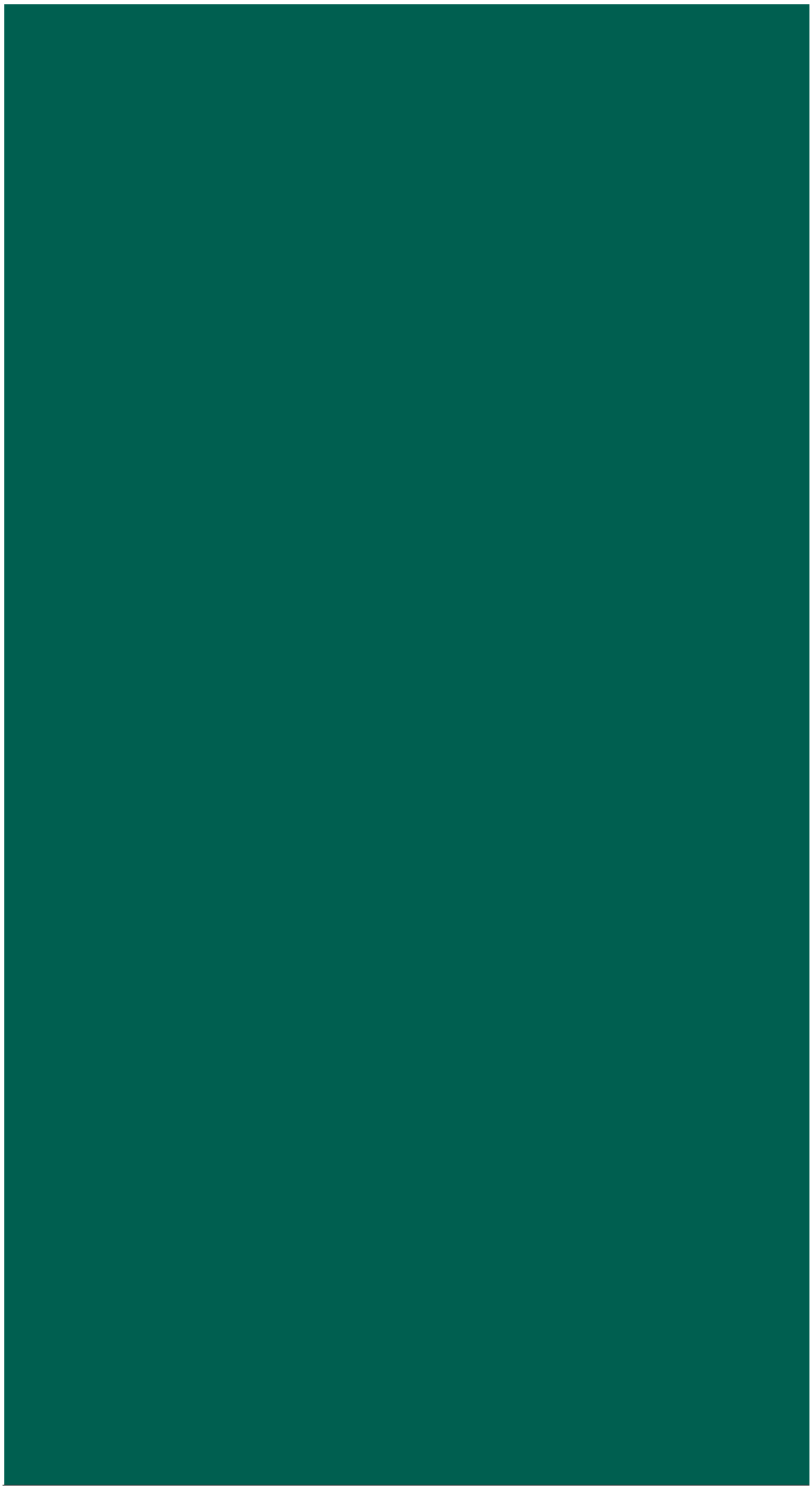
Appendix L. LMM method and results of the LMM analysis

