Norwegian Medical Products Agency

Setmelanotide (Imcivree)

For the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above.

ID2021_012

Single technology assessment of medicine funded by the specialist health service

05/03/2025

Foreword

The regional health authorities are responsible for the national system for the introduction of new methods in specialized healthcare, called "Nye metoder". The principles for prioritisation in the Norwegian healthcare sector are outlined in the white paper (Meld. St. 34 (2015-2016)), “Verdier i pasientens helsetjeneste – Melding om prioritering,” approved by the Parliament in November 2016 (“Principles for priority setting in health care” known as the “Priority-setting White Paper”). "Nye metoder" aims to ensure that medicines considered for introduction into specialized healthcare are evaluated systematically, thereby contributing to the responsible use of resources in the healthcare services. The system “Nye metoder” has been legally established since 2019 and is further described on the website, www.nyemetoder.no.

Before a new medicine can be introduced into specialized healthcare, a decision for its implementation must be made by the Decision Forum. This is a decision-making body consisting of the directors of the regional health authorities. The Decision Forum makes the final decision on the introduction of new medicines into specialized healthcare after a comprehensive evaluation of three prioritisation criteria: benefit, resource use, and severity. The Norwegian Medical Products Agency (NOMA) is responsible for conducting health technology assessments (HTA) that highlight the prioritisation criteria for the specific use of the method. The HTA is part of the decision-making basis for the Decision Forum.

The holder of the drug's marketing authorization is responsible for submitting the necessary documentation to NOMA before the HTA, as requested by the Ordering Forum. NOMA can also provide guidance to the pharmaceutical company.

The benefit is measured by how many good years of life the new treatment provides on average for patients in the relevant patient group compared to relevant treatment practices. A good year of life means a year with "perfect" health, i.e., completely without illness/discomfort, defined in professional terms as a quality-adjusted life year (1 QALY). This is a standardized calculation method that makes it possible to compare the benefit of different treatments used for various diseases.

Resource use is calculated based on the average drug cost and other healthcare resource usage, compared to the relevant treatment practice.

Severity is measured by how many QALYs patients in the relevant group lose on average due to the absence of the evaluated treatment.

NOMA evaluates the submitted data on clinical outcomes, severity, reported resource use, assumptions for the analysis, and the results of the presented analysis. NOMA may request additional information from the drug’s marketing authorization holder, clinical experts, and users, and may perform its own cost-effectiveness calculations. NOMA does not assess the benefit-risk balance, as this is evaluated by the European Medicines Agency (EMA) during the marketing authorization procedure.

NOMA does not have decision-making authority in the "Nye metoder"-system, but the HTA reports are part of the decision-making basis for the Decision Forum. The Hospital Procurement Trust HF negotiates the price of new medicines in “Nye metoder”. The price of a medicine affects the treatment cost, and thus the cost per quality-adjusted life year. The amount the society is willing to pay for a QALY is linked to the severity of the disease.

Some of the information in NOMA's reports may be confidential. NOMA considers the pharmaceutical company’s requests for exceptions from public disclosure and decides whether the information is

confidential (cf. the Public Administration Act §13,1, see here for guidelines). All HTA reports are published and publicly available on NOMA's website (www.dmp.no).

Summary

Methods

Single technology assessment of Imcivree (setmelanotide). The Norwegian Medical Products Agency (NOMA) has evaluated the priority criteria severity, benefit, and resource use, as well as uncertainty in the documentation and budget impact. The European Medicines Agency (EMA) has determined that setmelanotide has a benefit that outweighs the risks associated with its use, and the European Commission has issued a marketing authorisation for an extension of the indication for setmelanotide to include genetically confirmed Bardet-Biedl syndrome (BBS). The medicine was designated an orphan medicine status. This means that it was developed for use against a rare, life-threatening or chronically debilitating condition or, for economic reasons, it would be unlikely to have been developed without incentives.

For the single technology assessment, the relative benefit and incremental cost of the new method compared to current treatment options in Norwegian clinical practice are relevant. NOMA's assessment is based on documentation submitted by Rhythm Pharmaceuticals Netherlands B.V. Three medical experts have been appointed for the assignment. They have assisted NOMA with clarifications regarding the current treatment for the patient group and estimated number of eligible patients.

Overview of the single technology assessment	
Order	ID2021_012: A single technology assessment with a cost-utility analysis is conducted by the Norwegian Medical Products Agency for setmelanotide (Imcivree) for the treatment of obesity and hunger control associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children aged 6 and up. A price document is prepared by the Norwegian Hospital Procurement Trust HF.
Pharmaceutical company	Rhythm Pharmaceuticals Netherlands B.V.
Product	Imcivree
Active ingredient	Setmelanotide
ATC-code	A08AA12
Current indication	For the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 2 years of age and above*
Mechanism of action	Setmelanotide attaches to and activates a receptor called melanocortin receptor 4, which is normally activated through leptin and melanocyte-stimulating hormone, promoting a feeling of fullness after eating. By attaching to this receptor directly setmelanotide is expected to reduce excessive food intake and obesity.
Posology	Setmelanotide is titrated up to 3 mg/day over a period of 3 weeks according to age-specific schemes. Setmelanotide is administered once daily as a subcutaneous injection.
Health economic analysis assessed by NOMA	Yes ☒ Type: Cost-per-QALY-analysis No ☐

*The approved indication was changed to include children aged 2 and up (from 6 and up originally) after NOMA received documentation from Rhythm Pharmaceuticals and had started the assessment. This assessment covers the initially approved indication, from 6 years and up.

Disease

Obesity in Bardet-Biedl syndrome	
About the disease	Bardet-Biedl syndrome (BBS) is a rare genetic disorder that affects multiple body systems. It is characterized by symptoms such as vision loss due to retinal degeneration, obesity, kidney abnormalities, and extra fingers or toes (polydactyly). Cognitive impairment and developmental delays are also common, as well as hormonal imbalances that can impact growth and fertility. BBS is inherited in an autosomal recessive pattern and results from mutations in one of several genes related to cellular function.
Patient population in Norway	There are 63 patients with BBS registered at the Centre for rare disorders in Norway (2024), but this registry is not complete. Around 90% of patients with BBS are obese and may be eligible for treatment with setmelanotide.
Treatment in Norwegian clinical practice	According to medical experts consulted by NOMA, patients with BBS and obesity are treated similarly as other patients with obesity. Today's best supportive care (BSC) includes dietary advice with ongoing support, advice regarding physical activity, and, for some, weight-reducing medications.

Health economic analysis

Description of the health economic analysis underpinning NOMA's assessment	
Population	Patients with BBS, aged ≥6 years who have obesity
Intervention	Setmelanotide in addition to BSC
Comparator	BSC
Outcome	Reduction in body weight/BMI/BMI Z-score, QALYs, life years, resource use
Main source of effect data	RM-493-023, a phase 3, double-blind, placebo-controlled multicentre study, with open-label extension
Analytical perspective	Extended healthcare perspective
Time horizon	Lifetime

BBS, Bardet-Biedl syndrome; BMI, body mass index; BSC, best supportive care; QALYs, quality-adjusted life years

NOMA has evaluated the submitted health economic analysis from Rhythm Pharmaceuticals and the assumptions behind it. NOMA has conducted its own analyses based on the submitted analysis. The results from the analysis that NOMA considers most likely are presented in the table below. Results are shown per patient, based on discounted figures and the maximum AUP excluding VAT for all medications included in the analysis. The results from the health economic model must be interpreted with caution due to high uncertainty in input-data and modelling.

	Setmelanotide	BSC	Difference
Total cost (NOK)	32,937,814	1,404,432	31,533,383
Total QALYs Total life years	12.75 19.33	12.23 18.85	0.52 0.47
Incremental Cost (NOK) per gained QALY Incremental Cost (NOK) per gained year of life			60,559,608 66,485,892

Assessment of priority criteria, budget impact, and uncertainty in the implementation of the new method

NOMA's assessment of utility:

The phase 3, double-blind, placebo-controlled multicentre study RM-493-023 evaluated the effect of daily subcutaneous injection of setmelanotide compared with placebo over a period of 14 weeks, followed by a 52-week open-label phase during which all patients received setmelanotide. The study initially included 32 pivotal patients with BBS, who were obese (BMI ≥30 kg/m2 for patients aged ≥16 years; body weight ≥97th percentile for age and sex on growth chart assessment for patients aged 6 to 15 years). A protocol amendment allowed for the inclusion of a supplemental cohort of 12 additional patients. All primary and key secondary endpoints were based on data at 52-weeks (open-label, single arm). During the trial, paediatric patients in both study arms received nutritional counselling and monitoring to ensure they had adequate nutritional intake for proper growth and development. Adult and adolescent patients in both study arms did not receive specific guidance on lifestyle modifications regarding dietary intake or physical activity.

Results from the 14-week placebo-controlled study period showed a statistically significant reduction in BMI (mean difference: -4,5%, 95 % CI: -6,5, -2,5) and body weight (mean difference: -3,6%, 95% CI: -6,3, -0,9) in adults, a statistically significant reduction in BMI Z-score (mean difference: -0,32, 95% CI: -0,5, -0,14) in children, and are indicative of a lower 'daily hunger score' (mean difference: -14,4%, 95 % CI: -31,9, 3,1), in patients treated with setmelanotide compared to placebo. The long-term effect of setmelanotide is uncertain due to the lack of a control group and open-label design beyond the 14-week double blind, placebo-controlled study phase.

No data from the 14-week placebo-controlled study period was used in the health economic model. Instead, Rhythm Pharmaceuticals modelled treatment response based on uncontrolled data obtained at 52-weeks of treatment. A responder was defined as an adult patient who achieved ≥10% weight loss or a paediatric patient who achieved ≥0.2 reduction in BMI Z-score after 52 weeks of setmelanotide treatment. Among pivotal adult patients treated with setmelanotide, 7 of 15 (46,7%; 95% CI: 18,6, 55,9) were defined as responders, and among pivotal paediatric patients treated with setmelanotide, 12 of 14 (85,7%; 95% CI: 57,2, 98,2) were defined as responders. Patients treated with best supportive care (BSC) were assumed to have 0% response in the model submitted by Rhythm Pharmaceuticals.

In NOMA's main analysis it is estimated that patients treated with setmelanotide in addition to BSC, on average, gain 0.52 QALYs and 0.47 life-years (LYs) compared to those treated with BSC alone. Health benefits are primarily derived from reductions in BMI and BMI Z-scores, and more time spent in lower categories.

Overall, the most common treatment-emergent adverse events during the placebo-controlled period, were skin hyperpigmentation: 59,1%; Injection site erythema: 45,5%, Injection site pruritus: 31,8%, Injection site bruising: 27,3% and vomiting: 27,3%. Disutility and costs related to injection site reactions, nausea and vomiting occurring during the first two weeks of treatment were included in the health economic model.

NOMA's assessment of resource use

The yearly cost per patient for setmelanotide treatment in year 1 is approximately NOK 2.96 million increasing to approximately NOK 2.99 million in subsequent years. This estimate is based on the maximal reimbursable price (AUP) excluding VAT and assumes a patient distribution of 32% paediatric and 68% adult BBS patients. The health economic analysis also includes costs associated with BSC,

which is assumed to be similar for both groups. The average total cost for a treatment course with setmelanotide is about 32 million NOK per patient (discounted). This represents an increase of 31.5 million NOK per patient compared to the total costs estimated for treatment with BSC.

NOMA has estimated that the incremental cost for setmelanotide compared to BSC, based on the maximal reimbursable price (AUP) excluding VAT for all medications included in the analysis, is:

NOK 60.5 million per gained QALY
NOK 66.5 million per gained year of life

NOMA's assessment of severity:

The severity of the condition can influence whether the costs are considered reasonable in relation to the benefits of the treatment. NOMA has estimated that BBS treated with BSC has an absolute shortfall of approximately 30 QALY's.

Absolute shortfall for the sequela of obesity, targeted by setmelanotide, will be significantly lower but could not be reliably calculated in the submitted model. Absolute shortfall calculated for obesity in a previous single technology assessment was less than 10 QALYs.

Due to the lack of valid data on the impact of hyperphagia on health-related quality of life, severity for this aspect of the syndrome could not be calculated, although it is expected to be targeted by setmelanotide to an unknown extent.

NOMA's assessment of budget impact:

NOMA has estimated that the impact on the pharmaceutical budget of the specialist healthcare services from implementing setmelanotide for the treatment of BBS will be approximately NOK 145 million per year in the fifth budget year. It is assumed that 39 patients will be treated with setmelanotide in the fifth budget year, and the calculations are based on the maximal reimbursable price (AUP) including VAT for all medicines included in the analysis. The budget calculations are uncertain and simplified.

NOMA's assessment of uncertainty:

The study RM-493-023 included relevant patients and is regarded suitable as documentation for a single technology assessment. However, it is noteworthy that study patients received no or limited guidance on diet and physical activity, which differs from Norwegian clinical practice and affects the generalizability of the study findings. Additionally, the long-term effects of setmelanotide remain uncertain due to the limited duration of the placebo-controlled phase, especially considering that the treatment is intended for long-term use.

Rhythm Pharmaceuticals' assumption of a 0% response rate in the BSC-arm and the use of uncontrolled (open-label) response rates in the setmelanotide-arm, in the health economic model is an important source of uncertainty. As a result, NOMA assumes that the modelled response rate of setmelanotide is overestimated to an unknown extent.

In their base case analysis Rhythm Pharmaceuticals assumed that all treatment responders transition from a state of severe hyperphagia to a state of mild hyperphagia, and thereby a higher quality of life. This assumption was discarded by NOMA due to the lack of supporting clinical data, as hyperphagia was not assessed in the clinical study. Thus, only changes in BMI or BMI Z-score were included as

treatment effects in NOMA’s main analysis. The lack of clinical data hampers estimation of any treatment effect setmelanotide beyond weight-related outcomes.

Utility values used in the health economic model are also considered a major source of uncertainty. While Rhythm Pharmaceuticals collected utility values directly from their clinical study, these were discarded in favour of alternative utility weights derived from a vignette study, assumptions, and external literature. NOMA emphasizes that the utility values used in the model may not adequately reflect BBS-specific health-related quality of life (HRQoL), as they were derived from general obesity populations and mapped to EQ-5D-3L using external data and algorithms. Further, the methodology for deriving these values is poorly described. Although the choice to use externally derived utility values was considered a pragmatic solution given the trial limitations having few patients, this approach introduces uncertainty in the results.

NOMA's main analysis is based on the analysis submitted by Rhythm Pharmaceuticals and largely uses the same assumptions, although the model and assumptions have not been fully validated. Despite this, the evaluations made are considered sufficient to address the prioritisation criteria. However, since the model with its inputs and assumptions has not been fully validated, it cannot be automatically accepted in other health technology assessments.

NOMA assesses that there is significant uncertainty related to the documentation. High uncertainty regarding documentation and calculation methods should, all else being equal, result in lower priority, according to the Priority-setting White Paper.

Sammendrag

Metode

Metodevurdering av legemiddelet Imcivree (setmelanotid). Direktoratet for medisinske produkter (DMP) har vurdert prioriteringskriteriene alvorlighet, nytte og ressursbruk, samt usikkerhet i dokumentasjonen og budsjettkonsekvenser. Det europeiske legemiddelbyrået (EMA) har vurdert at setmelanotid har en nytte som overstiger risikoen ved bruk, og Europakommisjonen har utstedt indikasjonsutvidelse for markedsføringstillatelsen til setmelanotid slik at den omfatter genetisk bekreftet Bardet-Biedl syndrom (BBS). Setmelanotid ble utpekt som et orphan-legemiddel. Dette betyr at det ble utviklet for bruk mot en sjelden, livstruende eller kronisk tilstand, eller at det, av økonomiske årsaker, sannsynligvis ikke ville ha blitt utviklet uten insentiver. For metodevurderingen er det nytte og kostnader av den nye metoden sammenlignet med dagens behandlingsalternativ i norsk klinisk praksis som er relevant.

DMPs vurdering tar utgangspunkt i dokumentasjon innsendt av Rhythm Pharmaceuticals Netherlands B.V. Det er oppnevnt tre medisinske fageksperter til oppdraget om metodevurdering. Disse har bistått DMP med avklaringer rundt dagens behandling for pasientgruppen og estimert antall aktuelle pasienter.

Oversikt over metodevurderingen	
Bestilling	ID2021_012: En metodevurdering med en kostnad-nytte-analyse gjennomføres ved Direktoratet for medisinske produkter for setmelanotid (Imcivree) til behandling av fedme og kontroll av sult assosiert med genetisk bekreftet Bardet-Biedl syndrom (BBS) hos voksne og barn fra 6 år og oppover. Prisnotat utarbeides ved Sykehusinnkjøp HF.
Legemiddelfirma	Rhythm Pharmaceuticals Netherlands B.V.
Preparat	Imcivree
Virkestoff	Setmelanotid
ATC-kode	A08AA12
Aktuell indikasjon	For behandling av fedme og kontroll av sult assosiert med genetisk bekreftet Bardet-Biedl syndrom (BBS) hos voksne og barn fra 2 år og oppover*
Virkningsmekanisme	Setmelanotid binder seg til og aktiverer en reseptor kalt melanokortinreseptor 4, som normalt aktiveres gjennom leptin og melanocyttstimulerende hormon, og fremmer en metthetsfølelse etter måltider. Ved å binde seg til denne reseptoren, forventes setmelanotid å redusere overdrevent matinntak og fedme.
Dosering	Setmelanotid titreres opp til 3 mg/dag over en periode på 3 uker i henhold til aldersspesifikke tabeller. Setmelanotid administreres én gang daglig som subkutan injeksjon.
Helseøkonomisk analyse vurdert av DMP	Ja ☒ Type: Kostnad-per-QALY Nei ☐

*Den godkjente indikasjonen ble endret til å inkludere barn fra 2 år og oppover (fra opprinnelig 6 år og oppover) etter at DMP mottok dokumentasjon fra Rhythm Pharmaceuticals og hadde startet vurderingen. Denne vurderingen omfatter den opprinnelig godkjente indikasjonen, fra 6 år og oppover.

Sykdom

Fedme ved Bardet-Biedl syndrom	
Om sykdommen	Bardet-Biedl-syndrom (BBS) er en sjelden, arvelig lidelse som påvirker flere kroppssystemer. Tilstanden kjennetegnes av symptomer som synstap på grunn av retinal degenerasjon, fedme, forandringer i nyrene og ekstra fingre eller tær (polydaktyli). Kognitiv svikt og utviklingsforsinkelser er også vanlige, sammen med hormonelle ubalanser som kan påvirke vekst og fruktbarhet. BBS arves i et autosomalt recessivt mønster og skyldes mutasjoner i ett av flere gener knyttet til cellulær funksjon.
Pasientgrunnlag i Norge	Det er registrert 63 pasienter med BBS hos Senter for sjeldne sykdommer i Norge (2024), men dette registeret er ikke komplett. Rundt 90 % av pasienter med BBS har fedme og kan være aktuelle for behandling med setmelanotid.
Behandling i norsk klinisk praksis	Ifølge medisinske fageksperter som DMP har konsultert, behandles pasienter med BBS og fedme på samme måte som andre pasienter med fedme. Standard støttebehandling består av kostholdsråd med kontinuerlig støtte, råd om fysisk aktivitet, og for noen, vektreduserende medisiner.

Helseøkonomisk analyse

Beskrivelse av den helseøkonomiske analysen DMP har lagt til grunn	
Populasjon	Pasienter med BBS og fedme ≥ 6 år
Intervensjon	Setmelanotid som tillegg til standard støttebehandling
Komparator	Standard støttebehandling
Utfall	Reduksjon i kroppsvekt/BMI/BMI Z-skår, QALYs, leveår, ressursbruk
Hovedkilde til effektdata	RM-493-023, en fase 3, dobbelblindet, placebokontrollert multisenter studie, med åpen forlengelsesfase
Analyseperspektiv	Utvidet helsetjenesteperspektiv
Tidshorisont	Livstid

BBS, Bardet-Biedl syndrom; BMI, kroppsmasseindeks; BSC, beste støttende behandling; QALYs, livskvalitetsjusterte leveår

DMP har vurdert innsendt helseøkonomisk analyse fra Rhythm Pharmaceuticals og forutsetningene for denne. DMP har gjennomført egne analyser med utgangspunkt i den innsendte analysen. Resultatene fra analysen DMP mener er mest sannsynlig, er presentert i tabellen under. Resultater vises per pasient, basert på diskonterte tall og maksimal AUP uten mva. for alle legemidler som inngår i analysen. Resultatene må tolkes med forsiktighet på grunn av høy usikkerhet i input-data og modellering.

	Setmelanotid	Standard støttebehandling	Differanse
Totale kostnader (NOK)	32 937 814	1 404 432	31 533 383
Totale QALYs Totale leveår	12,75 19,33	12,23 18,85	0,52 0,47
Merkostnad (NOK) per vunnet QALY Merkostnad (NOK) per vunnet leveår			60 559 608 66 485 892

Vurdering av prioriteringskriteriene, budsjettkonsekvenser og usikkerhet ved innføring av den nye metoden

DMPs vurdering av nytte:

Den dobbelblindede, placebokontrollerte fase 3-studien RM-493-023 undersøkte effekt og sikkerhet av daglig subkutan injeksjon med setmelanotid sammenlignet med placebo over en periode på 14 uker, etterfulgt av en åpen fase på 52 uker hvor alle pasientene mottok setmelanotid. Studien inkluderte opprinnelig 32 pivotale pasienter med BBS og fedme (BMI ≥30 kg/m² for pasienter ≥16 år; kroppsvekt ≥97. persentil for alder og kjønn på vekstkurve for pasienter i alderen 6 til 15 år). En protokollendring åpnet for inklusjon av en supplerende kohort med 12 ekstra pasienter. Alle primære og viktige sekundære endepunkter var basert på data fra 52 uker (åpen, enarmet). Pediatriske pasienter i begge studiearmer mottok ernæringsrådgivning og overvåking for å sikre at de hadde tilstrekkelig ernæringsinntak for riktig vekst og utvikling i løpet av studieperioden. Pasienter i ungdoms- og voksenalder i begge studiearmer fikk ikke råd om livsstilsendringer angående kosthold eller fysisk aktivitet i løpet av studieperioden.

Resultater fra den 14 uker lange placebokontrollerte studieperioden viste en statistisk signifikant reduksjon i BMI (gjennomsnittlig forskjell: -4,5 %; 95 % KI: -6,5, -2,5) og kroppsvekt (gjennomsnittlig forskjell: -3,6 %; 95 % KI: -6,3, -0,9) hos voksne, en statistisk signifikant reduksjon i BMI Z-skår (gjennomsnittlig forskjell: -0,32; 95 % KI: -0,5, -0,14) hos barn, og indikerte lavere 'daily hunger score' (gjennomsnittlig forskjell: -14,4 %; 95 % KI: -31,9, 3,1), hos pasienter som fikk setmelanotid sammenlignet med placebo. Langtidseffekten av setmelanotid er usikker på grunn av manglende kontrollgruppe og åpent studiedesign utover den 14 uker lange dobbeltblindede, placebo-kontrollerte studieperioden.

Ingen data fra den placebokontrollerte studieperioden ble brukt i den helseøkonomiske modellen. I stedet har Rhythm Pharmaceuticals modellert behandlingseffekt ved bruk av ukontrollerte data fra 52-ukers oppfølging. En responder ble definert som en voksen pasient som oppnådde ≥10% vektreduksjon eller en pediatrisk pasient som oppnådde ≥0,2 reduksjon i BMI Z-skår etter 52 ukers behandling med setmelanotid. Blant pivotale voksne pasienter ble 7 av 15 (46,7 %; 95 % KI: 18,6, 55,9) definert som respondere, blant pivotale pediatriske pasienter ble 12 av 14 (85,7 %; 95 % KI: 57,2, 98,2) definert som respondere. Responsraten blant pasienter behandlet med standard støttebehandling ble antatt å være 0 % i den helseøkonomiske modellen fra Rhythm Pharmaceuticals.

I DMPs hovedanalyse estimeres det at pasienter som behandles med setmelanotid i tillegg til standard støttebehandling i gjennomsnitt får 0,52 flere gode leveår og 0,47 flere leveår sammenlignet med pasienter som kun får standard støttebehandling. Setmelanotid bedrer livskvaliteten ved å redusere BMI og BMI Z-skår og det er den forlengede tiden i lavere kategorier at helsegevinsten skjer.

Samlet sett var de vanligste behandlingsrelaterte bivirkningene som oppsto i løpet av den placebokontrollerte studieperioden: hyperpigmentering i huden (59,1 %); rødhet på injeksjonsstedet (45,5 %); pruritus (kløe) på injeksjonsstedet (31,8 %); blåmerker på injeksjonsstedet (27,3 %) og oppkast (27,3 %). Nyttetap og kostnader knyttet til reaksjoner på injeksjonsstedet, kvalme og oppkast som oppsto i løpet av de to første ukene av behandling ble inkludert i den helseøkonomiske modellen.

DMPs vurdering av ressursbruk:

Legemiddelkostnaden per pasient for behandling med setmelanotid er om lag 2,96 millioner NOK i første behandlingsår og øker til om lag 2,99 millioner i påfølgende år. Estimatet er basert på maksimal AUP uten mva. og forutsetter en aldersfordeling med 32 % pediatriske og 68 % voksne pasienter med BBS. Den helseøkonomiske analysen inkluderer også kostnader knyttet til standard støttebehandling, som forutsettes å være lik i begge grupper. Gjennomsnittlig totalkostnad for et behandlingsløp med

setmelanotid er ca. 32 millioner NOK per pasient (diskontert). Dette er 31,5 millioner NOK mer per pasient sammenlignet med totalkostnadene estimert for behandling med standard støttebehandling.

DMP har estimert at merkostnad for setmelanotid sammenliknet med standard støttebehandling basert på maksimal AUP uten mva. for alle legemidler som inngår i analysen er:

60,5 millioner NOK per vunnet kvalitetsjusterte leveår (QALY)
66,5 millioner NOK per vunnet leveår

DMPs vurdering av alvorlighet:
Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. DMP har estimert at BBS behandlet med standard støttebehandling har et absolutt prognosetap (APT) på om lag 30 QALYs.

APT for følgetilstanden fedme, som behandling med setmelanotid er rettet mot, vil være vesentlig lavere, men kunne ikke beregnes på en troverdig måte i innsendt modell. APT beregnet ved fedme i en tidligere metodevurdering var mindre enn 10 QALYs.

Grunnet mangel på data om hvordan hyperfagi påvirker helserelatert livskvalitet, kunne ikke alvorlighetsgraden av dette aspektet ved BBS beregnes, selv om det forventes å bli påvirket av setmelanotid i en ukjent grad.

DMPs vurdering av budsjettvirkninger:
DMP har estimert at budsjettvirkningen for sykehusenes legemiddelbudsjett ved å ta i bruk setmelanotid ved behandling av BBS vil være om lag 145 millioner NOK i det femte budsjettåret. Det er lagt til grunn at 39 pasienter vil behandles med setmelanotid i det femte budsjettåret, og beregningene er basert på maksimal AUP med mva. for alle legemidler som inngår i analysen. Budsjettberegningene er usikre og forenklede.

DMPs vurdering av usikkerhet:
Studien RM-493-023 inkluderte relevante pasienter og er egnet som dokumentasjonsgrunnlag for en metodevurdering. Studiepasientene mottok imidlertid lite eller ingen rådgiving knyttet til ernæring eller fysisk aktivitet underveis i studien, noe som skiller seg fra norsk klinisk praksis og påvirker overførbarheten av studieresultatene. I tillegg er langtidseffekten av setmelanotid usikker på grunn av den korte varigheten av den placebokontrollerte studieperioden, særlig med tanke på at dette er en behandling som er ment for langtidsbruk.

Rhythm Pharmaceuticals sin antagelse om 0 % respons blant pasienter som mottar standard støttebehandling og bruk av ukontrollerte responsrater fra den åpne studieperioden for setmelanotid i den helseøkonomiske modellen er viktige kilder til usikkerhet. Som følge av dette, vurderer DMP at den modellerte behandlingseffekten av setmelanotid er overestimert i ukjent grad.

I Rhythm Pharmaceutials sin grunnanalyse forutsettes det at alle pasienter som defineres som respondere går fra helsestadiet alvorlig hyperfagi til mild hyperfagi, og dermed får vesentlig bedre livskvalitet. DMP har ikke godtatt denne antagelsen på grunn av mangel på støttende kliniske data, da hyperfagi ikke ble målt i den kliniske studien. Følgelig er det kun endringer i BMI og BMI Z-skår som driver den modellerte behandlingseffekten av setmelanotid i DMPs hovedanalyse. Estimering av behandlingseffekt utover vektrelaterte utfall begrenses imidlertid av mangelen på kliniske data.

Nyttevektene som er benyttet i den helseøkonomiske modellen er også en viktig kilde til usikkerhet. Selv om Rhythm Pharmaceuticals samlet inn nyttevekter i den kliniske studien, ble disse forkastet til fordel for alternative nyttevekter basert på en vignettstudie, antakelser og ekstern litteratur. DMP understreker at nyttevektene som er benyttet i modellen muligens ikke reflekterer helserelatert livskvalitet spesifikt for pasienter med BBS, da de er utledet fra generelle populasjoner med fedme og mappet til EQ-5D-3L ved bruk av eksterne data og algoritmer. Videre er metoden for å utlede disse verdiene mangelfullt beskrevet. Selv om bruk av eksterne nytteverdier ble ansett som en pragmatisk løsning gitt begrensningene med få pasienter i studien, introduserer denne tilnærmingen usikkerhet i resultatene.

DMPs hovedanalyse er basert på Rhythm Pharmaceutical sin innsendte analyse, og bruker i stor grad de samme antagelsene, uten at modellen og antagelsene er fullstendig validert. De vurderingene som er gjort anses å være tilstrekkelige for å belyse prioriteringskriteriene og på et hensiktsmessig nivå med tanke på ressursbruk. Siden modellen med input og antagelser ikke er fullstendig validert vil den ikke automatisk kunne godtas i andre metodevurderinger.

Samlet sett er det stor usikkerhet i metodevurderingen. Stor usikkerhet knyttet til dokumentasjon og beregningsmetoder skal, alt annet likt, gi lavere prioritet, jf. Prioriteringsmeldingen.

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Log

Time log for the assignment	
Description	**Date/number of days**
Time for marketing authorization for the extension of the therapeutic indication	02-09-2022
Assignment commissioned by Bestillerforum RHF	18-01-2021
Documentation received by NOMA	22-01-2024
Medical experts recruited for the case	20-02-2024
Case assigned to case handlers	03-05-2024
Medical experts involved in the case from	02-08-2024
Report finished	21-02-2025
Total time at NOMA[1]	395 days
Including:	
Time awaiting information from the pharmaceutical company	87 days
Processing time at NOMA[2]	**308 days**
Including[3]:	
Time pending the recruitment of medical experts	29 days
Time in queue pending assignment to case handlers.	102 days

[1] Time from received documentation to completion of the report.
[2] Time from received documentation to completion, excluding time waiting for information from the pharmaceutical company.
[3] Time pending the recruitment of medical experts and time in queue awaiting assignment to case handler(s) may overlap.

Medical experts recruited for the assignment	
Name	**Affiliation**
Pétur Benedikt Juliusson	Western Norway Regional Health Authority
Cecilie Fremstad Rustad	South-Eastern Norway Regional Health Authority
Torstein Baade Rø	Central Norway Regional Health Authority
Medical experts have provided clarifications on key assumptions in the analysis (e.g., comparative treatment, patient population, and the transferability of study data to Norwegian clinical practice). NOMA is responsible for the content of the report. The medical experts have not participated in any consensus process or performed any 'peer-review' function during the preparation of the report.	

NOMA		
Name	**Role in the assessment**	**Position title**
Line Evensen	Project lead	Senior advisor
Fawaz Chaudry	Case handler	Advisor
Håvard Haugnes	Case advisor	Advisor
Anette Grøvan	To approve the final report	Head of unit

Abbreviations

Abbreviation	Meaning
AS	Absolute shortfall
AUP	Pharmacy Retail Price
BBS	Bardet-Biedl Syndrome
BMI	Body mass index
BSC	Best standard care
EMA	European Medicines Association
EPAR	European Public Assessment Report
GLP-1	Glucagon-like peptide-1
HRQOL	Health-related quality of life
ICER	Incremental Cost-Effectiveness Ratio
IWQOL	Impact of Weight on Quality of Life
MSH	Melanocyte-stimulating hormone
NICE	National Institute of Health and Care Excellence
NOMA	Norwegian Medical Products Agency
PedsQL	Paediatric Quality of Life Inventory
QALY	Quality-adjusted life year
TEAE	Treatment emergent adverse event
VAS	Visual analogue scale
VAT	Value added tax

1. Background

1.1 Overview of the assignment

In the single technology assessment, the criteria of prioritisation – severity, utility and resource use (cost-effectiveness) are evaluated – along with uncertainty in the documentation and budgetary consequences. The European Medicines Agency (EMA) has concluded that setmelanotide has a benefit that outweighs the risks of its use, and the European Commission has authorised an extension of the market authorisation for setmelanotide to include genetically confirmed Bardet-Biedl syndrome (BBS). For the health technology assessment, the relative effect and additional cost of the new method compared to current treatment options in Norwegian clinical practice are relevant. The assessment by the Norwegian Medical Products Agency (NOMA) is based on documentation submitted by Rhythm Pharmaceuticals Netherlands B.V.

1.1.1 Intervention

Table 1. The intervention addressed by this single technology assessment

Setmelanotide (Imcivree)	
Therapeutic indication relevant for the health technology assessment	For the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above*
Other approved indications and status in "Nye metoder" for setmelanotide	A separate health technology assessment for setmelanotide is ordered for the treatment of obesity and the control of hunger associated with loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above. This assessment is awaiting submission of documentation from the marketing authorization holder ("Nye metoder" reference ID: ID2024_015)
Mechanism of action	Setmelanotide is a selective MC4 receptor agonist. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4 receptor, setmelanotide is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.
Posology for the relevant therapeutic indication	Setmelanotide is administered once daily as a subcutaneous injection. For adults and children 16 years and older: - Weeks 1-2: 2 mg once daily - Weeks 3 and onward (if 2 mg dose daily is well tolerated): 3 mg once daily For children aged 6 to <16 years: - Week 1: 1 mg once daily - Week 2 (if 1 mg dose is well tolerated): 2 mg once daily - Week 3 and onward (if 2 mg dose is well tolerated): 3 mg once daily

*The approved indication was changed to include children aged 2 and up (from 6 and up originally) after NOMA received documentation from Rhythm Pharmaceuticals and had started the assessment. Thus, this assessment covers the initially approved indication.