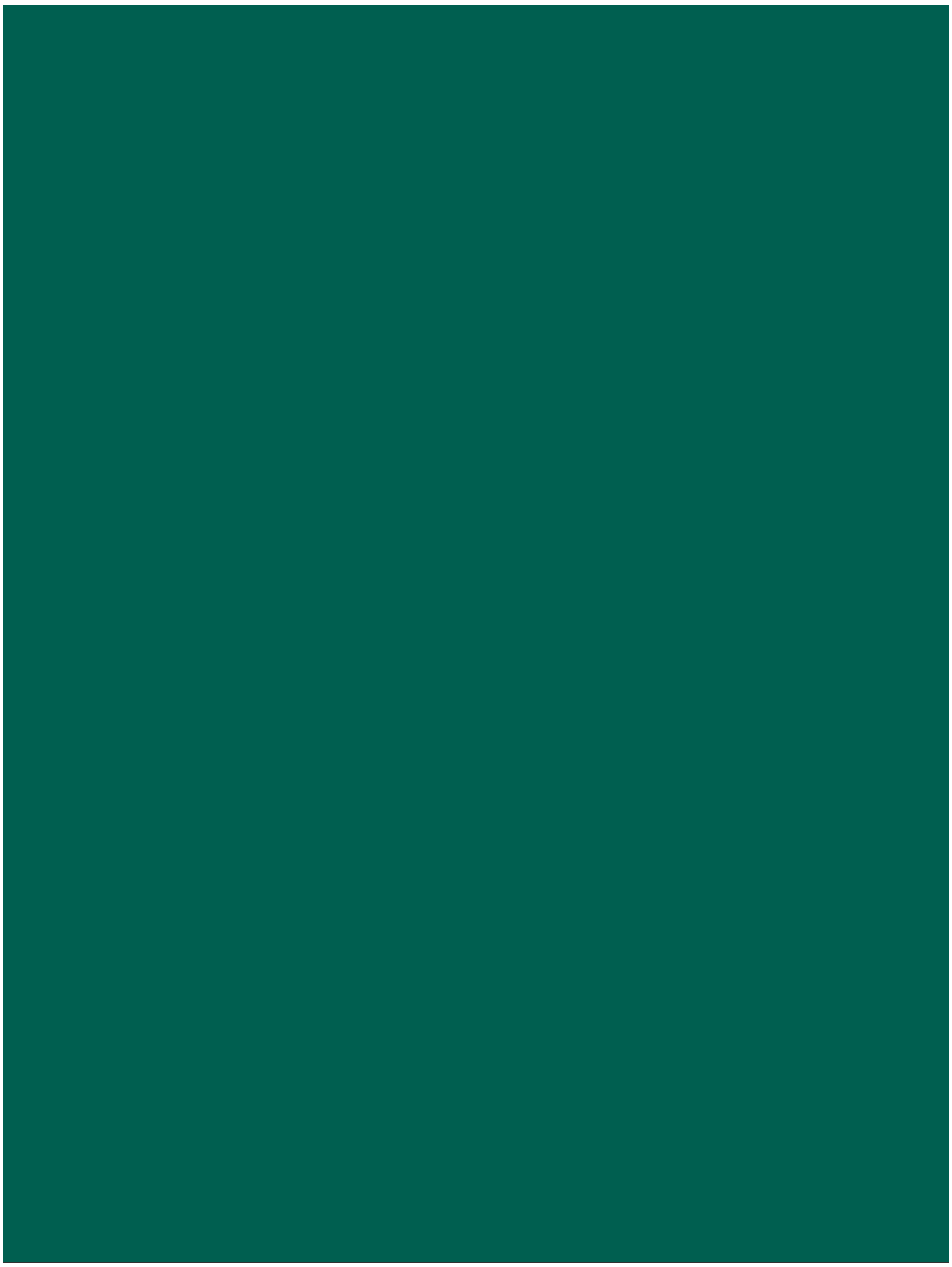


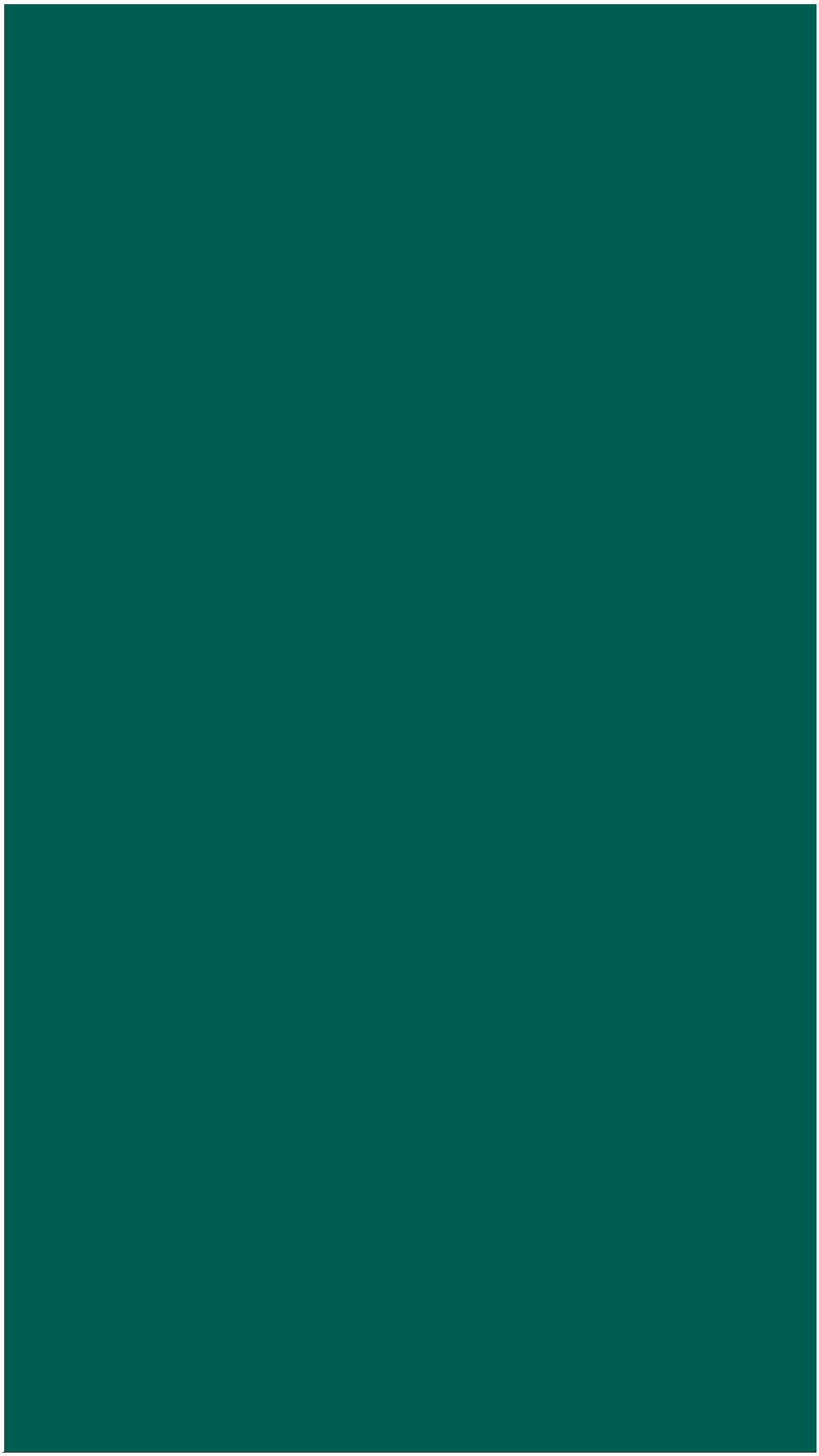


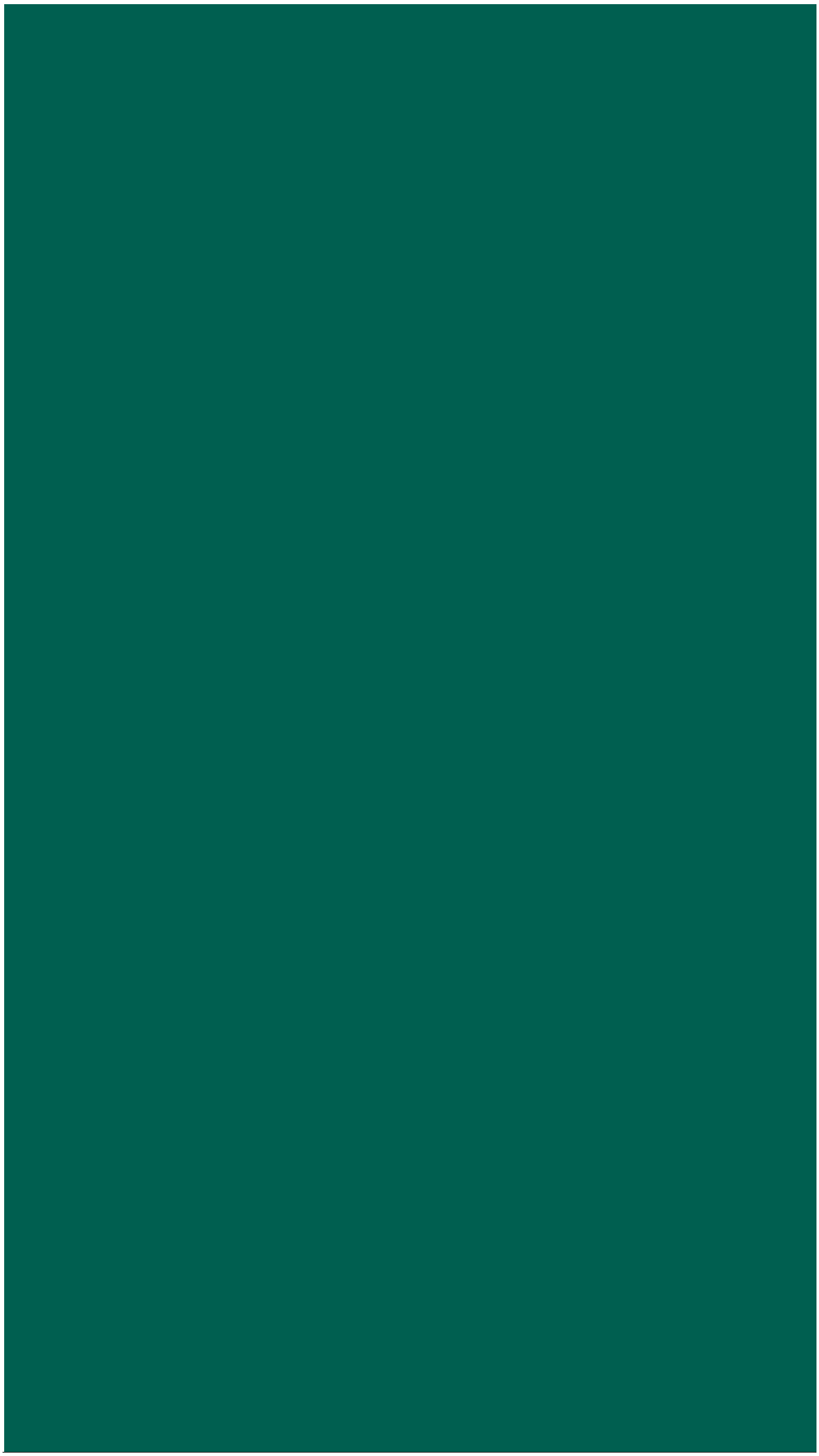


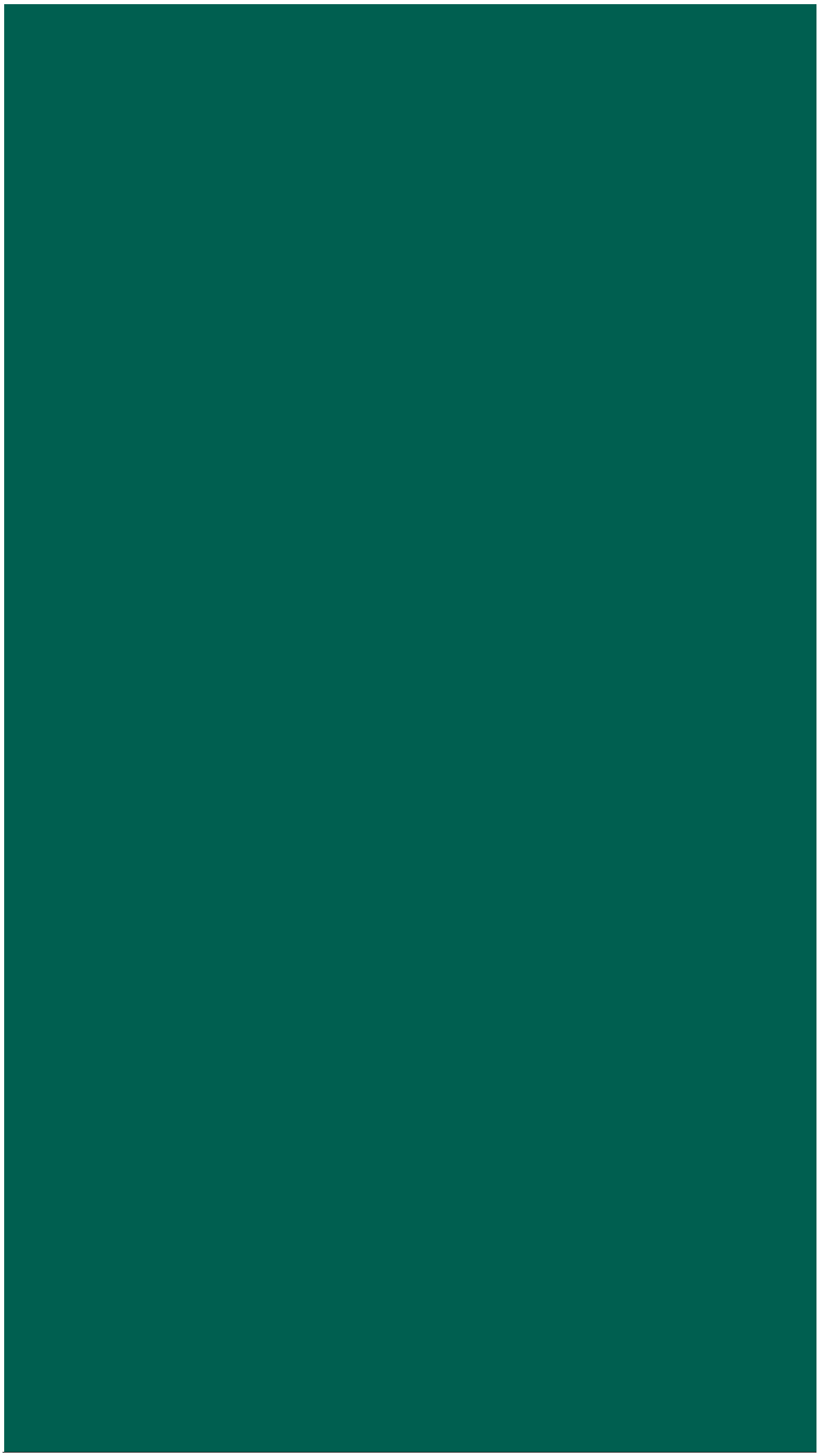


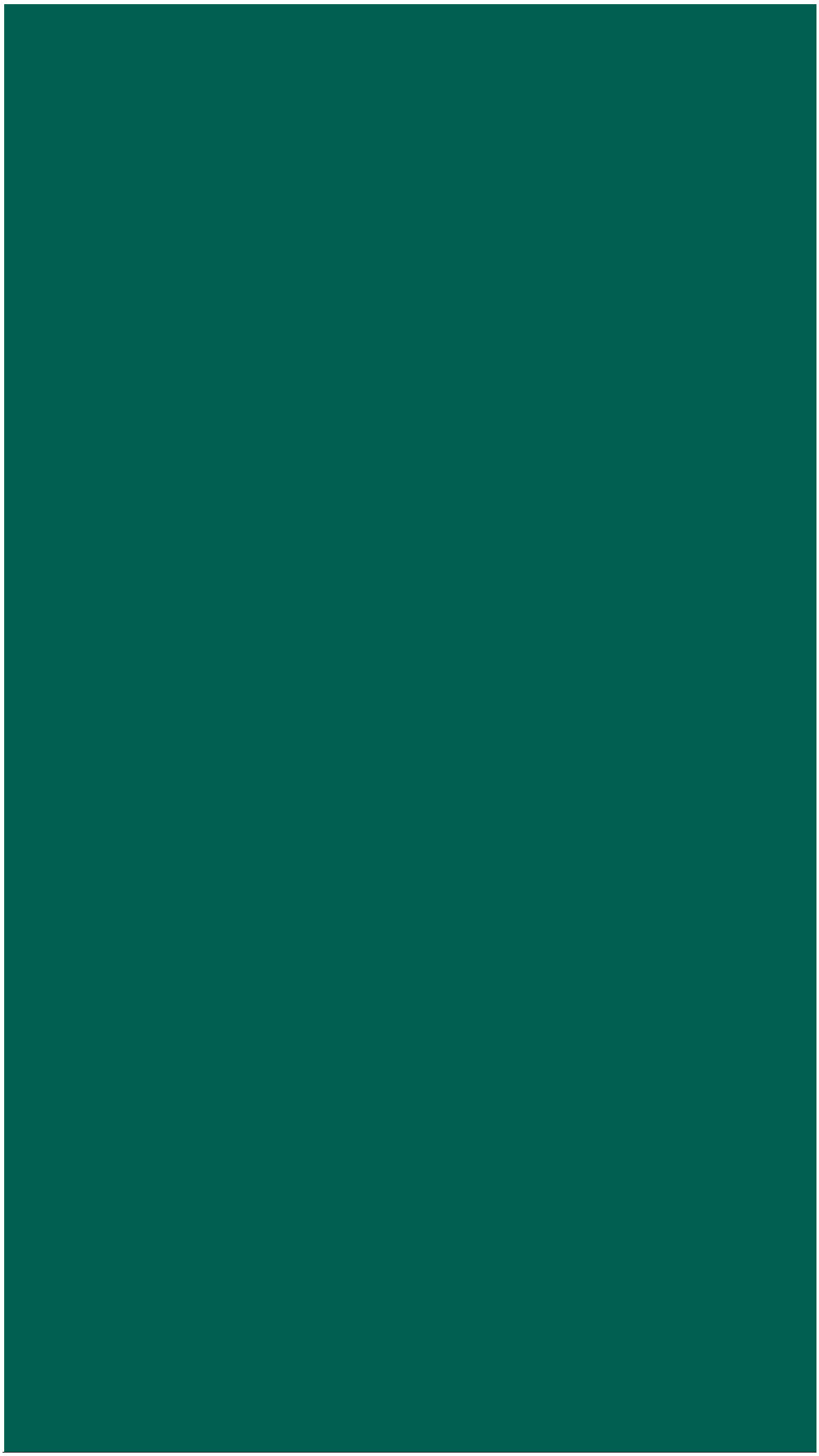


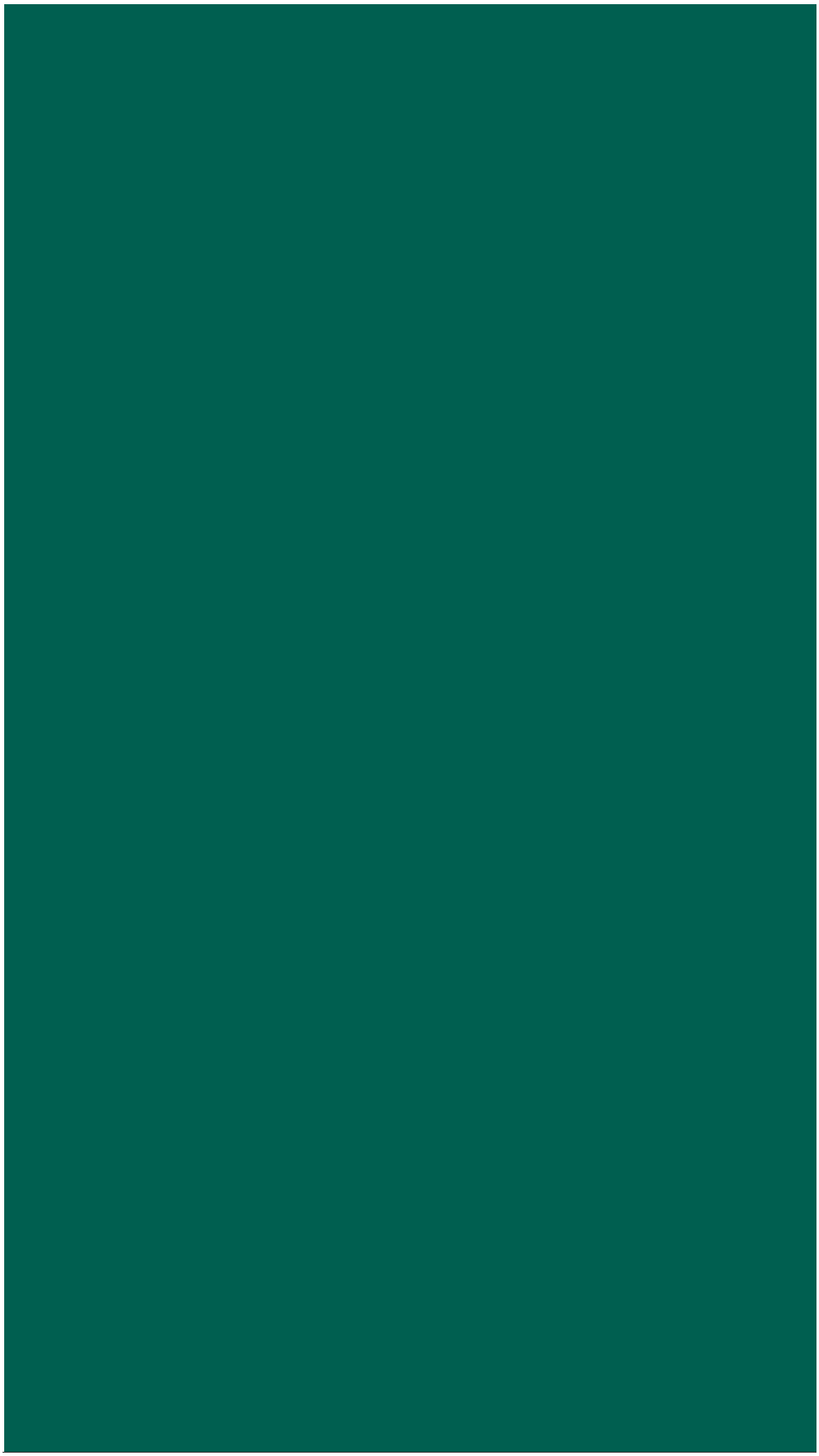


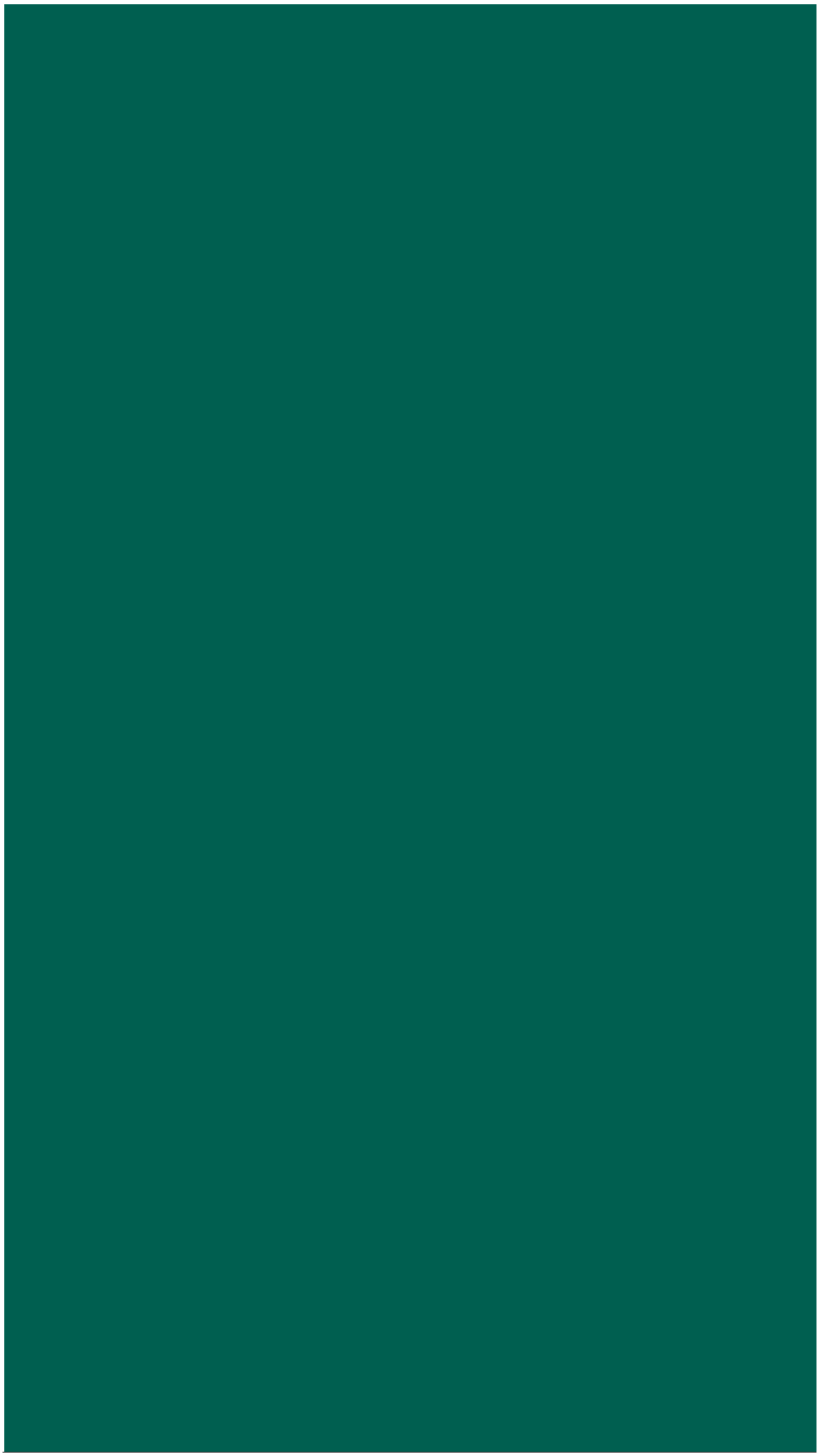


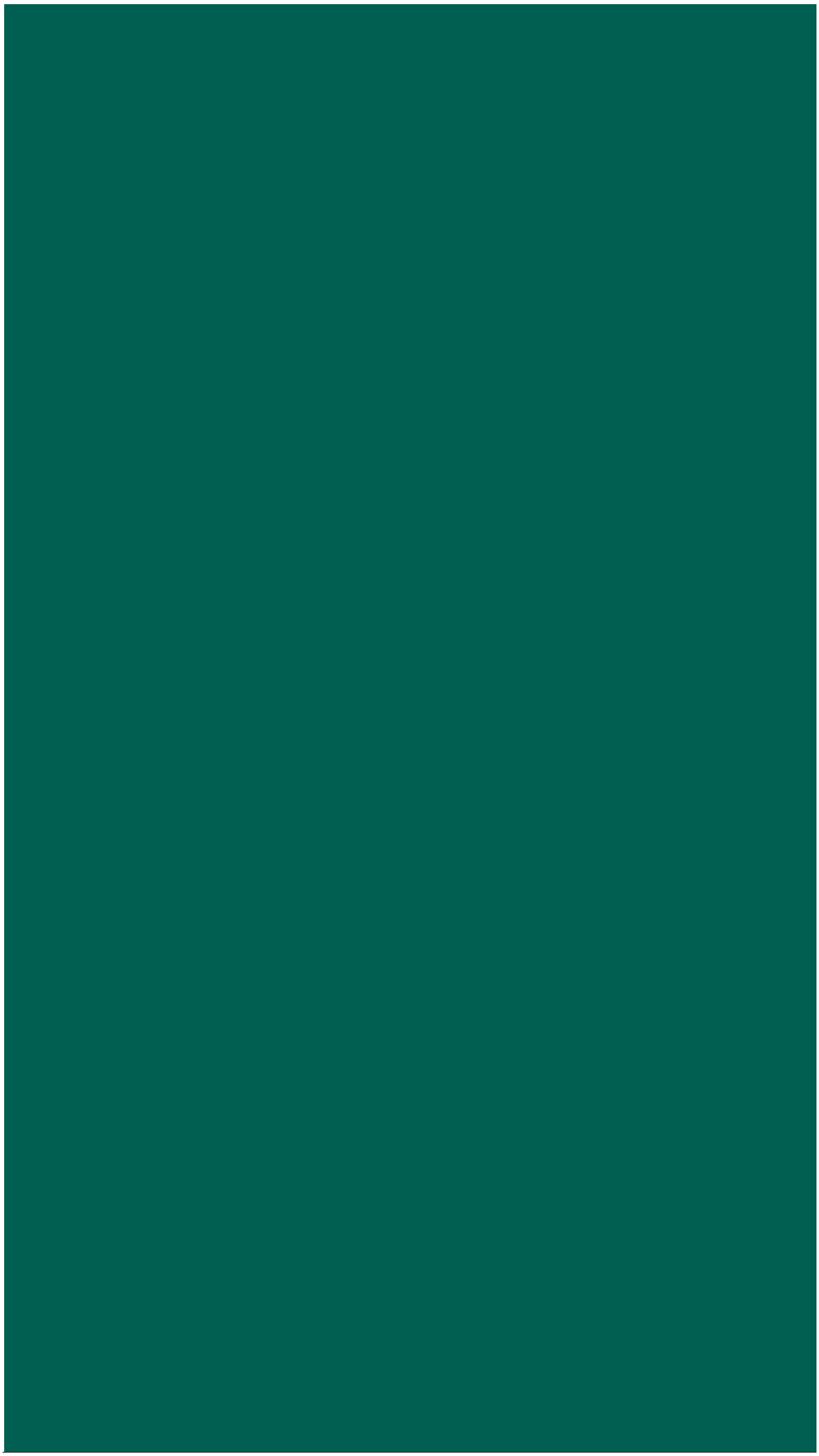


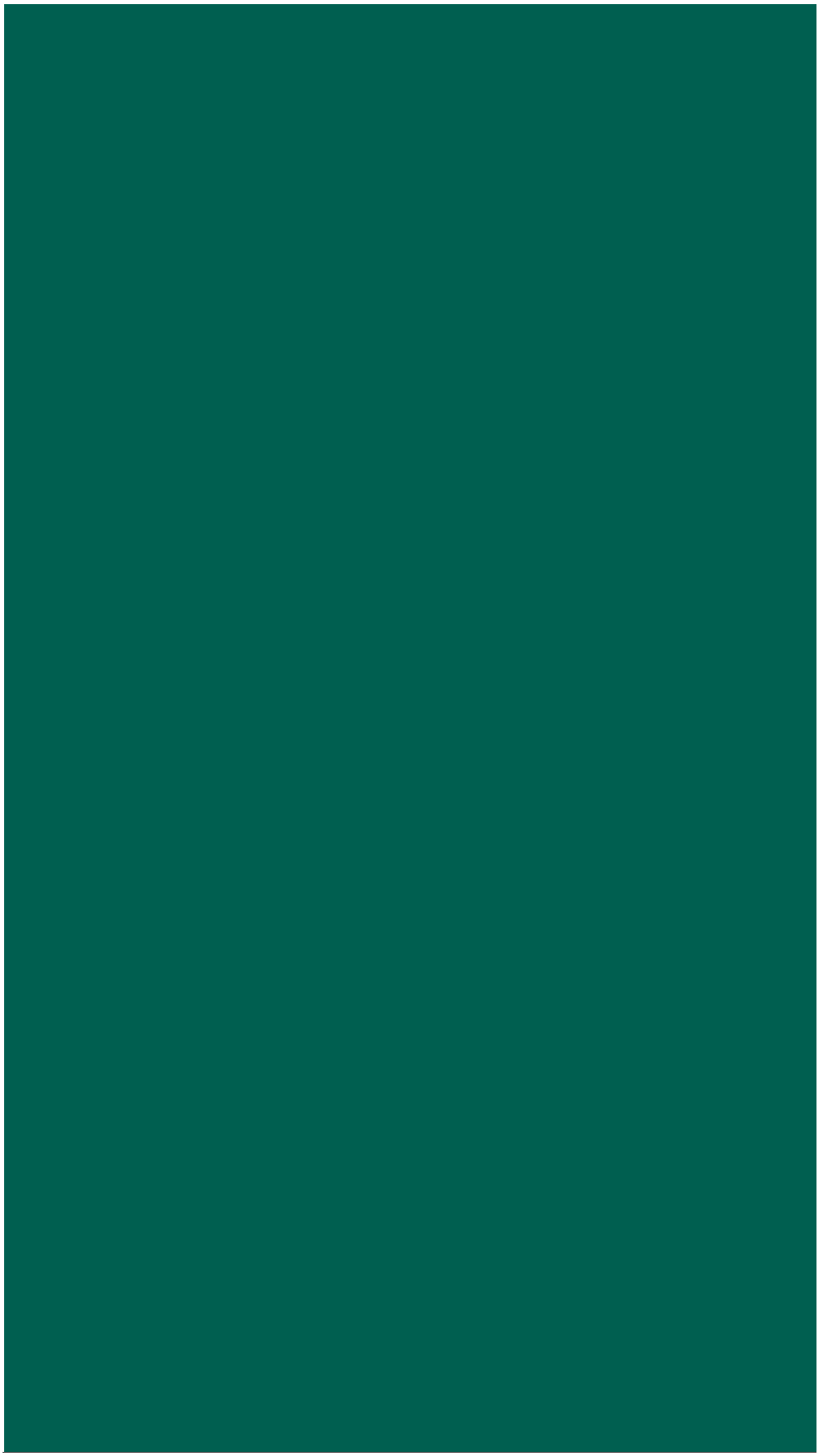


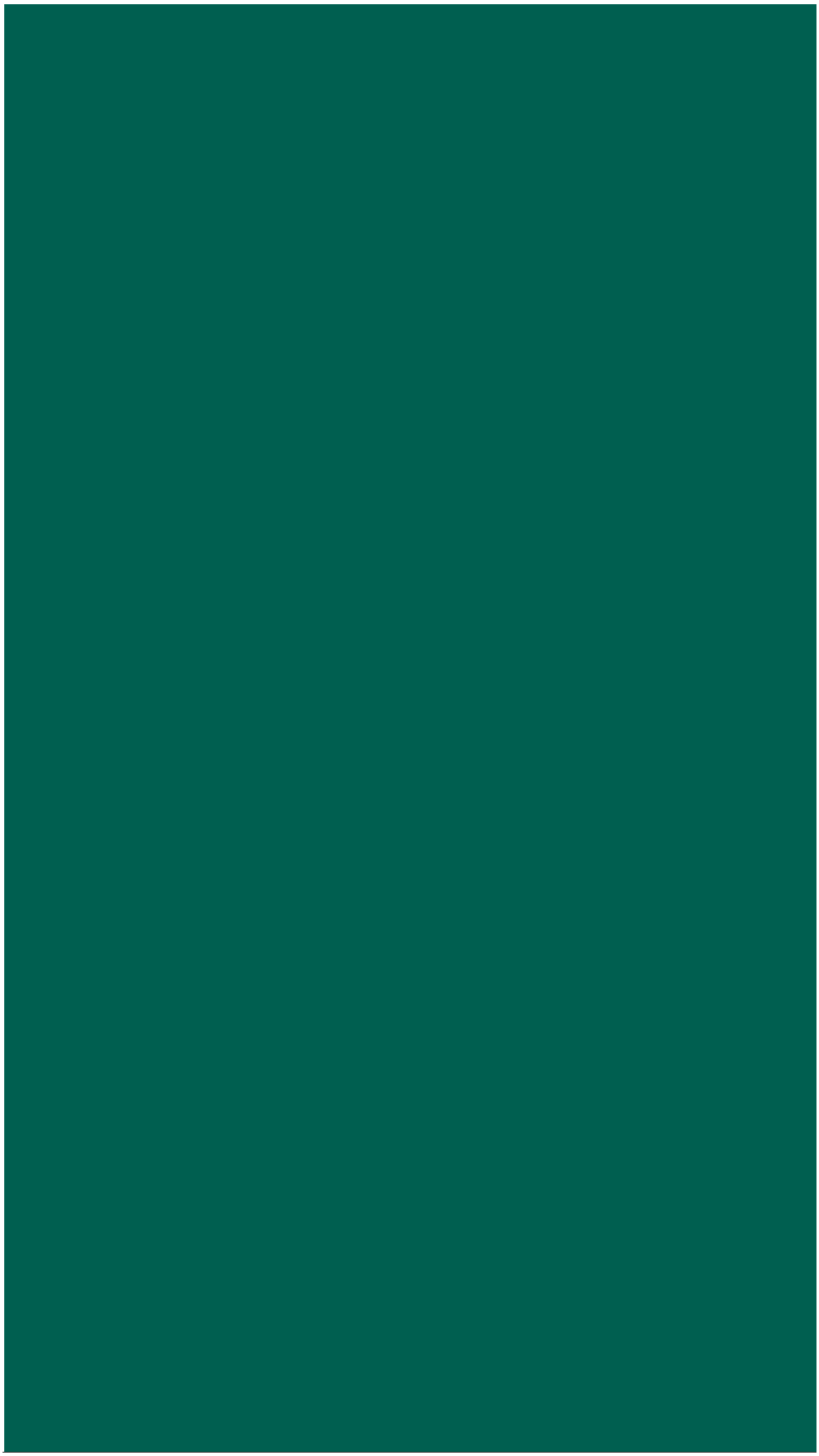


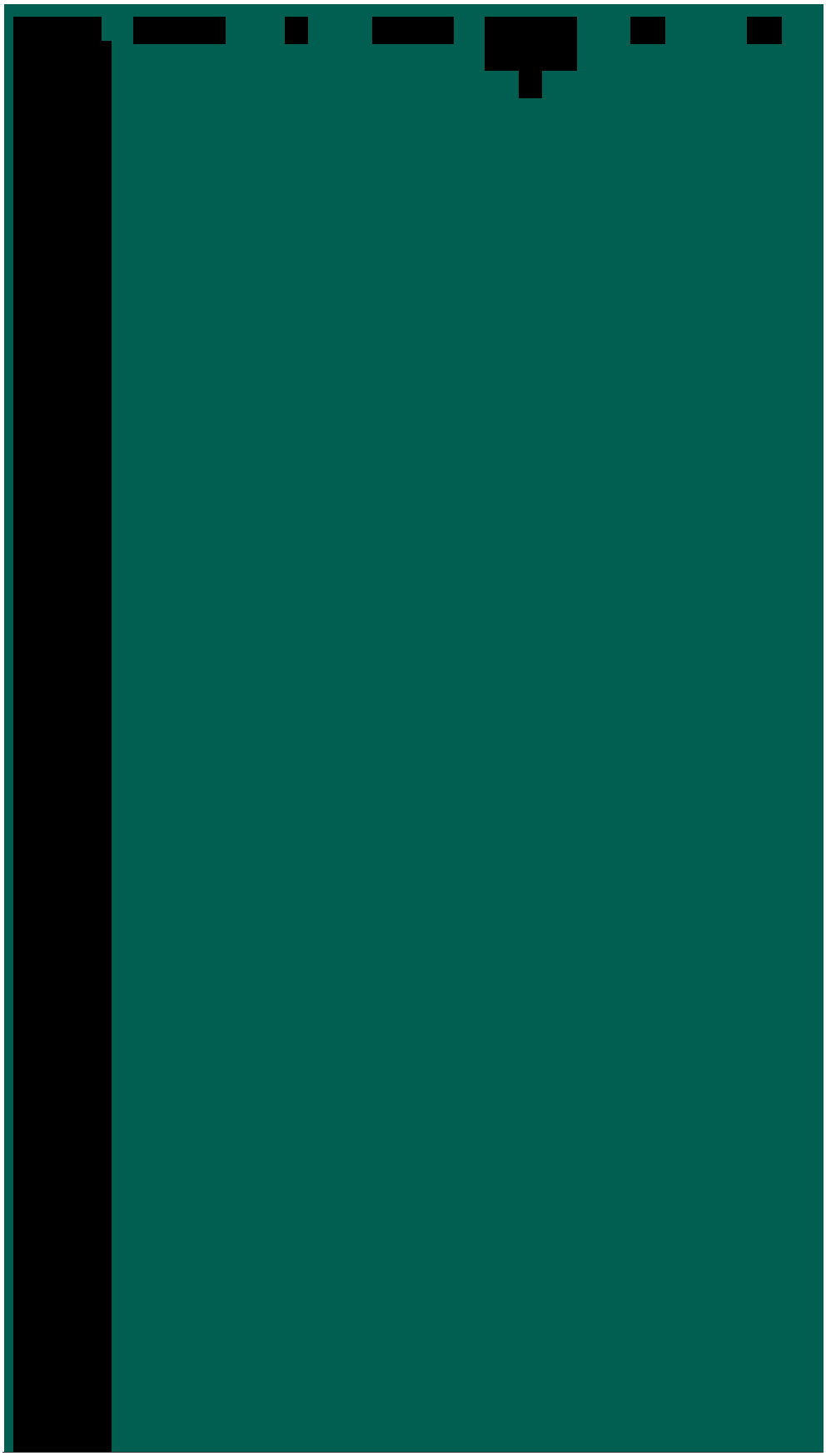