1.1.2 Terms of reference

The table below summarizes the order and framework for the assessment. The method represents an extension of the therapeutic indication and received marketing authorisation on September 2, 2022.

The order concerns only BBS, which one of several approved therapeutic indications for setmelanotide.

Table 2. Scope of the single technology assessment

Overview		
Order	ID2021_012: A health technology assessment, including a cost-benefit analysis, is conducted by the Norwegian Medical Products Agency for setmelanotide (Imcivree) for the treatment of obesity and the management of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children aged 6 years and older. A price document is prepared by the Norwegian Hospital Procurement Trust.	
Types of analyses	Cost-per-QALY, budget impact analysis	
PICO in submitted documentation		
	Description	**Chapter for evaluation**
Population	Adults and children aged 6 years and older with genetically confirmed Bardet-Biedl syndrome, obesity and severe hyperphagia*	*3.3*
Interventiom	Setmelanotide	*3.4*
Comparator	Best supportive care	*3.5*
Outcomes	Absolute or percentage change in body weight, BMI/BMI z-score, hunger score	*3.6*

*Severe hyperphagia is a sub-population of the licensed indication related to BBS. NOMA regards that this population (“severe hyperphagia” was not properly justified and defined in the submitted documentation. In this STA, NOMA evaluates the whole therapeutic indication for setmelanotide related to BBS.

This health technology assessment is based on one 14-week randomised placebo-controlled phase 3-study with an open label extension period providing approximately 52 weeks of data (RM-493-023).

1.2 Bardet-Biedl syndrome

Bardet-Biedl syndrome (BBS) is a rare genetic disorder caused by mutation in genes involved in cilia functioning and is therefore considered a primary ciliopathy. Primary cilia play a vital role in various intracellular signalling and trafficking processes, and their dysfunction can lead to diverse symptoms of varying severity in ciliopathies (1;2). BBS is inherited in an autosomal recessive manner, and to date, more than 20 genes have been identified to cause BBS. The overall prevalence of BBS range from 1 in 250,000 to 1 in 160,000 among individuals of European descent (1).

Signs and symptoms
BBS affects multiple body systems and is associated with a wide range of signs and symptoms. The development of vision impairment (retinitis pigmentosa) during childhood and adolescence is the most central feature of BBS and affects nearly everyone. Most become severely visually impaired in their late teens or early adulthood, and some lose their vision completely.

Obesity is another key feature of BBS, together with obesity-related complications (e.g., diabetes mellitus). The birth weight is typically normal, but excessive weight gain may start in early childhood. The obesity phenotype in BBS may result from low physical activity, metabolic changes, and

hyperphagia (2;3). Although there is not a clear universal definition of hyperphagia, it can be described as an extreme unsatisfied drive to consume food (4).

Other signs and symptoms of BBS include the presence of extra fingers or toes, cognitive impairments and learning difficulties, delayed speech and speech deficit, delayed development of motors skills, hearing loss, hepatic fibrosis, genitourinary malformations, delayed puberty and renal abnormalities (1;5).

Diagnosis
According to medical experts consulted by NOMA, the presence of distinct signs and symptoms may lead to clinical suspicion of BBS and prompt further evaluation. A clinical diagnosis can for instance be made according to the 'Beales criteria' (Table 3)Diagnostic features in Bardet-Biedl Syndrome (BBS). Modified from: Forsythe et al. (6) (at least four primary features or three primary features along with two secondary features) and confirmed through genetic testing (6), or by the updated criteria suggested in a recent (2024) publication by the Inter European Reference Networks (7). The medical experts estimate that approximately 75-80 % of patients with BBS have the diagnosis genetically confirmed. As the use of more advanced genetic analysis methods, for instance genome and long-read sequencing, increases, it is expected that more genetic causes will be identified, for instance variants in introns that might not be detectable by exome sequencing. Before the widespread use of genetic testing, the average age of BBS diagnosis was 9 years (8), often coinciding with the onset of visual disturbances (9). A more recent analysis of the Clinical Registry Investigating BBS (CRIBBS) database (n=552) shows a median diagnosis age of 5.8 years

Table 3. Diagnostic features in Bardet-Biedl Syndrome (BBS). Modified from: Forsythe et al. (6)

Diagnostic features	**Frequency**
Primary features	
Rod-cone dystrophy (incl. retinitis pigmentosa) (93%)	93%
Extra fingers or toes (polydactyly)	63-81%
Obesity	72-92%
Genital anomalies	59-98%
Renal anomalies	53%
Learning difficulties	61%
Secondary features	
Speech delay	54-81%
Developmental delay	50-91%
Diabetes mellitus	6-48%
Dental anomalies	51%
Congenital heart disease	7%
Short fingers or toes (brachydactyly) / fusion of finger or toes (syndactyly)	46-100% / 8-95%
Ataxia/poor coordination	40-86%
Loss of smell (anosmia) / Decrease sense of smell (hyposmia)	60%

1.3 Management of Bardet-Biedl syndrome in Norwegian clinical practice

NOMA is not aware of any specific national clinical guideline for the management of BBS, however, the Centre for Rare Disorders (Senter for sjeldne diagnoser) at Oslo University Hospital provides general recommendations for assessment and care of individuals with BBS (10). These emphasise regular, multidisciplinary care coordinated by a general practitioner. Key recommendations include biannual check-ups to monitor weight, BMI, blood pressure, and renal function. Psychological status should be assessed due to common issues like anxiety and depression. Annual consultations with an ophthalmologist, nephrologist, endocrinologist, and dentist are recommended, alongside education from a vision specialist. Multidisciplinary support, including genetic counselling, mental health services, and personalized care plans, is essential for comprehensive management. Since needs change over time and are not the same for everyone with BBS, it is important to coordinate the services according to the individual's needs (5;10).

According to medical experts consulted by NOMA, patients with BBS and obesity are treated similarly as other patients with obesity (11;12). Patients under 18 years with a BMI ≥ iso-BMI 30[4] and at least one additional comorbidity are referred to specialist healthcare. Adult patients (18 years and older) with significantly reduced health-related quality of life and a BMI ≥ 40 can also be referred, as well as those with a BMI ≥ 35 who have serious weight-related comorbidities (11;12). Today's best supportive care (BSC) includes dietary advice with ongoing support and advice regarding physical activity. However, due to reduced or severely impaired vision, engaging in physical activity can be challenging. Families are provided with general dietary advice and meal plans, and follow-up over time is essential. Effective lifestyle interventions typically require about 26 sessions annually, but in practice, children and families in Norway often receive 10-12 consultations. Many families with children with BBS maintain a high level of functionality, and lifestyle advice can help manage BMI effectively. However, hyperphagia poses significant difficulties for individuals with BBS and their families, as limiting food intake is often a major hurdle. Some patients also receive available weight-reducing medications (e.g. semaglutide and naltrexone/bupropion) (14). The extent of use and experience with these medications for treating BBS in Norway is uncertain.

According to the STA of setmelanotide by the Danish Medical Council, there is evidence that several BBS patients in the U.S. have experienced positive outcomes with semaglutide treatment. The Council notes that based on semaglutide's mechanism of action, there is no reason to assume it would be ineffective for BBS patients, and its indication is not restricted regarding genetically induced obesity. Therefore, the Danish Medicines Council supports attempting semaglutide treatment for patients aged 12 and older with BBS, as it offers a significantly cheaper treatment option. However, they emphasize that there is no knowledge regarding whether the function of the GLP-1 receptor is affected by changes in BBS genes or if variations within BBS may lead to GLP-1 receptor defects (2).

1.4 Expected placement of setmelanotide in the treatment algorithm

Setmelanotide is a synthetic octapeptide melanocortin 4 receptor (MC4R) agonist. It attaches to and activates MC4R, which is normally activated through leptin and melanocyte-stimulating hormone, promoting a feeling of fullness after eating. By attaching to this receptor directly, setmelanotide is expected to reduce excessive food intake and obesity. Setmelanotide is administered as a daily subcutaneous injection (1;2).

[4] Children and adolescents are assessed using different BMI values than adults. BMI is adjusted according to the child's age and gender. This gender- and age-adjusted BMI is referred to as iso-BMI (13).

Setmelanotide has no disease-modifying effect and does not directly impact other symptoms of BBS.

The medical experts consulted by NOMA consider the medical need for setmelanotide among patients with BBS and obesity to be significant. Those with the most severe degree of obesity may have a particularly high need compared to others, but both children and adults with obesity associated with BBS are relevant treatment groups. If introduced, setmelanotide will be given in addition to best supportive care. The medical experts speculate that, in patients who respond to setmelanotide, the treatment could lead to a decreased need for close monitoring typically required by lifestyle interventions. The treatment is not expected to change the need for management of BBS symptoms unrelated to hyperphagia and obesity.

If setmelanotide is introduced, it may be relevant to establish criteria for use. According to the medical experts, a starting criterion could be severe obesity (i.e., BMI/isoBMI>35).

Criteria for stopping treatment could be lack of a significant decrease in weight/BMI/isoBMI (e.g., 5 % weight loss in adults) over a given period of 6-24 months. Treatment discontinuation may be tested in patients achieving normal weight (BMI/isoBMI ≤25), but the treatment effects may then be reversed.

NOMAs conclusion on comparator
Patients with BBS and obesity in Norway are currently managed with best supportive care (BSC), which is considered relevant comparator for this assessment.

2. Clinical evidence base

2.1 Identification of relevant clinical studies

Rhythm Pharmaceuticals has conducted a systematic literature search in relevant databases. Search strategy, search results, and selection of studies are sufficiently documented. Initial systematic literature searches were conducted on June 3, 2021, followed by updates on August 4, 2022; January 10, 2023; and February 15, 2023. Of the 11 publications that met the inclusion criteria, three publications reported on clinical outcomes of setmelanotide treatment. These three publications reported from three different trials, RM-493-023 (NCT03746522) (15), RM-493-022 (NCT03651765) (16) and RM-493-014 (NCT03013543) (17). Following completion of the systematic literature search, Rhythm Pharmaceuticals identified a new publication related to trial RM-493-022 (NCT03746522) (18), that superseded prior publications from the trial.

2.2 Overview of relevant, submitted studies

This assessment is based on two clinical studies, one phase 3, double-blind, placebo-controlled multicentre study (RM-493-023 (NCT03746522) and one phase 3 open-label extension study for patients who completed 1 year of treatment in a prior setmelanotide trial RM-493-022 (NCT03651765). RM-493-014 (NCT03013543) is a phase II uncontrolled basket study that included patients with various forms of genetically induced obesity, including BBS. The latter study was not considered relevant for the assessment. An overview of submitted studies relevant to the single technology assessment are shown in Table 4.

Table 4. Overview of submitted studies relevant to the single technology assessment

RM-493-023 (15;18)	
Study ID	NCT03746522
Design	Phase 3, double-blind, placebo-controlled multicentre study (Figure 1. Study RM-493-023 design schematic. Source: EPAR (1))
Location	5 study centres in the US, Canada, Spain, France and the UK
Population	Patients aged ≥6 years with a clinical diagnosis of BBS* or Alström Syndrome** who were obese (BMI ≥30 kg/m2 for patients aged ≥16 years; weight ≥97th percentile for age and sex on growth chart assessment for patients aged 6 to 15 years) were included. Key exclusion criteria were weight loss of more than 2% as a result of diet or an exercise programme (or both) in the past 2 months, sustained weight loss of more than 10% from gastric bypass surgery, use of obesity medication in the past 3 months, glomerular filtration rate of less than 30 mL per min, and any previous exposure to setmelanotide. Initially, 38 patients (32 with BBS and 6 with AS) were enrolled and randomised. Patients were randomised in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or Alström syndrome), to receive setmelanotide or placebo. A protocol amendment allowed for the inclusion of a supplemental cohort of 12 additional BBS patients in the midcourse of the study. According to the EPAR, the purpose of the supplemental cohort was to gain more treatment experience. All main confirmatory analyses were performed using the pivotal cohort and results from the supplemental were only considered exploratory (1).

Intervention	Setmelanotide 3 mg*** daily via subcutaneous injection, for a 14-week, randomized, double-blind, placebo-controlled treatment period (Period 1) that was followed by a 38-week (Period 2) and a 14-week open-label treatment period (Period 3) in which all patients received setmelanotide.
Comparator	Matching placebo daily via subcutaneous injection at equivalent volume to 3 mg setmelanotide during the 14-week placebo-controlled period (Period 1), followed by a 38-week (Period 2) and a 14-week open-label treatment period (Period 3) in which all patients received setmelanotide. The purpose of this period was to allow patients who received placebo in period 1 to receive 52 weeks of treatment.
Primary endpoint	The primary efficacy endpoint was the proportion of patients ≥12 years of age who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment statistically compared to a proportion of 10 % based on data from a historical cohort. Exploratory subgroup analyses: • By disease type (BBS and Alström syndrome)** • Paediatric population by age-category (<17 years and <12 years)
Key secondary endpoint	• Mean percent change from baseline in body weight after ~52 weeks of treatment for patients ≥12 years • Mean percent change from baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment for patients ≥12 years • The proportion of ≥12 years with no cognitive impairment who achieve a ≥25% improvement from baseline in the weekly average of the daily hunger score statistically compared to a proportion of 10 % based data from a historical cohort
Other secondary endpoints	• Body weight percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients (≥12 years old). • Weekly average daily hunger score percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients (≥12 years old).
Observation time	14-weeks double-blind, placebo-controlled, 52-week open-label phase.
Data cut-off	Study completed: 08-03-2021
Does the study serve as the basis for the EMA's assessment of marketing authorization?	Yes, pivotal study.
Other	Adult and adolescent patients did not receive specific guidance on lifestyle modifications related to dietary intake or physical activity during the trial, although patients may have been familiar with, or had previously attempted, lifestyle modifications to control body weight gain. Nutritional counselling and monitoring were provided for paediatric patients to ensure adequate nutritional intake for proper growth and development.
RM-493-022 (16)	
Study ID	NCT03651765
Design	Phase 2/3 open-label extension study for patients with various rare, genetic melanocortin-4 receptor pathway disease who completed 1 year of treatment in a prior setmelanotide trial. For BBS either study RM-493-014 or RM-493-023.
Location	27 study centres in the US, Canada, France, Germany, Greece, Netherlands, Spain and the UK.
Population	Patients aged 2 or older (or aged >2 years as per local regulations) who have completed participation in a previous setmelanotide trial and demonstrated adequate safety and meaningful clinical benefit (efficacy).

	54 patients with BBS were enrolled in the study and received setmelanotide (28 patients aged <18 years, 26 patients aged ≥18 years).
Intervention	Setmelanotide 1.0 mg, 2.0 mg or 3.0 mg administered subcutaneously once daily, up to 2 years.
Comparator	NA
Primary endpoint	To characterize safety and tolerability of setmelanotide
Key secondary endpoint	NA
Observation time	3 years
Data cut-off	Ongoing, data cut-off June 2022
Does the study serve as the basis for the EMA's assessment of marketing authorization?	Yes, supportive study

*BBS clinical diagnosis as per Beales criteria (see chapter 1.2).
**Patients with Alström syndrome is not part of the assessment.
*** Dose escalation up to 3.0 mg based on age.

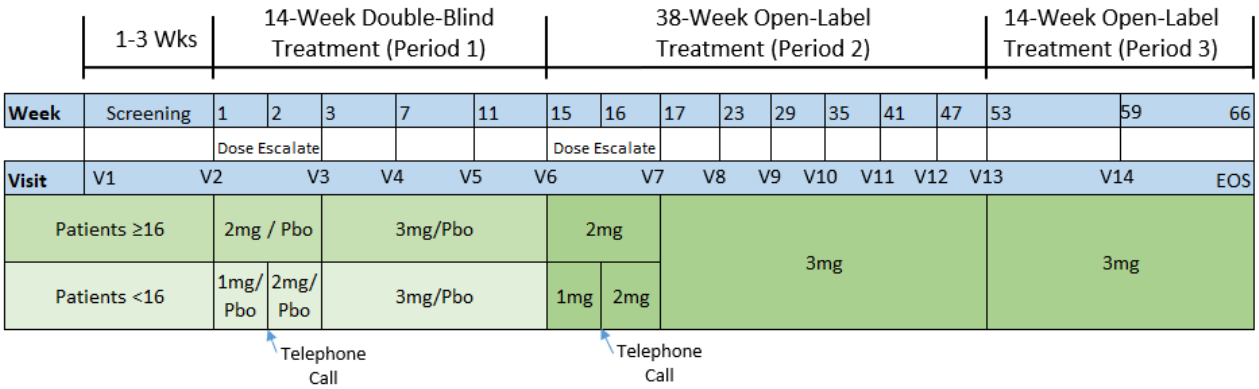

Figure 1. Study RM-493-023 design schematic. Source: EPAR (1)

Relevant ongoing studies

Rhythm Pharmaceuticals has not identified any ongoing studies apart from RM-493-022, as described above.

NOMA's assessment

RM-493-023 and RM-493-022 underpins the extension of the therapeutic indication for setmelanotide and are phase 2/3 or 3-studies assessed by EMA. However, only RM-493-023 was a randomized controlled trial and informs the relative effect of setmelanotide (14-week period), while data beyond 14-weeks are uncontrolled and not suitable for assessing relative effect. The comparator in RM-493-023 is considered acceptable. However, it is noteworthy that adults and adolescents did not receive specific lifestyle guidance during the trial, though some may have previously attempted weight management. This differs from Norwegian clinical practice and affects both the estimates of relative effect and the generalizability of the comparator arm in the study. Nevertheless, NOMA considers that data from RM-493-023 and RM-493-022 may be suitable as a basis for documentation to conduct a health economic analysis. The generalizability to Norwegian clinical practice is assessed in chapter 3.

3. Analytical method and PICO

3.1 Scope

To estimate the cost-effectiveness of setmelanotide, Rhythm Pharmaceuticals have submitted a cost-per-QALY analysis comparing setmelanotide with best supportive care (BSC) for the treatment of obesity and the control of hunger in patients with Bardet-Biedl Syndrome (BBS). The results of the analysis highlight the prioritisation criteria of health benefit and resource use, forming the basis for assessing the severity of BBS and its associated outcomes.

3.2 Health economic model

The submitted health economic analysis is a Markov model (Figure 2) and consists of eight health states, representing various categories of BMI/BMI Z-scores, along with a treatment effect for hyperphagia on quality of life and a state for mortality. It follows two patient populations, one with paediatric treatment initiation at age 6 and the other with adult treatment initiation at age 20. The most important variables included in the health economic model as provided by Rhythm Pharmaceuticals are provided in Table 5. The age distribution across the two populations in the base-case and scenario analysis, along with the probability of response and the annual treatment discontinuation rate, is also provided in Table 5.

Table 5. Overview of most important input data and assumptions in the base case analysis from Rhythm Pharmaceuticals

Submitted input variable	Paediatric population	Adult population	Source
Patient distribution	60%	40%	Base-case assumption*
Patient distribution	100%	0%	Scenario assumption*
Starting age	6 years	20 years	Initial patient distribution from RM-493-023 (NCT03746522)
Proportion female	50%	56%	Initial patient distribution from RM-493-023 (NCT03746522)
Baseline BMI z-score/BMI category BMI Z 0 to ≤ 1/BMI 20 to ≤25 BMI Z 1 to ≤ 2/BMI 25 to ≤30 BMI Z 2 to ≤2.5/BMI 30 to ≤35 BMI Z 2.5 to ≤3/BMI 35 to ≤40 BMI Z 3 to ≤3.5/BMI 40 to ≤45 BMI Z 3.5 to ≤4/BMI 45 to ≤50 BMI Z 4+/BMI 50+	 0% 6,3% 6,3% 12,5% 18,8% 18,8% 37,5%	 0% 0% 6,3% 12,5% 37,5% 18,8% 25,1%	Initial patient distribution from RM-493-023 (NCT03746522)
Baseline hyperphagia Level	100% severe	100% severe	Assumption*
Setmelanotide treatment effect on hyperphagia post treatment (in responders)	100% mild	100% mild	Assumption*
Response rate setmelanotide	85.7%	46.7%	Based on 52-week time point in RM-493-023 (NCT03746522). Paediatric responders defined as ≥0.02 reduction in BMI Z-score Adult responders defined as ≥10% weight loss
Response rate BSC	0%	0%	Assumption*
Treatment discontinuation	1% yearly	1% yearly	Assumption*

*Assumptions made by Rhythm Pharmaceuticals

Rhythm Pharmaceuticals included a figure outlining the drivers of cost-effectiveness as part of their submission. However, the model lacked a clear depiction of natural disease progression for BBS patients, particularly in mapping transitions between health states. The submission did not adequately distinguish hyperphagia and BMI health states or their connection to mortality, and the impact of hyperphagia as a multiplier was insufficiently detailed.

NOMA identified inconsistencies in the representation of disease progression and state transitions as a standard representation of state transition models used in health economic evaluations, prompting a review of the model and Excel file to better map BMI-Z score/BMI health states for paediatric and adult populations, as well as the integration of adverse events, comorbidities, and utility multipliers for hyperphagia states.

NOMA achieved this by first identifying the relevant health states for both paediatric and adult patient groups, followed by assessing the application of adverse events in the initial cycle and highlighting the differences in hyperphagia severity between the BSC and setmelanotide arms.

NOMA has made the following model schematic relevant for the Markov model submitted by Rhythm Pharmaceuticals in Figure 2.

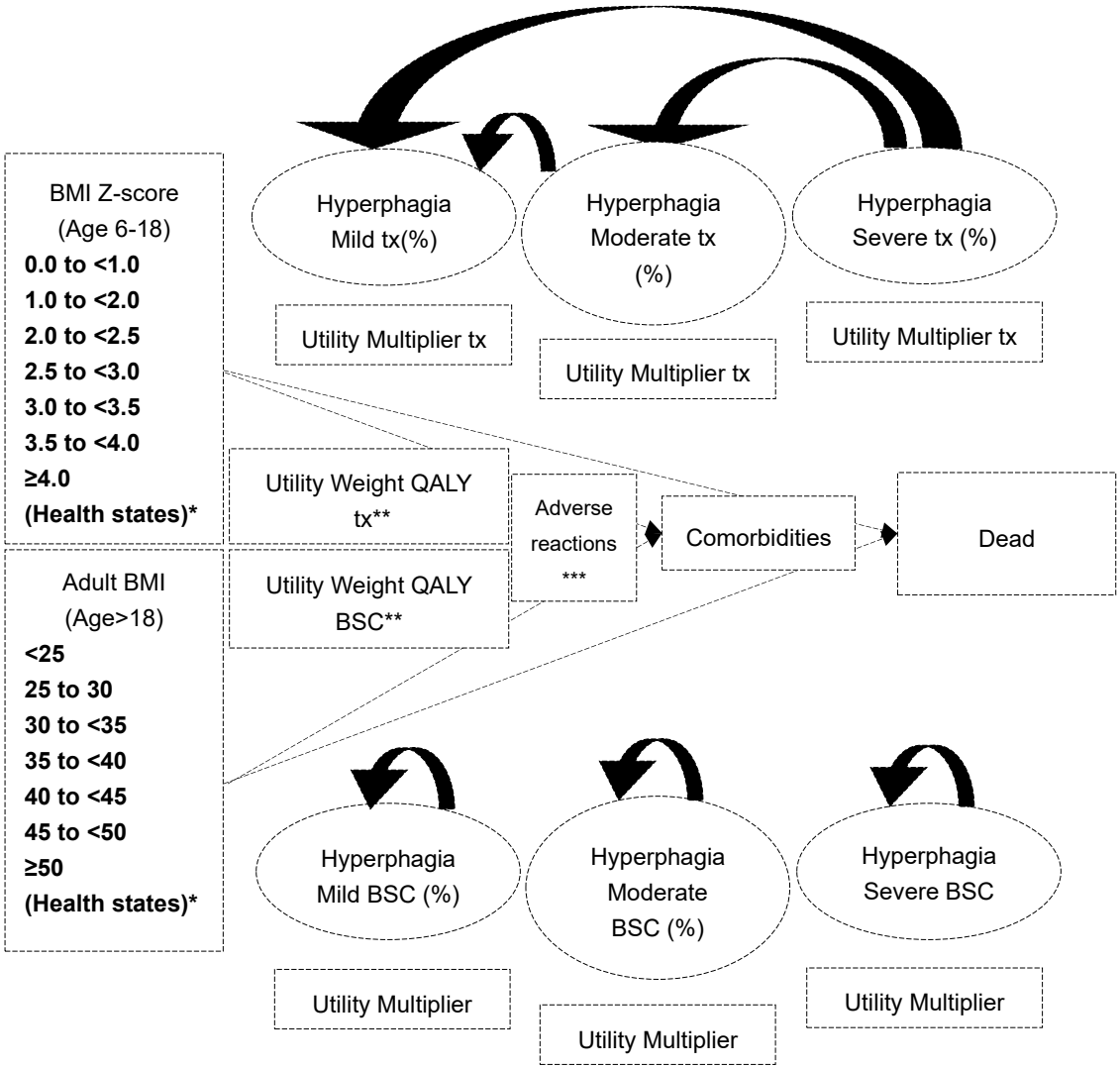

Figure 2. NOMA's outlined model schematic of the cost-effectiveness model submitted by Rhythm Pharmaceuticals

tx,treatment arm or (Setmelanotide); BSC, Best supportive care; QALY, quality adjusted life year
*Include recurring health states with BMI/Z-score categories for paediatric or adult patients. BSC does not alter distribution of patients in a BMI health state but transition to BMI Z-score to BMI is mapped after the age of 18. Treatment with setmelanotide alters the distribution of patients across BMI categories, once treatment is discontinued patient transition back to their original BMI/Z-score health state category.
**Utility weights for both treatment and BSC are estimated using utility multipliers based on the distribution of patients across the severity levels of hyperphagia for the treatment (setmelanotide) and BSC arm. The utility weights are applied to the QALYs from the BMI/Z-score health states for treatment and BSC arm. Fixed distribution of patients is assumed for hyperphagia levels in the BSC arm, but patients can switch between severity levels in the treatment arm from severe to moderate and mild.
***Adverse reaction or events are recorded in the initial cycle for the treatment arm only. The probability of adverse reactions adjusts the total QALYs for disutility associated with the reaction and costs are calculated based on the proportion of adverse reactions in the treatment arm. Adverse reactions are recorded but there is no mortality risk associated with regards to the event.
Note: NOMA assumes no impact of hyperphagia multipliers in its main analysis but in a scenario analysis (explained in section 3.6.1.3).

The BMI Z-score and BMI associated health states are the starting health states consisting of 7 categorial health states based on the patients' BMI distribution (Table 5). Patients with paediatric treatment initiation transition from their BMI Z-score category to the aligned BMI category at 18 years

old. The mapping of BMI Z-score to BMI health states provided in the submission is presented in Table 6. The hyperphagia health states are presented as health states that determine the baseline distribution of hyperphagia severity across both study arms. Utility multipliers for each hyperphagia severity level, along with transitions from baseline hyperphagia due to treatment, are used to calculate the utility weights for both the BSC and setmelanotide arm (BSC plus setmelanotide). Furthermore, adverse reactions are recorded in the model for their respective utility decrements, whereas comorbidities experienced by patients are recorded for both their costs and utility decrement separately. The BMI-specific mortality is recorded in the dead state.

Table 6. Mapping BMI Z-score to BMI

		BMI Z-score						
		0.0 to <1.0	1.0 to <2.0	2.0 to <2.5	2.5 to <3.0	3.0 to <3.5	3.5 to >4.0	≥4.0
BMI (kg/m^2)	20 to <25	100%	0%	0%	0%	0%	0%	0%
	25 to <30	0%	100%	0%	0%	0%	0%	0%
	30 to <35	0%	0%	100%	100%	0%	0%	0%
	35 to <40	0%	0%	0%	0%	100%	0%	0%
	40 to <45	0%	0%	0%	0%	0%	100%	33%
	45 to <50	0%	0%	0%	0%	0%	0%	33%
	≥50	0%	0%	0%	0%	0%	0%	33%

Table 7. Main formalities of the health economic model

Theme	**Description**
Model Type	Markov model
Half-cycle correction	Yes
Cycle length	1 year (Half cycle correction applied)
Discounting rate	4% for both health benefits and costs during the first 39 years, 3% from 40 to 74 years, and 2% after 75 years.
Perspective	Extended health care perspective
Time horizon	Lifetime (100 years)

The health economic model submitted by Rhythm Pharmaceuticals is based on data from the clinical trial RM-493-023, which assessed the effects of setmelanotide in BBS patients, and assumptions from Pomeroy et al. (8) regarding the BMI Z-score stabilization upon responding to treatment. BMI Z-scores

for paediatric patients and BMI for adults were modelled, with outcomes stabilizing at the 52-week endpoint due to limited long-term data.

The model evaluates the progression of BMI categories based on trial data, whereas hyperphagia effects are based on assumptions and external literature. In RM-493-023, key endpoints were achieving ≥10% weight loss for adults and reducing BMI Z-scores by ≥0.2 for paediatric patients after 52 weeks.

Non-responders, defined as those who do not achieve a ≥10% weight reduction or ≥0.2 BMI Z-score reduction, discontinue treatment after 14 weeks, and remain at their baseline BMI as they revert to BSC. The costs associated with treatment discontinuation are based on 52-week data, while the 14-week cost for setmelanotide treatment is considered for cost calculations. Hyperphagia improvements are modelled separately, with responders transitioning from severe to mild hyperphagia, and reverting to severe if treatment is discontinued. Non-responders remain in severe hyperphagia. The submitter considers a 1% annual discontinuation rate for responders, based on their claim regarding high drug tolerability and early discontinuations due to lack of efficacy or adverse events.

The model includes costs and HRQoL impacts of obesity-related comorbidities (e.g., sleep apnoea, non-alcoholic steatohepatitis, type-2 diabetes mellitus) and BMI-driven mortality risks (hazard ratio (HR) of all-cause mortality of 1.21 for every 5-point increase in BMI above 25. HRs by BMI level were multiplied by the BMI SMR parameter).

Lastly, caregiver burden is accounted in the model as costs for caregivers and an annual utility decrement in the BSC treatment arm and for patients who discontinue treatment with setmelanotide. In the first model cycle, caregiver burden is also applied as an annual disutility for patients receiving setmelanotide treatment.

NOMA's assessment

The submitted health economic model lacks clarity and transparency. This makes it difficult to evaluate transitions between BMI categories and their connection to hyperphagia, as well as insufficient clinical data on their effects on HRQoL. The cost-effectiveness drivers figure provided by Rhythm Pharmaceuticals is complex and fails to clearly illustrate natural disease progression or distinguish treatment effects. This limits the internal validation of key drivers. Despite these challenges, NOMA was able to present a model schematic based on the submitted data.

NOMA accepts the choice of an extended healthcare perspective but does not support the inclusion of caregiver burden (further explained in section 3.6.3). Additionally, the chosen discount rate and half-cycle correction align with NOMA's guidelines. The cycle length considered in the model is considered reasonable for both paediatric and adult patients with BBS, given the selected time horizon for the analysis.

While NOMA can adjust key parameters, such as responder and non-responder probabilities, a comprehensive assessment reveals a lack of clear transitions among BMI categories in both the BSC-arm and the setmelanotide-arm. This modelling approach restricts a straightforward overview of transitions, hindering thorough internal validation. The extensive use of complex formulas without clear mapping contributes to this weakness, making it difficult to perform necessary adjustments within the economic model. Despite challenges in fully validating the model, NOMA considers the model to provide a useful approximation for addressing the prioritisation criteria at an appropriate level.

In conclusion, NOMA considers the modelling of hyperphagia to lack direct evidence, particularly regarding its robustness in accurately modelling outcomes, even though its link to obesity may have

clinical significance for outcomes such as weight changes in BBS patients. However, the lack of validated measures for hyperphagia further complicates its assessment in the economic model. Stronger evidence, particularly on hyperphagia and its management, is essential to accurately capture the long-term health and economic impact of setmelanotide and refine its cost-effectiveness evaluation.

During the case processing, NOMA has informed Rhythm Pharmaceuticals about shortcomings and ambiguities in the submitted documentation and modelling through emails, telephone and a digital meeting, and has asked several follow-up questions in order to establish a more reliable scenario for the use of setmelanotide in Norwegian clinical practice. However, the necessary information and modifications required to significantly reduce the uncertainty in the assessment have not been fully obtained.

NOMA's conclusion on the health economic model
NOMA assesses that the submitted health economic model is poorly suited to analyse the disease and treatment pathway, with the intention of elucidating the cost-effectiveness of setmelanotide for patients with BBS, especially with respect to the hyperphagia assumption in the model. Despite challenges in fully validating the model, NOMA considers it to provide a useful approximation for addressing the prioritisation criteria at an appropriate level.

The analysis perspective, discount rate, and half-cycle correction are in line with NOMA's guidelines. The cycle length is reasonable, and the time horizon is acceptable. NOMA has changed some of the assumptions of the model to better reflect the Norwegian clinical setting based on expert recommendation, as well as assumptions regarding hyperphagia effects and caregiver burden effects. This is further explained and summarized in section 3.3.4 and 4.1.2.

3.3 Patient population

3.3.1 Submitted clinical documentation

RM-493-023 included patients with either BBS or Alström syndrome, but only data from BBS patients are relevant for this assessment and described further. Initially, 32 BBS patients (16 in each group) were included as pivotal patients, and a protocol amendment allowed for the inclusion of a supplemental cohort of 12 additional BBS patients (6 in each group) in the midcourse of the study. Baseline characteristics for all 44 BBS patients included in RM-493-023, are presented in Table 8.

According to the EPAR, the purpose of the supplemental cohort was to gain more treatment experience. All primary confirmatory analyses were conducted using the pivotal cohort, while results from the supplemental cohort were considered exploratory, as participants in the latter could exit the study to enrol in the RM-493-022 extension trial at any time after completing the placebo-controlled period (1).