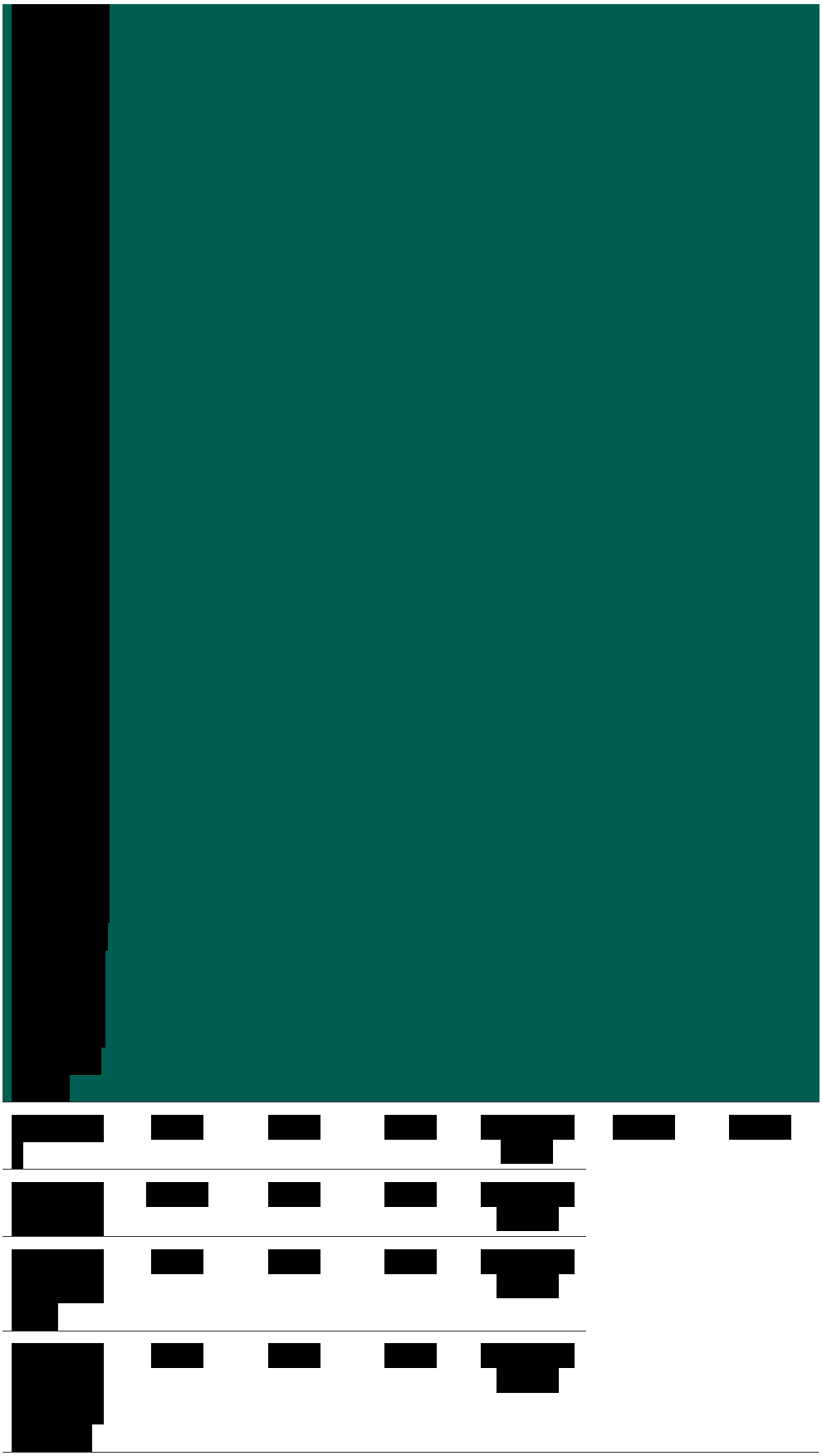












Appendix M. Statistical methods and results for propensity score weighting

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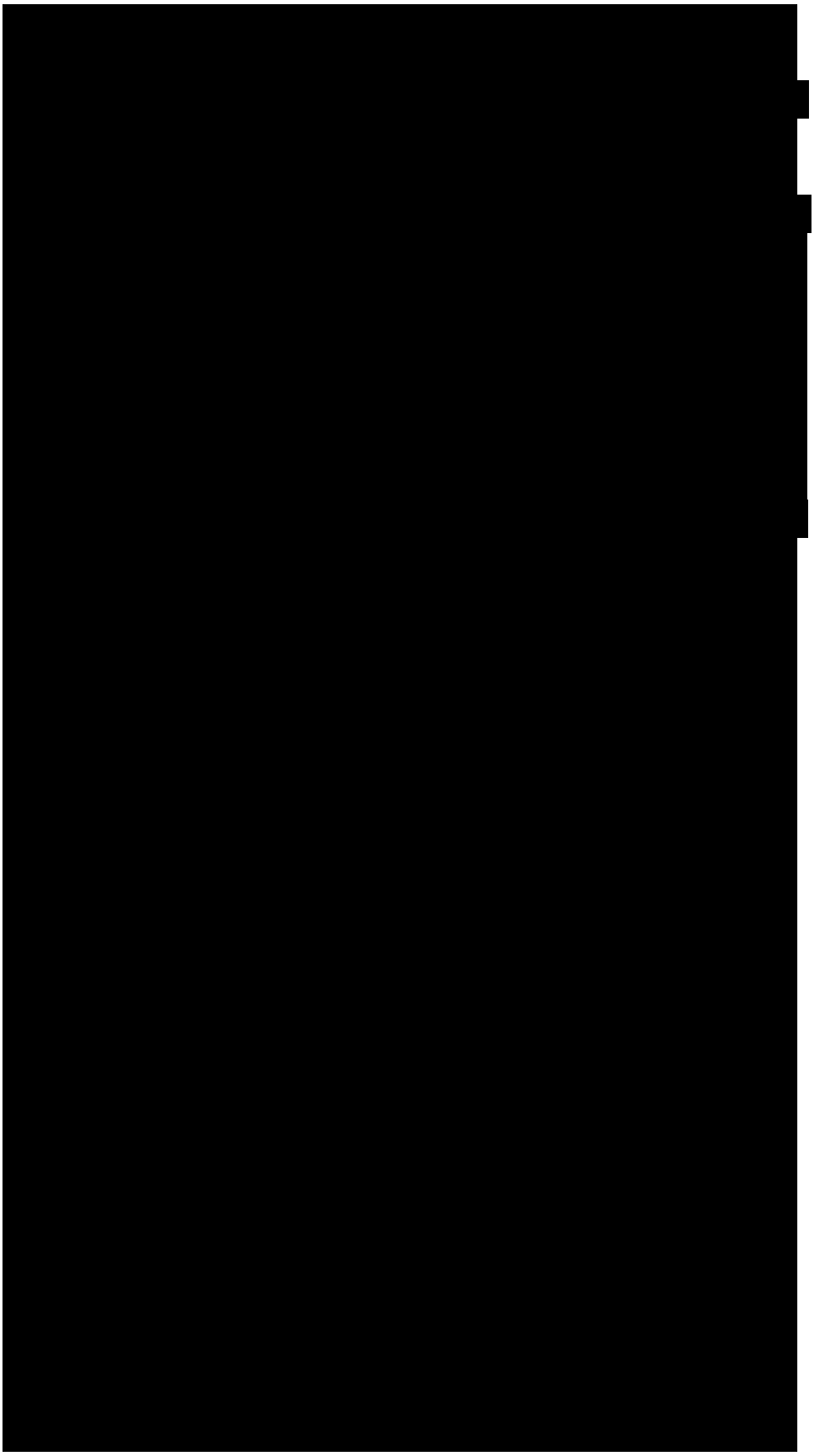
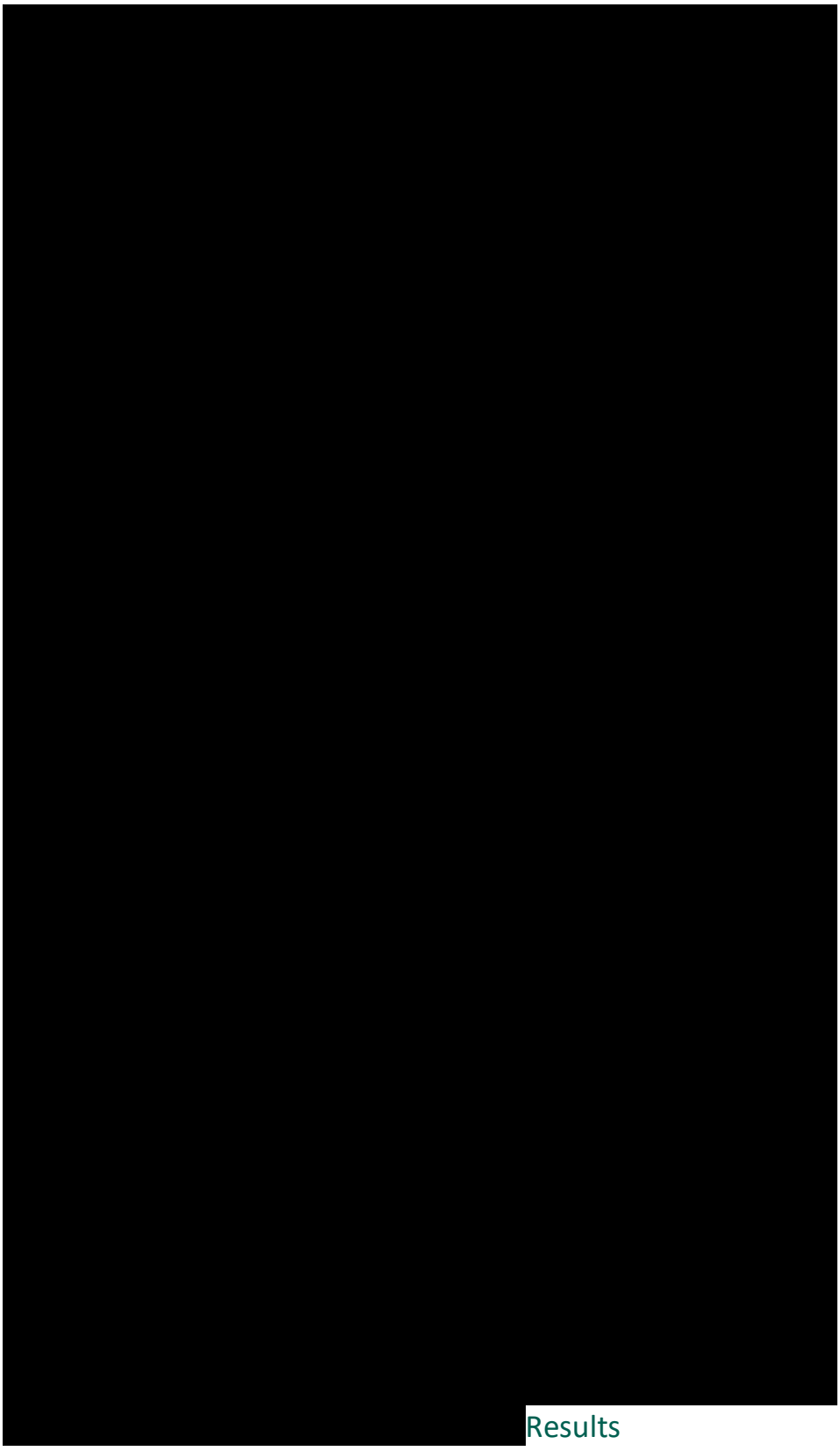




Results

The 1% percentile happens to be the same as the Min and therefore coincidentally truncation doesn't get implemented at the lower end of the weights distribution.

[redacted]

(A) (B)