Mean age at baseline was around 20 years and mean BMI around 40 in both groups. In children and adolescents (6-17 years), mean BMI z-score was around 4 at baseline in both groups. Mean maximal hunger score was 6-7 in both groups. However, there was a higher proportion with cognitive impairment (54,5% versus 36,4%) and very high BMI-classification in the setmelanotide-group compared to the placebo-group. There was also a lower proportion of women (40,9% versus 68,2%) among the setmelanotide-treated patients. All patients were diagnosed as per Beales criteria (chapter 1), and 89% had a genetically confirmed diagnosis (18).

Data on concomitant medication was not available for BBS patients separately, but for all patients with BBS or Alström syndrome in the safety analysis set (SAS pivotal patients, n=38 of which BBS n=32) (18). All had ≥1 concomitant medication during the study. Common concomitant medications included vitamin D and analogues (65,8%), angiotensin-converting enzyme inhibitors (28,9%), paracetamol (28,9%), metformin (26,3%), osmotically acting laxatives (23,7%), progestogens and oestrogens (21,1%), and selective beta-2-adrenoreceptor agonists (21,1%).

Table 8. Baseline patient characteristics for patients with BBS in RM-493-023. The study included two patient cohorts. The pivotal patient cohort (n=32) and a supplemental cohort (n=12). Source: Haqq et al. 2022 (18) and the Danish Medicines Council (2).

Parameter	Setmelanotide (n=22)	Placebo (n=22)
Age, mean (SD)[a]	18,5 (9,7)	21,5 (12,6)
Proportion adults (≥ 18 years), n (%)	46%	55%
Female, n (%)	9 (40,9)	15 (68,2)
Ethnicity, n (%)		
Hispanic or Latino	1 (4,5)	0
Not Hispanic or Latino	18 (81,8)	19 (86,4)
Not reported	1 (4,5)	2 (9,1)
Unknown	2 (9,1)	1 (4,5)
Race, n (%)		
White	15 (68,2)	19 (86,4)
Black or African American	1 (4,5)	1 (4,5)
Asian	0	1 (4,5)
Other	6 (27,3)	1 (4,5)
Weight, mean (SD), kg	110,4 (35,8)	106,5 (31,8)
BMI, mean (SD)[a]	41,4 (10,0)	41,6 (10,1)
BMI Z-score (children <18 years), mean (SD)	4,1 (1,4)	4,2 (2,0)
BMI category (adults) / BMI Z-score category (children), % [b]		
BMI 25 to ≤ 30/BMI Z 1 to ≤ 2	0%	0%
BMI 30 to ≤ 35/BMI Z 2 to ≤ 2,5	6%	13%
BMI 35 to ≤ 40/BMI Z 2,5 to ≤ 3	13%	20%
BMI 40 to ≤ 45/BMI Z 3 to ≤ 3,5	19%	33%
BMI 45 to ≤ 50/BMI Z 3,5 to ≤ 4	25%	13%
BMI > 50/BMI Z > 4	38%	27%
Cognitive impairment, n (%)	12 (54,5)	8 (36,4)
Patients ≥ 12 years without cognitive impairment, able to report 'daily hunger score', % [a,c]	32%	63%
Maximal hunger score, mean (SD)[a,c] - Score 0-10	6,3 (1,1) N=6	6,6 (2,1) N=12

Gene with identified variation*		
BBS1	50%	56%
BBS2	6%	13%
BBS3	0%	0%
BBS4	0%	6%
BBS5	0%	0%
BBS6	0%	6%
BBS10	44%	19%
BBS-related	0%	0%
No confirmed variation	0%	0%

BMI, body mass index; SD, standard deviation
[a]At placebo-controlled period baseline
[b]Data only presented for the pivotal cohort (n=32)
[c]In patients ≥12 years old without cognitive impairment; self-reported.

3.3.2 Submitted health economic model

The patient population in the submitted health economic model is mainly based on the population in RM-493-023. However, Rhythm Pharmaceuticals assumes that all patients have *severe* hyperphagia at baseline, although hyperphagia was not assessed in the study. This is also narrower than the marketing authorisation for BBS. Further, in RM-493-023, there was an equal distribution of paediatric and adult patients. However, in the submitted model Rhythm Pharmaceuticals assumes that 60% of patients initiate treatment in childhood (<18 years old) and 40% as adults (≥18 years old). Rhythm Pharmaceuticals also conducted a scenario analysis on 100% paediatric treatment initiation.

Patient characteristics included in the health economic model are present earlier in Table 5.

3.3.3 Norwegian clinical practice

NOMAs is not aware of any published data on characteristics of patients with BBS in Norway. One medical expert consulted by NOMA estimates that the mean age of patients in Norway that currently would be eligible for treatment with setmelanotide is 15-20 years. This is because they at this time are aware of more adults than children with diagnosed BBS. However, the average age in prevalent patients is expected to decrease, as more patients are diagnosed earlier, and treatment is initiated at a lower age. Another of the medical expert estimates that mean age at treatment initiation would be 5-10 years if relevant gene panels are used more consistently than today.

Although the prevalence of obesity is expected to be close to 100% among patents with BBS in Norway, little is known about the *degree* of obesity in this population. One medical expert state that children with BBS in a Norwegian clinic have a mean BMI Z-score of around 3, estimated from Norwegian reference standards. However, this number may not be directly comparable to Z-scores estimated with standards from other sources, e.g., WHO.

According to a medical expert, there are currently no valid, objective measures for dietary intake or hyperphagia for use in clinical practice. However, an assessment of dietary intake and eating behaviour is generally noted in the medical journal of these patients. Typically, in current practice, questions such as the following are asked: number of meals, snacks, quantities, difficulty in limiting the child, reactions when told the child cannot have more, who portions the food, who decides what will be

eaten, and fuzzy eating (picky eating). One medical expert presumes that most patients with BBS have some degree of hyperphagia.

The prevalence of *severe* hyperphagia and cognitive impairment among patients with BBS in Norway is unknown.

3.3.4 NOMA's assessment

Although study arms appear to be comparable for most baseline characteristics, the prevalence of cognitive impairment is notably higher among setmelanotide-treated patients. This impacts the evaluation of the outcome 'daily hunger score', which was only measured in patients without cognitive impairment.

The lack of data on patients with BBS in Norway hampers the assessment of generalizability. Based on the information shown in Table 8, one medical expert consulted by NOMA perceives that the population in RM-493-023 is generally applicable to eligible patients in Norway. However, NOMA notes that mean age of the study population is somewhat higher than the currently eligible patients in Norway. Regarding obesity, one medical expert noted that mean BMI Z-score in the paediatric study population was somewhat higher than in patients in Norway, although the numbers may not be directly comparable due to different reference standards (the reference standard used in the study is not known). NOMA assesses that the noted differences probably are of limited significance for the study's generalizability.

In their analysis, Rhythm Pharmaceuticals assumes that all patients in the study had *severe* hyperphagia at baseline, although this was not measured in the study. Based on input from medical experts, NOMA acknowledges that the prevalence of hyperphagia among patients with BBS and obesity probably, is high. However, NOMA notes that the prevalence of *severe* hyperphagia both in the study population and in Norwegian clinical practice is unknown. Moreover, a mean baseline '*daily hunger score'* of 6-7 out of 10, is not indicative of severe hyperphagia in all study patients. Notably, this tool is not validated, and its correlation with hyperphagia remains unclear.

NOMA changes the baseline distribution of hyperphagia to 25% mild, 50% moderate, and 25% severe hyperphagia. NOMA underscores that this is not based on empirical data but is an arbitrary assumption that may be a more realistic distribution for BBS patients in Norway. This adjustment is reflected in NOMA's main analysis but does not impact the ICER, as a reduction in severity of hyperphagia and its effect on QALYs (via utility multipliers) is also excluded from NOMAs main analysis due to a lack of clinical evidence on effect (see chapter 3.6.3 and 4.2). However, NOMA includes a treatment effect on hyperphagia in a scenario analysis (see chapter 4.1.3).

According to one medical expert, there are 63 patients with BBS registered in the registry data from The Centre for Rare Disorders in Norway. Of these, approximately 20 are under the age of 18. Based on these data NOMA adjusts the patient distribution in the model to align with Norwegian demographics, assuming 32% paediatric and 68% adult treatment initiation in the main analysis. Despite an aging general population, the age at treatment initiation is expected to decrease with time, and a distribution of 80% paediatric and 20% adult at treatment initiation was explored in a scenario analysis. These changes account for external validity while ensuring internal validity, as the effects in paediatric and adult patients are modelled separately and weighted in the health economic model. Likewise, the weighted approach in the model allows for the separate dosing criteria for both paediatric and adult patients.

NOMA does not modify the distribution across BMI/BMI Z-score categories, as this aligns with data from RM-493-023 and is deemed acceptable for generalization to Norwegian clinical practice.

NOMA's conclusion on the patient population
NOMA mainly relies on the same assumptions as Rhythm Pharmaceuticals but changes the distribution of hyperphagia severity at baseline and the distribution of paediatric vs. adult treatment initiation. The impact of these modifications on the ICER is described in chapter 4.

3.4 Intervention

3.4.1 Submitted documentation in relation to Norwegian clinical practice

Table 9. Characteristics of the intervention. Source: Rhythm Pharmaceuticals and SmPC (19)

	Clinical Documentation	Health Economic Model	Norwegian Clinical Practice
Posology	Patients aged <16 years received a starting dose of 1.0 mg once daily which could be increased to 2.0 mg after 1 week and to 3.0 mg after 2 weeks based on safety/tolerability. Patients aged ≥16 years received a starting dose of 2.0 mg once daily which could be increased to 3.0 mg after 2 weeks.	Average dose year 1 of treatment for paediatric patients < 16 year: 2.46 mg/day Average dose years 2+ of treatment for paediatric patients: 2.50 mg/day Average dose year 1 of treatment for adult patients ≥16 years: 2.77 mg/day Average dose years 2+ of treatment for adult patients: 2.80 mg/day.	It is assumed that setmelanotide will be dosed according to the SmPC. The recommended dosage is: For adults and children 16 to 17 years of age: Weeks 1-2: 2 mg once daily Weeks 3 and onward (if 2 mg dose daily is well tolerated): 3 mg once daily For patients aged 6 to <16 years: Week 1: 1 mg once daily Week 2 (if 1 mg dose is well tolerated): 2 mg once daily Week 3 and onward (if 2 mg dose is well tolerated): 3 mg once daily
Method of administration	Setmelanotide is administered once daily as a subcutaneous injection.	Setmelanotide is administered once daily as a subcutaneous injection.	Setmelanotide is administered once daily as a subcutaneous injection.
Treatment duration	Up to 52 weeks of treatment in RM-493-023. Six of 16 (37,5%) patients in the pivotal study discontinued and did not receive 52 weeks of treatment.	Lifelong. Discontinuation: after 14 weeks for non-responders (30%), and further 1% yearly in responders.	Lifelong, or until unacceptable toxicity or loss of response
Relative Dose Intensity (%)	Mean post-titration dose for adult patients: 2.9 mg/day	The modelled dose is based on RM-493-023 and other relevant literature.	Unknown

	Mean post-titration dose for paediatric patients: 2.7 mg/day	Average dose year 1 of treatment for paediatric patients: 2.46 mg/day Average dose years 2+ of treatment for paediatric patients: 2.50 mg/day Average dose year 1 of treatment for adult patients: 2.77 mg/day Average dose years 2+ of treatment for adult patients: 2.80 mg/day	

If setmelanotide is introduced, it may be relevant to establish criteria for prescribing (chapter 1.4).

3.4.2 Implementation of the intervention in the health economic model

Dosage:
In the submitted health economic model, the dosage for setmelanotide is calculated based on RM-493-023 and adjusted for expected real-world usage. For paediatric patients the starting dose is 1.05 mg on day 1, followed by a 2-week titration period with a dose of 1.55 mg/day. After titration, the predicted post-titration dose is 2.50 mg/day. This results in an average year 1 dose of 2.46 mg/day, with the dose for years 2 and beyond assumed to be 2.50 mg/day. For adult patients, the starting dose is 2.0 mg on day 1, with a 2-week titration period of 2.05 mg/day. The post-titration dose is predicted to be 2.80 mg/day, leading to an average year 1 dose of 2.77 mg/day. From year 2 onwards, the dose is assumed to stabilize at 2.80 mg/day.

Stopping rule:
In their base case, Rhythm Pharmaceuticals assumes that discontinuation in non-responders occurs soon after treatment initiation. Individuals with minimal weight loss and no meaningful hunger reduction were assumed to stop treatment after 14 weeks and were not included in the annual stopping rate (1%). However, the model allows for the analysis to explore the impact of non-responders continuing treatment for up to 1 year before the stopping rule is applied. Non-responders in the model were adults with <10% weight loss and paediatric patients with <0.2 BMI Z-score reduction at 52 weeks, regardless of whether the stopping rule was applied at 14 or 52 weeks. Non-responders were assumed to revert to baseline BMI and severe hyperphagia upon stopping treatment, and switch to BSC with no lingering effects of setmelanotide treatment.

For patients who continue treatment beyond the first year, Rhythm Pharmaceuticals assumes a 1% annual discontinuation rate. This rate was provided as a measure of adherence rather than as a proxy for treatment waning. The submitter claims that the 1% rate reflects the assumption that setmelanotide is well tolerated, with very low discontinuation rates expected among responding patients.

3.4.3 NOMA's assessment

Based on input from the medical experts, NOMA assumes that setmelanotide will be used in accordance with the approved product information in Norwegian clinical practice. While most patients will likely require lifelong treatment, some may discontinue due to insufficient effect, unacceptable toxicity or other causes.

NOMA does not alter the dosing assumptions in the main analysis. However, in a scenario analysis NOMA assumes that setmelanotide dosing will follow the SmPC for both adults and paediatric patients as shown in Table 9.

NOMA does not accept the stopping rule at 14 weeks for non-responders, as evaluation of treatment effect is expected to occur later in Norwegian clinical practice. As suggested by the medical experts, the stopping rule depends on the criteria used. If weight/BMI/BMI z-score is to be used as a criterion, a well-defined cut-off and extended evaluation period might be needed to capture meaningful progress and avoid prematurely classifying patients as non-responders. Based on the input from the medical experts, NOMA changes the 14 weeks stopping rule to 1 year in its main analysis. Notably, in Norwegian clinical practice, a less stringent response criterion of 5% weight loss in adults (compared to 10% in RM-493-023) may be used, which will result in a higher rate of patients being defined as responders (see chapter 1.4).

The submitted model does not allow for modification of the response criterion. The model defines adult responders as adult patients achieving at least 10% weight loss, a more stringent criterion than the 5% weight loss that may be used for adult patients in Norwegian clinical practice. This mismatch complicates generalizability of the results, probably leading to lower average utility and a higher ICER.

NOMA notes that the 1% annual discontinuation rate beyond year 1 is highly uncertain. This was an assumption taken by Rhythm Pharmaceuticals. In lack of alternative values NOMA has opted not to alter the 1% annual discontinuation rate. Notably, NICE, in its assessment of setmelanotide, acknowledged that the 1% rate might be underestimated but still incorporated it due to limited available evidence and its alignment with the treatment's observed short-term effects. NICE also concluded that, while the stopping rate for setmelanotide is likely low, the requirement for daily self-injections might lead some patients to discontinue treatment (3). Thus, the real-world rate might be slightly higher due to factors such as the burden of daily self-injections. Therefore, NOMA included a scenario analysis for discontinuation rate of 3% to assess its impact on the ICER (see chapter 4.1.3).

NOMA's conclusion on intervention:
NOMA largely aligns with the same assumptions as Rhythm Pharmaceuticals but changes the stopping rule for non-responders from 14 weeks to 1 year. NOMA also includes a scenario analysis for discontinuation rate of 3% beyond year 1. The impact of this adjustment on the ICER is described in chapter 4.

3.5 Comparator

3.5.1 Submitted documentation in relation to Norwegian clinical practice

Treatment of patients with BBS and obesity in Norwegian clinical practice is outlined in chapter 1.3.

In RM-493-023, placebo was used as comparator. During the trial, adult and adolescent patients in both study arms did not receive specific guidance on lifestyle modifications regarding dietary intake or physical activity, although they may have been aware of or previously attempted such modifications to manage body weight gain. In contrast, paediatric patients in both study arms received nutritional counselling and monitoring to ensure they had adequate nutritional intake for proper growth and development.

3.5.2 Implementation of the comparator in the health economic model

In the submitted health economic model, BSC was used as the comparator. This included lifestyle and dietary interventions, as well as behavioural therapy, but did not involve any pharmacological treatments. Dietary and exercise guidance were expected to occur during regular physician visits (4

visits/year in year 1 and 2 visits/year thereafter). The BSC as comparator does not include any effects on weight or BMI/BMI *Z*-score in the model and does not incur any extra costs.

3.5.3 NOMA's assessment

In RM-493-023, only paediatric patients received nutritional counselling and monitoring, while adult patients did not receive specific guidance on lifestyle modifications regarding dietary intake or physical activity. This is not representative for how patients with BBS and obesity are treated in Norwegian clinical practice. Consequently, the effect of BSC may be underestimated in the clinical study and in the health economic model.

NOMA retains the assumption of 0% response rate in the BSC arm in its main analysis. However, NOMA acknowledges that the study RM-493-023 lacks consistent counselling on diet and exercise for patients over 12 years, potentially underestimating the effect.

As discussed by the Danish Medicines Council in its evaluation of setmelanotide, the conclusion that the effect of BSC may be underestimated is backed by the design of the study RM-493-023. In this study, the primary efficacy endpoint was the proportion of patients ≥12 years of age who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment statistically compared to a proportion of 10% based on data from a historical cohort (Table 4) (2).

NOMA's conclusion on comparator
NOMA uses the same assumptions as Rhythm Pharmaceuticals but underscores that the effect of BSC may be underestimated.

3.6 Clinical outcome measures

The relative effect and safety in the health economic model for setmelanotide compared to placebo are based on results from RM-493-023. Relative effect outcomes are informed by the full analysis set (FAS), which includes all patients who received at least 1 setmelanotide dose and provided baseline data. Some outcomes are informed by the pivotal patients only (n=16+16), and some are informed by the pivotal and supplemental cohort (n=22+22).

Safety outcomes are informed by the safety analysis set, which includes all patients who received at least 1 dose of study drug (placebo or setmelanotide) in RM-493-023. In addition, data from the extension study RM-493-022 was used to inform maintenance of efficacy of setmelanotide but was not used to inform the cost effectiveness model.

3.6.1 Relative effect

The RM-493-023 study has been completed. An overview of outcomes reported in the study, reported in the study and included in the health economic model and outcomes not reported in the study, but included in the health economic model, is shown in Table 10.Table 1

Because no data from the 14-week placebo-controlled study period was used in the health economic model, NOMA presents these, and other results from RM-493-023 considered relevant for the assessment of the clinical effect of setmelanotide in chapter 3.6.1.1 below.

Thereafter, the relationship between the relative effect in the clinical documentation and the modelled relative effect in the health economic model is described and assessed for the outcome measures included in the model (chapter 3.6.1.2 and onward).

Table 10. An overview of outcomes reported in the study RM-493-023, reported in the study and included in the health economic model, and outcomes not reported in the study, but included in the health economic model

Outcome	Reported in RM-493-023	Reported in RM-493-023 and included in the health economic model	Not reported in RM-493-023, but included in the health economic model
Mean percentage change in body weight compared to baseline after 14 weeks for adults (≥ 18 years)	x		
Mean percentage change in body BMI compared to baseline after 14 weeks for all patients	x		
Mean percentage change in weekly average 'daily hunger scores' compared to baseline after 14 weeks for patients ≥ 12 years without cognitive impairment	x		
Mean absolute change in BMI z-score compared to baseline after 14 weeks for children (< 18 years)	x		
Percentage change in body weight compared to baseline after 52 weeks for adults (≥ 18 years)	x		
Percentage change in BMI compared to baseline after 52 weeks for adults (≥ 18 years)	x		
Absolute change in BMI z-score compared to baseline after 52 weeks for children (< 18 years).	x		
Mean change in BMI 95th percentile score compared to baseline after 52 weeks for children (< 18 years).	x		
Proportion of adult patients (≥ 18 years) who achieved a ≥10% reduction in body weight from baseline after ~52 weeks	x	x	
Proportion of paediatric patients (<18 year) who achieved ≥0.2 reduction in BMI Z-score after 52 weeks	x	x	
Mean change in hyperphagia compared to baseline after 52 weeks			x

3.6.1.1 Relative effect – outcomes not included in the health economic model

Overall, in the pivotal full analysis set (patients ≥12 years old with BBS and Alström syndrome) in RM493-023, the primary endpoint was met - a statistically significant proportion of 32.3% of patients had a weight decrease of at least 10% versus active treatment baseline compared to a 10% historic control of untreated patients Few patients below the age of 12 were included in the trial, and

subgroup analyses by age were only exploratory. However, according to the EPAR the totality of the evidence supports the use of setmelanotide in BBS patients between 6 and 12 years (1).

In their submission, Rhythm Pharmaceuticals presents outcomes separately for those aged ≥18 years and <18 years (unlike the main trial results, where results are reported for patients aged ≥12 years). It is unclear whether these age categories were pre-specified. In growing children, body weight is significantly affected by physical development and maturation. Therefore, body weight and BMI is mainly used for patients aged ≥18 years, while weight-related parameters that adjust age and sex differences (such as BMI Z-score) are used for patients aged <18 years.

Table 11. Overview of outcome measures in the assessment of the clinical effect of setmelanotide versus placebo. Modified from the Danish Medicines Council (2) and Rhythm Pharmaceuticals.

	Setmelanotide	**Placebo**	**Difference**
Mean percentage change in body weight compared to baseline after 14 weeks of treatment for all patients*	-3,93%, SD=3,8 n=22	-0,34%, SD=2,1 n=22	-3,6%, 95% CI: -6,3, -0,9
Mean percentage change in body BMI compared to baseline after 14 weeks of treatment for adults (≥18 years)	-4,6%, SD=4,1 n=10	-0,13%, SD=2,9) n=12	-4,5%, 95 % CI: -6,5, -2,5
Mean percentage change in weekly average 'daily hunger scores' compared to baseline after 14 weeks of treatment for patients ≥12 years without cognitive impairment	-30,1%, SD=20,3 n=6	-15,7%, SD=14,5 n=12	-14,4%, 95 % CI: -31,9, 3,1
Mean absolute change in BMI z-score compared to baseline after 14 weeks of treatment for children (<18 years)*	-0,39, SD=0,24 n=12	-0,07, SD=0,14 n=10	-0,32, 95 % CI: -0,5, -0,14
Percentage change in body weight compared to baseline after 52 weeks of treatment with setmelanotide for adults (≥18 years)	-7,6%, 95 % CI: -11,5, -3,6 n=15	NA	NA
Percentage change in BMI compared to baseline after 52 weeks of treatment with setmelanotide for adults (≥18 years)	-9,1%, 95 % CI: -13,4, -4,8 n=15	NA	NA
Absolute change in BMI Z-score compared to baseline after 52 weeks of treatment with setmelanotide for children (<18 years).	-0,75, 95 % CI: -1,0, -0,49 n=14	NA	NA
Mean change in BMI 95th percentile score compared to baseline	-17,3, 95 % CI: -21,7, -12,9)		

after 52 weeks of treatment with setmelanotide for children (<18 years).	n=14		

*For some outcome measures (body weight and BMI Z-score after 14 weeks), data are reported based on the full population (pivotal and supplementary patients, while the other outcome measures are reported in the pivotal patient population in RM-493-023.

BMI and body weight

14-weeks of treatment with setmelanotide led to a significantly larger percentage decrease than placebo in body weight (mean difference: -3,6%, 95% CI: -6,3, -0,9) in adults, and in BMI (mean difference: -4,5%, 95% CI: -6,5, -2,5) across all patients (Table 11).

After 52-weeks of treatment, the mean reduction in BMI was 9,1% (95% CI: -11,5, -3,6) and in body weight 7,1% (95% CI: -13,4, -4,8), relative to baseline in adults (Table 11). The longitudinal change in body weight indicates that the reduction plateaus after approximately 34 weeks of treatment (Figure 5, in Appendix 1).

Figure 3 illustrates the individual change in percentage BMI for all patients during the 14-week placebo control study period. The figure shows that, except for one, all setmelanotide-treated patients experienced a reduction in percentage BMI, whereas roughly half of the placebo-controlled patients saw a reduction, while the other half gained weight. Importantly, there was considerable individual variation in the treatment response.

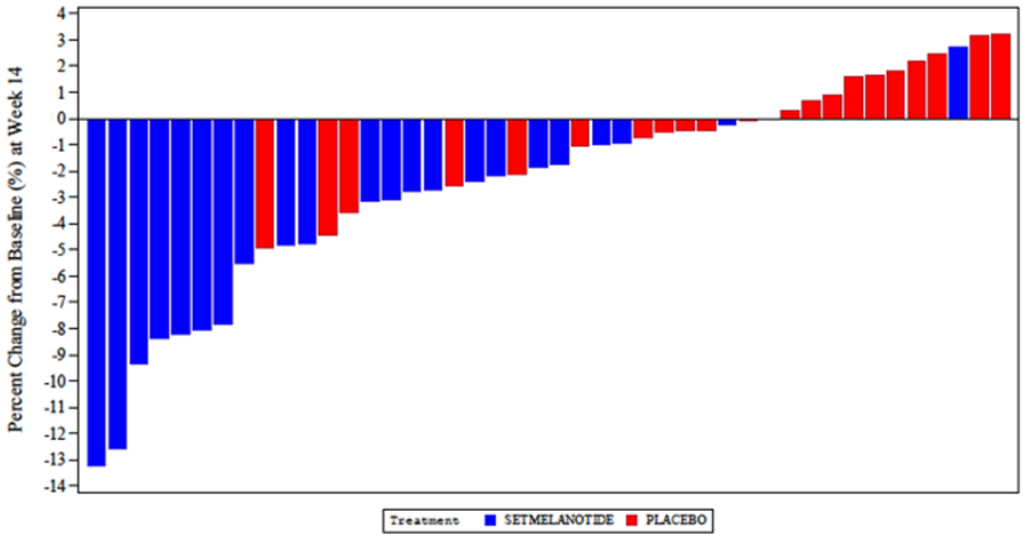

Figure 3. Waterfall plot of percent change in BMI from baseline to week 14 (study RM-493-023, all patient PCAS).
Source: Rhythm Pharmaceuticals

BMI Z-score in children

In children and adolescents, 14-weeks of treatment with setmelanotide led to a significantly larger decrease than placebo in BMI Z-score (mean difference: -0,32, 95% CI: -0,5, -0,14) (Table 11).

After 52 weeks of treatment, the mean decrease in BMI Z-score was -0,75 (95% CI: -1,0, -0,49) and for the 95th BMI percentile score, -17,3 (95% CI: -21,7, -12,9), relative to baseline (Table 11). The longitudinal change in BMI Z-score shows that the reduction continued throughout the treatment period (Figure 6, Appendix 1).

Daily self-assessment of hunger

In RM-493-012, hunger was assessed through a daily self-assessment tool in patients ≥12 years of age without cognitive impairment. This tool was apparently developed specifically for the setmelanotide development program, and the tool has not been used in other trials or undergone validation.

Three aspects of hunger were self-reported by patients daily. The questionnaire assessed average hunger ("In the last 24 hours, on average, how hungry did you feel?), maximal hunger ("In the last 24 hours, how hungry did you feel when you were the most hungry?"), and morning hunger ("This morning when you woke up for the day, how hungry did you feel?). Responses were based on a numerical Likert-type scale ranging from 0 to 10, with 0 = "not hungry at all" and 10 = "the hungriest possible." Each hunger aspect of the daily hunger questionnaire was scored separately, and scores were averaged on a weekly basis. For a week of hunger scores to be considered evaluable, data needed to be recorded and available for analysis on at least 1 of the 7 days. As noted in the EPAR and by the Danish Medicines Council, NOMA considers "worst hunger" to be the most meaningful of the three daily hunger scores (1;2).

The investigator determined whether the patient had cognitive impairment (e.g., could not assess their own hunger); a formal diagnosis was not required. Thus, this outcome was only available for six patients in the setmelanotide group and 12 patients in the placebo group.

After 14-weeks of treatment, treatment with setmelanotide led to a numerically larger percentage decrease in 'daily hunger score compared to placebo (mean difference: -14,4%, 95 % CI: -31,9, 3,1, Table 11). The reduction in the 'daily hunger score' was mainly observed during the first eight weeks of treatment and remained stable thereafter Figure 4.

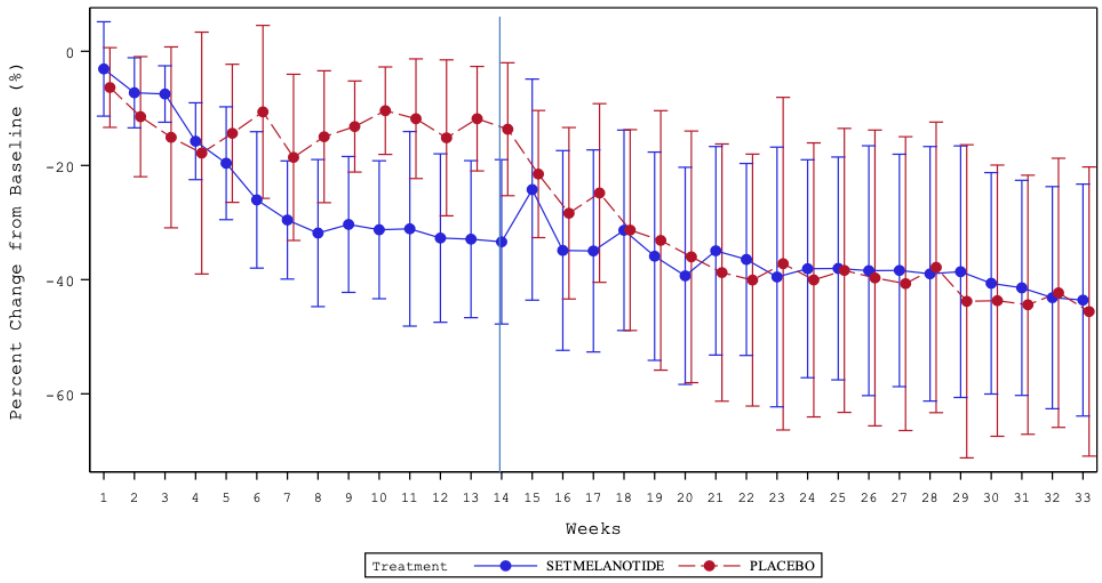

Figure 4. Average 'daily hunger score' measured as average 'worst hunger'. Source: EPAR (1)
The vertical blue line indicates 14 weeks, at which point patients in the placebo group transition to treatment with setmelanotide

NOMA's assessment

Results from the 14-week placebo-controlled study period showed a significant reduction in BMI and body weight in adults, a significant reduction in BMI Z-score in children and are indicative of a lower 'daily hunger score' in patients treated with setmelanotide compared to placebo. The long-term effect of setmelanotide is uncertain due to the lack of a control group and open-label design.

As stated in the EMA Guideline on clinical evaluation of medicinal products used in weight management, a statistically significant, placebo-corrected weight loss of at least 5% of baseline weight after 12 months of treatment is regarded as a valid criterion for adults (20). According to a medical expert consulted by NOMA, a reduction in BMI Z-score of at least 0.25 is generally regarded as a clinically relevant difference in children adolescents (21). Against this background, the observed effects on body weight and BMI Z-score in RM-493-023 can probably be considered clinically relevant, with more convincing results seen in children. However, due to the study design, the relative effect beyond 14 weeks is uncertain and results obtained at 52 weeks are not placebo corrected. Moreover, it is notable that less than half of the adult patients achieved the primary endpoint of at least 10% reduction in body weight relative to baseline after 52 weeks of treatment.

Although effects on outcomes related to appetite and food behaviour are important, the clinical relevance of a reduction in the 'daily hunger score' remains uncertain. This is because the tool has not been validated, and there is no clear understanding of what constitutes a high score or a clinically significant change. Medical experts consulted by NOMA, state that they have no experience with the tool. The outcome is associated with further uncertainty due the small number of observations, considerable placebo effect and is prone to bias, as there were more patients with cognitive impairment in the setmelanotide arm, and these did not inform this outcome.

In RM-493-023, only patients <12 years old received guidance on dietary advice. Beyond this, no lifestyle guidance was given to the patients. In Norwegian clinical practice, patients with BBS and obesity are managed with guidance on diet and physical activity. This introduces uncertainty regarding the generalizability of study results. It is likely that the treatment effect in the BSC arm is underestimated compared to what would be expected in a Norwegian context, leading to an inflation of the estimated relative effect.

3.6.1.2 Change in body weight (≥18 years) and BMI Z-score (<18 years) - included in the health economic model

Submitted clinical documentation

A responder was defined as adult patients who achieved ≥10% weight loss or paediatric patients who achieved ≥0.2 reduction in BMI z-score after 52 weeks of setmelanotide treatment.

Among pivotal adult patients, 7 of 15 (46,7%; 95% CI: 18,6, 55,9) were defined as responders. Among pivotal paediatric patients, 12 of 14 (85,7%; 95% CI: 57,2, 98,2) were defined as responders.

Implementation of change in body weight and BMI Z-score in the health economic model

In the health economic model, the treatment effect of setmelanotide on body weight is quantified through changes in BMI and BMI Z-score categories for treatment responders.

In order to inform the economic model, Rhythm Pharmaceuticals conducted a post-hoc analysis of BMI/BMI z-score category shift in patients aged ≥18 years and <18 years (Table 12 and Table 13). Only data from setmelanotide responders were used to inform on these transitions, as non-responders were assumed to discontinue setmelanotide treatment in clinical practice. Rhythm Pharmaceuticals assumed that adult patients who were classified as responders had a decrease of one BMI class level and paediatric patients who were classified as responders had a decrease of two BMI z-score class levels. The model assumes that this treatment effect on BMI/BMI z-score will not manifest until the end of the first year of treatment.

Responders who discontinued treatment were assumed revert immediately to their baseline BMI/BMI Z-score, with no tapering effect assumed. Patients who responded to setmelanotide were assumed to

maintain stable BMI/BMI Z-scores for the rest of their lifetime, assuming continued treatment. For this assumption Rhythm Pharmaceuticals refer to a publication by Pomeroy et al. 2021, which presumably showed that BMI Z-scores in BBS patients peak between ages 2 and 5 and subsequently stabilize or decrease (8).