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Appendix N. List prices for drug compounds

Table 87 Package and list price Rituximab, juni 2023

Drug name	Strength	Package	List price	Source
Rituximab, Mabthera	100 mg	2 stk. conc.inf.l	3115,99 kr.	Medicinpriser.dk
Rituximab, Mabthera	500 mg	1 stk. conc.inf.l	7789,98 kr.	Medicinpriser.dk
Rituximab, Mabthera	1400 mg	1 stk. conc.inf.l	12.377,73 kr.	Medicinpriser.dk
Rituximab, Rixathon	100 mg	2 stk. conc.inf.l	2.675,8 kr.	Medicinpriser.dk
Rituximab, Rixathon	500 mg	1 stk. conc.inf.l	6.687 kr.	Medicinpriser.dk
Rituximab, Ruxience	100 mg	1 stk. conc.inf.l	1.597,94 kr.	Medicinpriser.dk
Rituximab, Ruxience	500 mg	1 stk. conc.inf.l	7.989,71 kr.	Medicinpriser.dk

Table 88 Package and list price Gemcitabin, June 2023

Drug Name	Dose	Package	List price	Source
Gemcitabin “Sandoz”	40 mg/ml	25 ml conc.inf.l	1000 kr.	Medicinpriser.dk
Gemcitabin “Sandoz”	40 mg/ml	50 ml conc.inf.l	1200 kr.	Medicinpriser.dk