Table 12. BMI shift data for individual patients aged ≥18 years who were classified as 52-week responders (study RM-493-023, pivotal patients). Source: Rhythm Pharmaceuticals

Obesity class	BMI	001-005	001-008	001-009	001-010	003-003	007-002	013-002
	50+				54.63	54.82		
IV	45 to <50		46.78		49.85	46.79	43.80	47.44
III	40 to <45	42.99	40.02				36.15	
II	35 to <40	38.24		39.46				39.07
I	30 to <35			34.98				
Overweight	25 to <30							
Class change		1	1	1	1	1	1	2

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

Table 13. BMI Z-score shift data for individual patients aged <18 years who were classified as 52-week responders (study RM-493-023, pivotal patients). Source: Rhythm Pharmaceuticals

BMI Z-score	001-001	001-002	001-003	001-004	001-007	005-001	005-002	005-004	006-001	006-002	006-003	006-004
4+		5.51/ 4.31		4.25		4.37/ 4.08			7.08/ 6.29			
3.5 to <4					3.83					3.59		3.76
3 to <3.5				3.36			3.15					
2.5 to <3	2.65				2.87					2.79		2.82
2 to <2.5			2.13				2.42	2.48/ 2.2				
1 to <2	1.91										1.77	
<1			0.22								0.85	
Class change	2	0	2	2	2	0	2	0	0	2	1	2

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

NOMA's assessment

NOMA acknowledges that the primary endpoint in the clinical study is used in the health economic model. However, in the absence of a control group, the response data are solely based on comparisons with baseline values. Given that a placebo effect was indicated in the results from the placebo-controlled treatment period, NOMA believes that the response rate for setmelanotide used in the health economic model is likely overestimated.

Based on the submitted data, NOMA is not convinced that all paediatric patients responding to setmelanotide treatment will experience a decrease of two BMI Z-score categories. Hence, a scenario

analysis was conducted where paediatric patients who were classified as responders were assumed to have a decrease of one BMI class levels instead of two BMI class levels, as assumed in the submitters base-case.

NOMA's conclusion on change in body weight and BMI z-score
NOMA mainly relies on the same assumptions as Rhythm Pharmaceuticals, but notes that the modelled treatment effect of setmelanotide is likely overestimated to an unknown extent. NOMA explores the impact of changing BMI Z-score class change in paediatric treatment responders in a scenario analysis, as described in chapter 4.

3.6.1.3 Change in hyperphagia - included in the health economic model

Submitted clinical documentation
No clinical documentation was provided on the relative effect of setmelanotide on hyperphagia.

Implementation of hyperphagia in the health economic model
Setmelanotide responders (defined by change in body weight and BMI-z score) are expected to transition from severe hyperphagia to a state of mild hyperphagia and remain in that state for as long as they continue treatment. It is assumed in the model by Rhythm Pharmaceuticals that responding patients will experience a significant reduction in hyperphagia levels as a necessary precursor to achieving meaningful improvements in their weight/BMI Z-score. Non-responders are assumed to be identified at 14-weeks (as discussed in Chapter 3.4) and discontinue treatment and do not experience lasting treatment effects. These patients revert to their baseline BMI/BMI Z-score and hyperphagia states. Rhythm Pharmaceuticals bases this assumption on the presumption that clinicians can accurately identify non-responders at 14 weeks based on changes in hyperphagia and other clinical parameters, leading to discontinuation of treatment for those patients.

In the submitted model, changes in hyperphagia were not directly linked to BMI changes. Instead, hyperphagia improvements were modelled independently and accounted for primarily through their impact on HRQoL.

Patients receiving only BSC are assumed to experience no change in hyperphagia and remain in severe hyperphagia throughout their lifetime.

NOMA's assessment
Change in hyperphagia state among setmelanotide responders is a main driver in the base case submitted by Rhythm Pharmaceuticals, although this is not supported by any available data and solely relies on assumptions. Although the observed reduction in '*daily hunger score'* indicates a potential effect of setmelanotide on appetite and food behaviour, NOMA expresses concern about the lack of evidence supporting a significant reduction in hyperphagia. Moreover, as pointed out by the Danish Medicines Council, it is unclear why available tools to assess hyperphagia, validated in patients with Prader-Willis syndrome, were not used in RM-493-023 (2).

Consequently, NOMA excludes the effect of setmelanotide on hyperphagia state in the main analysis and includes only the effect on BMI/BMI Z-score, where an effect has been documented. However, an effect on hyperphagia is included as a scenario analysis to determine how the utility multipliers of hyperphagia impact the effect of transitioning from one state to the other based on the changes in baseline distribution for the patients, as described in chapter 3.3.4. The utility value of each model cycle is calculated by applying a hyperphagia-severity utility multiplier to utility values by BMI/BMI Z-score category and age.

Importantly, the inclusion of undocumented effects in a scenario analysis represents an exemption from NOMA's usual practice. This is justified by the rarity of BBS coupled with challenges in gathering reliable data on hyperphagia, along with the rationale that effects on BMI and hyperphagia may be correlated. However, this assumption is highly uncertain, as hyperphagia is regarded as a particular symptom in BBS. Consequently, results from this scenario analysis carries significant uncertainty and will not automatically be accepted in other HTAs.

NOMA's conclusion on hyperphagia:
NOMA does not accept the assumption of a treatment effect on hyperphagia and excludes this from the main analysis. Consequently, the primary driver in NOMA's analysis is the documented effect of setmelanotide on changes in body weight and BMI Z-score. However, a potential effect on hyperphagia is included in a scenario analysis. The inclusion of undocumented effects is an exception to NOMA's usual practice, and results from this scenario carry significant uncertainty and will not be automatically accepted in other assessments. The impact of this adjustment on the ICER is outlined in chapter 4.

3.6.2 Adverse events

Submitted clinical documentation

Table 14 shows adverse events reported in RM-493-023. The safety population included 44 patients with BBS and 8 patients with Alström syndrome, and 50 out of 52 were exposed to setmelanotide. The majority of patients, regardless of group, experience at least one treatment-emergent adverse event (TEAE) or related TEAE. During the placebo-controlled period, two (7,4%) setmelanotide-treated patients experienced a TEAE leading to study drug withdrawal, increasing to 6 (11,5%) during the 52-week extension period.

Table 14. Overview of treatment-emergent adverse events overall by treatment group in RM-493-023 (safety population; n = 52). Source: EPAR (1)

	14-week placebo-controlled period		**52 weeks uncontrolled period**
Patients with at least 1	**Setmelanotide (N = 27), n (%)**	**Placebo (N = 25), n (%)**	**Setmelanotide (N = 52), n (%)**
TEAE	26 (96,3)	24 (96,0)	52 (100)
Treatment-emergent Related Adverse Event[1]	24 (88,9)	22 (88,0)	51 (98,1)
Serious TEAE	1 (3,7)	2 (8,0)	3 (5,8)
Serious Related TEAE	0	1 (4,0)	1 (1,9)
TEAE leading to death	0	0	0
TEAE leading to Study Drug Withdrawal[2]	2 (7,4)	3 (12,0)	6 (11,5)
Related TEAE leading to Study Drug Withdrawal	-	-	5 (9,6)
Severe TEAE	-	-	3 (5,8)

[1]Related indicates the adverse event was noted as possibly or probably related to the study drug
[2]Study drug permanently withdrawn

An overview of adverse events in BBS patients only is shown in Table 15. Overall, the most common TEAEs among setmelanotide-treated patients during the placebo-controlled period, with the corresponding incidence among placebo-treated patients, were skin hyperpigmentation: 59,1% versus 0%; Injection site erythema: 45,5% versus 50,0%, Injection site pruritus: 31,8% versus 40,9%, Injection site bruising: 27,3% versus 40,9% and vomiting: 27,3% versus 0%.

Table 15. Overview of treatment-emergent adverse events overall by treatment group in RM-493-023 (BBS Population; N = 44). Source: Rhythm Pharmaceuticals

	14-week placebo-controlled period		**52 weeks uncontrolled period**
System Organ Class/ Preferred Term	**Setmelanotide (N = 22), n (%)**	**Placebo (N = 22), n (%)**	**Setmelanotide (N = 44), n (%)**
TEAEs, n (%)	21 (95.5)	21 (95.5)	44 (100.0)
Skin hyperpigmentation	13 (59.1)	0 (0.0)	26 (59.1)
Injection site erythema	10 (45.5)	11 (50.0)	23 (52.3)
Injection site pruritus	7 (31.8)	9 (40.9)	18 (40.9)
Injection site bruising	6 (27.3)	9 (40.9)	18 (40.9)
Nausea	5 (22.7)	6 (27.3)	16 (36.4)
Injection site pain	3 (13.6)	7 (31.8)	13 (29.5)
Vomiting	6 (27.3)	0 (0.0)	13 (29.5)
Injection site induration	5 (22.7)	4 (18.2)	13(29.5)
Diarrhoea	2 (9.1)	1 (4.5)	10 (22.7)
Headache	5 (22.7)	7 (31.8)	11 (25.0)
Injection site oedema	2 (9.1)	1 (4.5)	6 (13.6)
Melanocytic nevus	1 (4.5)	0 (0.0)	6 (13.6)
Injection site haemorrhage	3 (13.6)	2 (9.1)	6 (13.6)
Spontaneous penile erection	1 (4.5)	0 (0.0)	5 (11.4)
Fatigue	0 (0.0)	2 (9.1)	5 (11.4)

Submitted health economic model

Rhythm Pharmaceuticals included nausea/vomiting and injection site reactions in the health economic model. Although skin pigmentation was frequently reported, it was deemed not to affect the quality of life of the patients and therefore not included. The remaining adverse reactions were not included in the analysis as their frequency of occurrence was low in the study population and thus assumed to have a negligible effect. The included adverse events (nausea, vomiting, and injection site erythema) were expected to resolve during the treatment titration period. Therefore, the disutilities associated with these adverse events were only applied for the first 2 weeks of the analysis's first year. Additionally, the costs associated with treatment of adverse events were included in the health economic model, as described in chapter 3.7.3.

NOMA's assessment

NOMA does not assess whether the safety profile of setmelanotide is acceptable in relation to the expected benefits, as this has been evaluated by the EMA through the marketing authorization

procedure. For the health technology assessment, the differences between the intervention and the comparator in the incidence of side effects, particularly those affecting quality of life and/or resource use, and how these are addressed in the health economic model, are most relevant.

As noted in the EPAR, long-term safety data on setmelanotide is limited. Additionally, the small number of treated patients makes it unlikely to detect rare adverse reactions. The brief placebo-controlled period, combined with a population that has multiple comorbidities, further complicates establishing a clear causal relationship. Uncertainties persist around hyperpigmentation, the risk of prolonged erections, depression, and the impact of anti-drug antibodies (ADAs). Ongoing safety monitoring is planned through the ongoing PASS (observational registry) study on POMC/LEPR deficiency populations, which will be extended to include paediatric and adult patients with BBS (1).

Adverse events have limited impact on the results of the health economic analysis and are not discussed further.

NOMA's conclusion on adverse events
NOMA relies on the same assumptions as Rhythm Pharmaceuticals

3.6.3 Quality of life

Submitted clinical documentation

Health related quality of life (HRQoL) was assessed in pivotal patients in RM-493-023. Of these, 20 patients, including 10 without cognitive impairment, had HRQoL data at baseline and week 52 (< 18 years old, n = 9; ≥ 18 years old, n = 11). The following instruments were used: the *Impact of Weight on Quality of Life (IWQOL)-Lite* scores in patients ≥18 years, *EuroQoL-5D-5L (EQ-5D-5L)* in patients ≥ 16 years and *Paediatric Quality of Life Inventory (PedsQL)* scores in patients <18 years. According to the EPAR, these were exploratory outcomes (1), and were only assessed in the setmelanotide group and presented descriptively.

After 52 weeks of treatment, there was a numerical change indicating improvements across most quality of life-endpoints (Tables 16-18). These results must be interpreted with caution due to data from selected patients, lack of a control group and open-label design. It is unclear why not all subscores from the PedsQL were reported.

Table 16. Effect of setmelanotide on IWQOL-LITE score in patients aged ≥18 years providing baseline and week-52 data (study RM-493-023, pivotal patients): Source: Rhythm Pharmaceuticals

	Active-treatment baseline (n=11)	**Change from baseline to Week 52 (n=11)**
IWQOL-Lite total score, mean (SD)	**74.9 (12.6)**	**+12.0 (10.8)**
IWOQOL-Lite physical function score, mean (SD)	63.0 (13.9)	+15.3 (12.1)
IWOQOL-Lite sexual life score, mean (SD)	90.1 (14.9)	+9.3 (14.1)
IWOQOL-Lite work score, mean (SD)	83.7 (17.0)	+9.5 (14.7)
IWOQOL-Lite public distress score, mean (SD)	75.0 (20.0)	+12.7 (15.7)
IWOQOL-Lite self-esteem score, mean (SD)	79.1 (20.0)	+11.1 (16.7)

IWQOL-Lite, Impact of Weight on Quality of Life
Note: The questionnaire is a 31-item, obesity-specific assessment of HRQOL consisting of a total score and 5 domain scores. Raw scores are transformed on a scale of 0–100, with 0 representing the worst possible and 100 the best possible HRQOL (22).

Table 17. Effect of setmelanotide on PedsQL score in patients aged <18 years who provided baseline and week-52 data (study RM-493-023, pivotal patients). Source: Rhythm Pharmaceuticals

	Active-treatment baseline (n=9)	**Change from baseline to Week 52 (n=9)**
PedsQL total score, mean (SD)	**67.2 (20.1)**	**+11.2 (14.4)**
PedsQL physical function score, mean (SD)	60.4 (29.8)	+14.0 (29.3)
PedsQL psychosocial score, mean (SD)	70.7 (16.3)	+9.3 (10.5)

PedsQL, Paediatric Quality of Life Inventory
Note: The PedsQL is a 23-item, self- or caregiver-reported, age-dependent assessment of HRQOL in children and adolescents with or without acute or chronic health conditions that encompasses 4 domain scores (physical, emotional, social, and school functioning).

Table 18. Effect of setmelanotide on EQ-5D-5L score in patients aged ≥16 years who provided baseline and week-52 data (study RM-493-023, pivotal patients). Source: Rhythm Pharmaceuticals

	Active-treatment baseline (n=13)	**Change from baseline to Week 52 (n=13)**
Mobility score, mean (SD)	1.69 (0.82)	-0.46 (0.84)
Self-care score, mean (SD)	1.31 (0.46)	0.00 (0.39)
Usual activities score, mean (SD)	1.54 (0.63)	-0.38 (0.74)
Pain/discomfort score, mean (SD)	1.46 (0.63)	0.08 (0.62)
Anxiety/depression score, mean (SD)	1.38 (0.62)	-0.08 (0.92)
VAS, mean (SD)	69.38 (16.24)	8.15 (13.48)

VAS, visual analogue scale
Note: EQ-5D-5L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems (1), slight problems (2), moderate problems (3), severe problems (4) and extreme problems (5). The EQ VAS records the patient's self-rated health on a vertical visual analogue scale (0-100) where the endpoints are labelled 'The best health you can image' and 'The worst health you can image' (23).

Submitted health economic model

Rhythm Pharmaceuticals argues that EQ-5D does not fully capture the impact of hyperphagia, and that the VAS score slightly below population norms shown in RM-493-023 was unreasonable given the disease manifestations of BBS. Therefore, Rhythm Pharmaceuticals considered EQ-5D-data from RM-493-023 inappropriate for use in the cost-effectiveness analysis. Rhythm Pharmaceuticals performed a systematic literature search (updated in February 2023), as described in chapter 2.1, aimed at identifying both clinical and HRQoL data. However, none of the 11 identified studies were deemed relevant. Instead, utility weights derived from a vignette study and various sources from the literature were used to inform the model.

The general deliverables of quality-of-life documentation provided by Rhythm Pharmaceutical compared to NOMA's guidelines/requirements for describing how clinical data on quality of life has been implemented in the health economic model are detailed in Appendix 2.

The model has seven BMI/BMI Z-score defined health states where utility weights are applied. The impact on quality of life was estimated through 1) BMI/BMI Z-score category and age, 2) hyperphagia severity, 3) disutility due obesity-related comorbidities, 4) disutility of non-obesity-related BBS symptoms, 5) disutility associated with treatment-related adverse events, and 6) caregiver disutility. The utility value for each model cycle was calculated by applying a hyperphagia-severity utility-multiplier to utility values by BMI/BMI Z-score category and age, applying a multiplier for non-obesity-related BBS symptoms, and then applying comorbidity disutilities by BMI/BMI Z-score category, adverse events (only the first model cycle), and caregiver disutilities as absolute decrements.

Utility values for BMI and BMI Z-score

To estimate utility values related to BMI Z-score categories in paediatric patients, Rhythm Pharmaceuticals used a UK study where a sample of 96 obese and 444 healthy children answered a UK-version of a generic paediatric QOL inventory (PedsQL 4.0) (24). Data from the early to post-pubertal subgroup with BMI Z-score averages of 3.5 (obese) and 0.3 (healthy) were used to populate the model BMI Z-score 0.0 to <1.0 and 3.5 to <4.0 categories, respectively. These values were mapped from PedsQL to EQ-5D (UK EQ-3D-3L tariff set) using the ordinary least squares regression mapping algorithm by Khan et al. (25). Then, linear extrapolation was used to calculate utility values for the remaining BMI Z-score categories (Table 19).