Gemcitabin “SUN”	10 mg/ml	120 ml conc.inf.l	310 kr.	Medicinpriser.dk
Gemcitabin “SUN”	10 mg/ml	160 ml conc.inf.l	350 kr.	Medicinpriser.dk
Gemcitabin “SUN”	10 mg/ml	180 ml conc.inf.l	370 kr.	Medicinpriser.dk
Gemcitabin “SUN”	10 mg/ml	200 ml conc.inf.l	385 kr.	Medicinpriser.dk
Gemcitabin “SUN”	10 mg/ml	220 ml conc.inf.l	420 kr.	Medicinpriser.dk
Gemstada	38mg/ml	26,3 ml conc.inf.l	283 kr.	Medicinpriser.dk

Table 89 Package and list price of Oxaliplatin, June 2023

Drug name	Dose	Package	List price	Source
Oxaliplatin “Accord”	5 mg/ml	10 ml conc.inf.l	145 kr.	Medicinpriser.dk
Oxaliplatin “Accord”	5 mg/ml	20 ml conc.inf.l	240 kr.	Medicinpriser.dk
Oxaliplatin “Accord”	5 mg/ml	40 ml conc.inf.l	480 kr.	Medicinpriser.dk
Oxaliplatin “Fresenius Kabi”	5 mg/ml	10 ml conc.inf.l	41,18 kr.	Medicinpriser.dk
Oxaliplatin “Fresenius Kabi”	5 mg/ml	20 ml conc.inf.l	68,80 kr.	Medicinpriser.dk
Oxaliplatin “Fresenius Kabi”	5 mg/ml	40 ml conc.inf.l	127,82 kr.	Medicinpriser.dk

Table 90 Package and list price of Dexamethasone, June 2023

Drug name	Dose	Package	List price	Source

Dexametason “Abcur”	1 mg	20 stk. tablets	133 kr.	Medicinpriser.dk
Dexametason “Abcur”	1 mg	100 stk. tablets	519,2 kr.	Medicinpriser.dk
Dexametason “Abcur”	4 mg	20 stk. tablets	216,59 kr.	Medicinpriser.dk
Dexametason “Abcur”	4 mg	100 stk. tablets	600 kr.	Medicinpriser.dk
Dexametason Abcur	1 mg	100 stk. tablets	522.51 kr.	Medicinpriser.dk
Dexametason “2care4”	4 mg	20 stk. tablets	216,59 kr.	Medicinpriser.dk
Dexametason “2care4”	4 mg	100 stk. tablets	1201,10 kr.	Medicinpriser.dk
Dexametason “Krka”	4 mg	20 stk. tablets	400 kr.	Medicinpriser.dk
Dexametason “Krka”	4 mg	100 stk. tablets	600 kr.	Medicinpriser.dk
Neofordex	40 mg	10 stk	1490 kr.	Medicinpriser.dk

Table 91 Package and list price of Cisplatin, June 2023

Drug name	Dose	Package	List price	Source
Cisplatin “Accord”	1 mg/ml	50 ml conc.inf	100 kr.	Medicinpriser.dk
Cisplatin “Accord”	1 mg/ml	100 ml conc.inf	200 kr.	Medicinpriser.dk
Cisplatin “Ebewe”	1 mg/ml	50 ml conc.inf	401,05 kr.	Medicinpriser.dk
Cisplatin “Ebewe”	1 mg/ml	100 ml conc.inf	493,75 kr.	Medicinpriser.dk

Table 92 Package and list price of Cytarabine, June 2023

Drug name	Dose	Package	List price	Source
Cytarabin "Fresenius Kabi"	100 mg/ml	10 ml conc. Inf.l	100 kr.	Medicinpriser.dk
Cytarabin "Fresenius Kabi"	100 mg/ml	20 ml conc. Inf.l	150 kr.	Medicinpriser.dk
Cytarabin "Accord"	20 mg/ml	5 x 5 ml conc. Inf.l	625 kr.	Medicinpriser.dk
Cytarabin "Accord"	100 mg/ml	10 ml conc. Inf.l	150 kr.	Medicinpriser.dk
Cytarabin "Accord"	100 mg/ml	20 ml conc. Inf.l	200 kr.	Medicinpriser.dk
Cytarabin "Pfizer"	20 mg/ml	5 ml conc. Inf.l	125 kr.	Medicinpriser.dk

Appendix O. Naïve efficacy comparison between EPCORE-NHL-1 (data cut April 2023) and Danish RWE register study

A naïve efficacy data comparison has been conducted between EPCORE-NHL-1 April data cut and the Danish RWE study.

The Danish RWE study

The Danish RWE study was a retrospective study based on the population-based Danish Lymphoma Registry (LYFO) (coverage >95%). Adult patients (≥18 years) diagnosed with DLBCL between 1 January 2012 and 31 December 2019 were screened for eligibility.

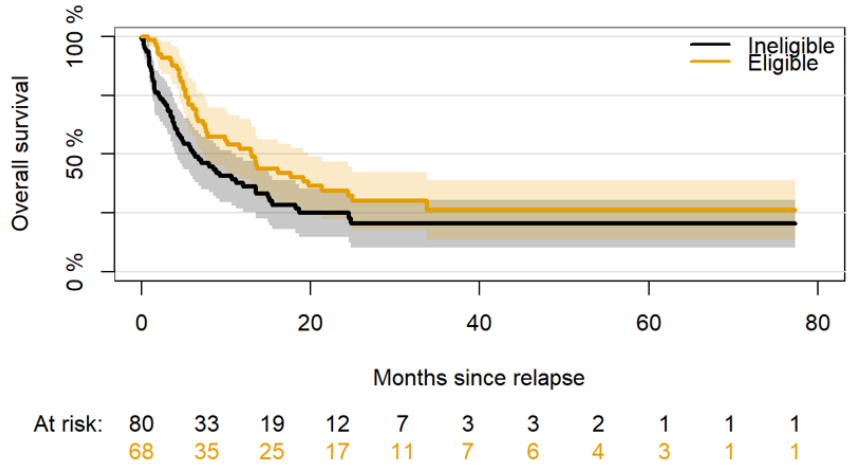
Trial eligibility status was defined as no CNS involvement at relapse, an ECOG performance score (PS) ≤2 and no organ dysfunction. Survival probabilities with OS and PFS were estimated using the Kaplan–Meier estimator. The objective response rate (ORR) was defined as the proportion of patients achieving partial remission (PR) or complete remission (CR). Only patients with DLBCL after the third or subsequent lines of therapy were included.

A total of 3753 patients with DLBCL diagnosed between 1 January 2012 and 31 December 2019 were screened for eligibility and 189 patients (5%) were included. The index line equaled third line (3L) therapy was identified in 182 out of 189 patients. Sixty-eight of 182 patients (37%) fulfilled the defined trial eligibility criteria.

Among the 68 who fulfilled the defined trial eligibility criteria among the 3L candidates, 19 (of 68 eligible patients) were enrolled in clinical trials. The remaining were treated with DHAP/GDP/ICE (n = 12; 7%), low-intensive regimens (n = 17; 9%) or 'other' treatment (n = 20; 11%). The median age was 70.5 years, and 49% had an IPI >2 (Table 93). Moreover. the 2-year OS and PFS were 34.5% (95% CI: 22.3–46.8) and 14.4% (95% CI: 5.3–23.5) respectively. Median OS was 13 months (95% CI: 7.6–19.8) (Figure 20).

More data that support the findings of this study are not available due to Danish privacy regulations.

Figure 20 Overall Survival stratified by trial eligibility. Patients treated with BSC were excluded.



Comparison between EPCORE-NHL-1 (data cut [redacted]) and the Danish RWE study

The patient characteristics of the EPCORE-NHL-1 (data cut [redacted]) DLBCL population (N=139) showed a median age of [redacted] years, and [redacted] had an IPI >2 (≥3). Moreover, [redacted] were subjects with primary refractory disease (Table 93).

Table 93 Baseline characteristics and survival outcomes in EPCORE-NHL-1 (data cut [redacted]) and the Danish RWE study

	EPCORE-NHL-1 (data cut [redacted]) N=139	All eligible patients from The Danish RWE study N = 189	Trial eligible patients from The Danish RWE study N = 68
Median age (years)	[redacted]	71.0	70.5
IPI >2	[redacted]	51.9%	49%
Subjects with primary refractory disease	[redacted]	75.7%	Not reported
2-year OS (% CI)	[redacted]	25.1% (18.5–31.7)	34.5% (22.3–46.8)
Median OS (months)	[redacted]	5.8 (4.6–7.8)	13 (7.6–19.8)
2-year PFS (% CI)	[redacted]	11.7% (6.8–16.7)	14.4% (5.3–23.5)
Median PFS (months)	[redacted]	2.8 (2.0–3.2)	Not reported

Kaplan-Meier curves of PFS and OS for the unadjusted DLBCL population (N=139, data cut [redacted]) are presented in Figure 21 and Figure 22 below. The median observed PFS

is [redacted] months [95% CI: [redacted]] and the median observed OS is [redacted] months [95% CI: [redacted]].

Figure 21 Kaplan-Meier curve of PFS for the unadjusted DLBCL population

Figure 22 Kaplan-Meier curve of OS for the unadjusted DLBCL population

Discussion

The results show that EPCORE-NHL-1 trial data have [redacted] than in the Danish RWE study. The median age differs with [redacted] years (where the DLBCL population in EPCORE-NHL-1 trial is [redacted]) and the IPI score is [redacted]. The survival outcomes show also [redacted] OS and PFS (IRC assessment) with epcoritamab compared to R-CIT combinations in the Danish RWE study, with a median PFS of [redacted] months and median OS of [redacted] months in the EPCORE-NHL-1 trial compared to median OS of [redacted] months in the Danish RWE study on the trial eligible patients.

This is a naïve indirect comparison where an adjusted ITC has not been possible to conduct between EPCORE-NHL-1 and the trial eligible patient population in AL-Mashhadi et al. (N=68), due to lack of data availability for the comparator arm (in this case data access to the Danish RWE study) and too many differences between the study populations (e.g., in terms of age and disease severity). Specifically primary refractory is an important prognostic factor and has not been reported for the eligible trial population.

However, we can still conclude that epcoritamab shows beneficial survival outcomes compared to conventional CIT treatments for 3L DLBCL patients compared to both the latest RWE publication on a Danish 3L DLBCL population and to the still largest multi-center patient reported outcome data from SCHOLAR-1.

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