Table 19. Utility values by BMI Z-score category for the paediatric patient population. Source: Rhythm Pharmaceuticals

BMI Z-score category	From the instrument	To the instrument	Results
0.0-1.0	PedsQL, 82.8 (12.4)	EQ-5D-Y	0.89
1.0-2.0			0.87*
2.0-2.5			0.86*
2.5-3.0			0.85*
3.0-3.5			0.83*
3.5-4.0	PedsQL, 70.1 (17.0)	EQ-5D-Y	0.82
≥4.0			0.81*

*Extrapolated

To estimate utility values related to BMI-categories in adult patients, Rhythm Pharmaceuticals used a U.S. study based on Medical Expenditure Panel Survey data (26). Rhythm Pharmaceuticals provided no description of the methodology, and NOMA was not able to access the full text publication of the study. According to the Danish Medicines Council, the study models a microsimulation of weight changes, health status, and gastric bypass costs for severely obese patients. Quality of life data is based on EQ-5D-5L measurements, and the population is drawn from data on over 28,000 patients published by the College of Surgeons with utility values based on U.S. standards (2). The resulting utility values used in the health economic model is shown in Table 20.

Table 20. Utility values by BMI-category for the adult patient population. Source: Rhythm Pharmaceuticals

BMI category (kg/m²)	Age 18-30	Age 31-40	Age 41-50	Age 51-60	Age 61-70	Age >70	Instrument
20- <25	0.91	0.89	0.86	0.83	0.81	0.79	EQ-5D-5L
25- <30	0.91	0.89	0.86	0.83	0.81	0.79	
30- <35	0.89	0.86	0.82	0.8	0.79	0.76	
35- <40	0.88	0.83	0.79	0.77	0.76	0.74	
40- <45	0.84	0.82	0.75	0.73	0.71	0.69	
45- <50	0.84	0.82	0.75	0.73	0.71	0.69	
≥50	0.8	0.77	0.7	0.69	0.66	0.66	

Utility values for hyperphagia

To obtain utility values for the impact of hyperphagia on quality of life, Rhythm Pharmaceuticals used a vignette study where participants from the United Kingdom general population valued four health state vignettes drafted from literature review and input from clinicians (Appendix 3). The resulting utility multipliers are shown in Table 21.

Table 21. Utility multipliers for hyperphagia obtained from the vignette Study. Source: Rhythm Pharmaceuticals

Health state	Utility multiplier	Method
No hyperphagia	0.98	Vignette-based TTO
Mild hyperphagia	0.91	Vignette-based TTO
Moderate hyperphagia	0.72	Vignette-based TTO
Severe hyperphagia	0.38	Vignette-based TTO

TTO, time trade-off

Utility values for non-obesity symptoms

Rhythm Pharmaceuticals applied an arbitrary utility multiplier of 0.8 for non-obesity-related symptoms, such as blindness and cognitive impairment.

Comorbidity-specific disutilites

Rhythm Pharmaceuticals obtained comorbidity specific disutilites for sleep apnoea, osteoarthritis, diabetes mellitus type 2 and cardiovascular events based on Søltoft et al. 2009 (27) and Sullivan et al. 2011 (28). The impact of comorbidities was assumed to worsen with increasing obesity severity. To reflect this, each comorbidity disutility was disaggregated across BMI Z-score categories along a log-linear distribution, using the mean BMI Z-score and corresponding standard deviation in Lindberg et al. 2020 (29), producing specific disutilities by BMI category for each comorbidity.

Disutility associated with adverse events

Rhythm Pharmaceuticals included disutilites related to nausea and vomiting, and injection site erythema obtained from studies related to type 2 diabetes mellitus (30;31). These were assumed to only impact patients during the first two weeks in year 1 of treatment (Table 22)

Table 22. Disutility associated with adverse events. Source: Rhythm Pharmaceuticals

Adverse event	Disutility	Instrument	Assumed duration
Nausea and vomiting	-0.04	Standard gamble adjusted utility scores*	2 weeks
Injection site erythema	-0.011	Standard gamble adjusted utility scores*	2 weeks

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

Disutilites associated with caregiver burden

Rhythm Pharmaceuticals implemented caregiver burden as an annual disutility in the BSC arm and the patients who discontinued treatment with setmelanotide (except in the first model cycle, when caregiver burden is also implemented as an annual disutility in patients who are on treatment with setmelanotide).

The utility decrement was applied assuming an average of 1.5 caregivers per paediatric patient and 1 caregiver per adult patient, with a disutility of 0.0986. This was implemented as in the NICE submission for metreleptin for treatment of lipodystrophy, based on evidence from Janssen 2019 and UK general population norms (32).

NOMA's assessment

According to NOMA's submission guidelines: *"Whenever EQ-5D measurements of health-related quality-of life (HRQoL) are collected in the pivotal clinical studies for the intervention in question, these must be submitted and included as an option in the model."* This was not an option in the model submitted by Rhythm Pharmaceuticals. NOMA considers the arguments presented by the submitter for not including these data to be insufficiently substantiated, and that it is a significant weakness of the submitted model that utility values are not derived from the study RM-493-023, but from a vignette study, assumptions and external literature. However, due to the low number of patients informing HRQoL-outcomes in RM-493-023 and the lack of validated hyperphagia measures, considerable uncertainty in utility values would be expected anyway. Thus, the submitted material was considered a pragmatic solution in this specific case. The limitation of the methodology is discussed in the following paragraphs.

Rhythm Pharmaceuticals conducted a systematic search for external literature in relevant databases, but this did not yield any relevant studies on quality of life in patients with BBS. It remains unclear how the studies that eventually informed the model were identified and selected as this process has not been described. A description of the selected studies and their methodology is also lacking, which hampers NOMA's assessment. This is a great concern.

The resulting utility values in the company's base case are implausibly low. For patients in the BSC arm, mean quality of life is close to zero for the majority of the model's time horizon, and when including carer disutility, it goes into the negative. The excessive use of utility multipliers and mixing of a multiplicative approach for utilities and additive approach for disutilities seems to contribute to these extreme values. Based on data from RM-493-023, the average EQ-5D VAS score among patients without cognitive impairment was 69.38. Index scores on the different EQ-5D dimensions, show fairly high values. These patients would also likely have the comorbidities and non-obesity-related symptoms that Rhythm Pharmaceuticals deduct utility for in their base case analysis. While the trial is small and may not capture differences in quality of life related to hyperphagia, the values shown indicate that patients are not close to "worse-than-death" health states. These concerns were communicated to Rhythm Pharmaceuticals, who replied that they were confident that these values accurately capture the patient experiences and comorbidities associated with the condition.

Rhythm Pharmaceuticals has not age adjusted the utility values in the submitted model. This is not in line with NOMA's submission guideline, where age-adjustment using a multiplicative method is recommended.

NOMA is also concerned about the method for obtaining utility values for BMI Z-score categories in paediatric patients. This included mapping of aggregated PedsQL-values to EQ-5D-values for two categories and extrapolating these across remaining categories using linear regression. This method may fail to capture non-linear health impacts across the BMI spectrum, which could affect the accuracy of QALY estimates for paediatric patients. In both adult and paediatric patients, utility values were derived from general obese populations rather than patients with BBS. This risks oversimplifying or inaccurately representing the unique health challenges of BBS patients. Further, the utility values for BMI in adults are weighted using U.S. preferences, which does not align with NOMA's guidelines. In lack of other sources, NOMA has included the submitted utility values in the analysis.

Due to the lack of direct evidence, NOMA also includes the utility values for categories of hyperphagia, although these are regarded as very uncertain due to the use of a vignette study. Importantly, a treatment effect on hyperphagia was not accepted in NOMA's main analyses (see chapter 3.6.1.3).

Rhythm Pharmaceuticals also included an arbitrary utility multiplier of 0.8 for non-obesity BBS symptoms in their submitted model. The multiplier increases the severity of BBS profoundly, but also reduces the utility gain with weight loss. While the use of a multiplier is considered acceptable, NOMA questions its value, viewing it as largely unfounded. However, in lack of alternative values, the utility multiplier of 0.8 is included in NOMA's analysis to account for BBS symptoms unrelated to obesity

NOMA has not included disutilities related to caregiver burden, as the same documentation requirements for changes in quality of life apply to caregivers as to patients, and these requirements are not met in this case. Moreover, incorporating caregiver utilities resulted in implausibly negative QALY values in the initial cycles of the BSC arm, indicating values worse than death. Excluding the caregiver utilities was considered appropriate to avoid potential underestimation of QALYs in the BSC arm.

Additionally, NOMA considers the utility values for BMI/BMI Z-scores to inherently account for the impact of comorbidities, thereby excluding the need for comorbidity-specific disutilities. The methodology for obtaining comorbidity-specific utility values has not been assessed by NOMA.

Overall, NOMAs regards that the utility values submitted by Rhythm Pharmaceutical lack both internal and external validity. Therefore, all outputs from the health economic model must be interpreted with great caution. The methodology will not automatically be accepted by NOMA in other assessments.

NOMAs conclusion on quality of life
All sources of utility values are associated with limitations, resulting in considerable uncertainty in the analysis. In NOMA's main analysis, disutilities related to comorbidities are excluded, as the utility values for BMI/BMI Z-scores are assumed to already account for these factors. Similarly, disutilities for caregiver burden are also excluded.

Overall, NOMA considers that the utility values submitted by Rhythm Pharmaceuticals lack both internal and external validity. Consequently, the outputs from the health economic model should be interpreted with caution. Similarly obtained utility values will not automatically be accepted by NOMA in other assessments.

3.7 Resource use, costs, and other inputs in the health economic model

3.7.1 Drug costs for intervention and comparator

Submitted Documentation

The drug prices in Rhythm Pharmaceutical's submitted base case analysis are based on the pharmacy's maximum retail price (maximum AUP) excluding VAT, as required by current guidelines. Table 23 summarizes the assumptions Rhythm pharmaceutical has made in its analysis for calculating the drug cost of setmelanotide and BSC.

Table 23. Drug costs for intervention and comparator in the health economic analysis. Prices based on maximum AUP excluding VAT

Treatment	Package size and form	Dose (mg)	Cost per Package (NOK)	Relative dose-intensity (RDI)	Distribution in treatment arm
Setmelanotide	1 ml	10 mg/ml	30,287.04	NA	100 %
Treatment group for Setmelanotide	**Description**			**Cost per cycle (NOK) Year 1**	**Cost per cycle (NOK) Year 2**
Paediatric	The drug cost per cycle is based on the drug dosage criteria presented in Table 9.			2,724,015	2,765,585
Adult				3,065,801	3,097,456

NOMA's assessment

NOMA used the dosage and cost assumptions provided by Rhythm Pharmaceuticals in its main analysis, applying the maximum AUP (pharmacy price excluding VAT) without accounting for discounts, price reductions, or patent expiration. For BSC, no drug costs are included, as it involves non-pharmacological interventions like diet and exercise guidance within standard monitoring.

The model reflects the treatment regimen submitted (e.g., mg, package sizes) and assumes no wastage, as leftover medication is expected to be reused. Administration costs are excluded,

assuming self-administration with a caregiver support if relevant. Compliance has not been modelled or accounted for by the submitter but discussed in terms of the non-responder.

In summary, the cost and dosage modelling align with the submitted data, with no adjustments for factors like wastage or compliance variability, therefore NOMA does not change this assumption with regards to its main analysis.

NOMA's conclusion on drug costs for the intervention and the comparator
NOMA primarily bases its assessment on the same approach as the Rhythm Pharmaceuticals regarding the maximum AUP price excluding VAT, assuming no wastage and adopts the implicit assumption of adherence as indicated in the submitted treatment regimen.

3.7.2 Administration costs

Submitted documentation
In their submission, Rhythm Pharmaceuticals assumed that the administration of setmelanotide would not incur additional costs, as patients are responsible for self-administering the treatment. To facilitate this, the company proposed a patient support program, which includes training for both patients and caregivers if applicable on the correct administration of the drug. This strategy aims to ensure proper treatment administration while minimizing the need for additional healthcare resources.

NOMA's assessment
NOMA assesses the assumptions made by the company regarding the administration costs of setmelanotide are reasonable. The company has assumed there would be no additional costs, as patients or carers administer the treatment. To facilitate this, patients and caregivers will be trained in proper administration as part of a patient support program. NOMA considers that this assumption is reasonable, although the training will involve some costs associated with healthcare personnel, such as a nurse time for instruction. However, these costs are minimal compared to other treatment-related expenses and are unlikely to significantly impact the overall results.

NOMA considers the assumption that setmelanotide incurs no additional administration costs to be reasonable. Moreover, any potential variations in administration costs are unlikely to significantly affect the overall results of the cost-effectiveness analysis.

NOMA's conclusion on administration costs
NOMA agrees with the assumptions made by the company with respect to administration cost and does not make any adjustments to these for its main analysis.

3.7.3 Costs of adverse events

Submitted documentation
In their submission, Rhythm Pharmaceuticals have accounted for the cost of adverse events as general monitoring costs during the first year, specifically for the first 14 weeks, when adverse events typically occur. These costs include safety and adverse event management, such as regular visits to healthcare providers, medications to manage symptoms, and potentially additional diagnostic tests. While most injection site reactions are mild (e.g., redness, swelling, or tenderness) and generally resolve on their own without requiring significant medical intervention, they may still incur minimal

costs for drug administration. For nausea and vomiting the submitter has not claimed this to be severe and are assumed to be self-limiting and may not require significant medical intervention.

NOMA's assessment

NOMA considers the approach of including the cost of adverse events within the monitoring costs for the first year, specifically the first two weeks, to be reasonable. It notes that any minor variation in costs due the adverse events are unlikely to have a significant impact on the ICER, particularly in the short term.

NOMA's conclusion on costs of adverse events

NOMA accepts the approach of not separately including the cost of adverse events, as these events are of short duration and can be accounted for within the monitoring costs for the first year.

3.7.4 Costs associated with the health states in the health economic model

Submitted documentation

In the submitted documentation, Rhythm Pharmaceuticals used data from a Danish register-based study to estimate average annual healthcare costs per person by BMI category for both adult and paediatric patients (33). The submitter was not able to report the average annual healthcare costs per person by BMI/BMI z-score category in Norway as no studies were identified. Consequently, Danish data was used as proxy method to approximate the costs associated with different BMI categories in the absence of direct local data.

The study categorized individuals by BMI, from obesity class I (BMI 30-34.9 kg/m²) to class III (BMI ≥40 kg/m²), and provided cost estimates for each category based on healthcare utilization, including primary care visits, inpatient hospitalizations, outpatient visits, home care, and prescription medicines.

These costs were converted from EUR to NOK using the average exchange rate from December 2022 to May 2023.

The submitter estimated healthcare costs for BMI categories not directly reported in the Danish study. For individuals with a BMI of 25 to <30 kg/m², the cost was estimated at 55,310.25 NOK through linear extrapolation from higher BMI categories. The cost for those with a BMI of 20 to <25 kg/m² was assumed to be 0 NOK. The same healthcare costs were applied to paediatric patients based on BMI z-score, using the adult cost categories.

The submitter claims that the costs associated with non-obesity-related comorbidities, such as visual impairment and learning difficulties, are not included in the economic model, primarily because they are considered indirectly related to obesity or the condition being treated.

These costs are presented in Table 24 for the paediatric and adult patients.

Table 24. BMI/BMI Z-score average annual healthcare costs in NOK.

BMI/BMI Z-Score Category	Average annual healthcare costs per person (NOK)	Source
Paediatric BMI Z-Score (0.0 to <1.0)	0	Assumption
Paediatric BMI Z-Score (1.0 to <2.0)	55,310.25	Extrapolated

Paediatric BMI Z-Score (2.0 to <2.5)	61,637.46	Extrapolated
Paediatric BMI Z-Score (2.5 to <3.0)	67,964.67	Extrapolated
Paediatric BMI Z-Score (3.0 to <3.5)	68,042.51	Extrapolated
Paediatric BMI Z-Score (≥4.0)	68,042.51	Extrapolated
Adult BMI (20 to <25 kg/m²)	0	Assumption
Adult BMI (25 to <30 kg/m²)	55,310.25	Linear Extrapolation
Adult BMI (30 to <35 kg/m²)	61,637.46	Danish Study (33)
Adult BMI (35 to <40 kg/m²)	67,964.67	Danish Study (33)
Adult BMI (≥40 kg/m²)	68,042.51	Danish Study (33)

NOMA's assessment

In the absence of specific data for Norway regarding the average annual healthcare costs per person by BMI categories, using Danish data as a proxy is considered reasonable. The Danish study included adults (≥18 years) who had been registered in the Danish National Patient Register from 2002 through 2018 with a hospital diagnosis of obesity (33).

Furthermore, NOMA assesses the linear extrapolation used for estimating costs for the BMI category of 25 to <30 kg/m² to be a standard approach in the absence of direct data. Although extrapolation methods have limitations, it is often considered in health economic modelling, especially when other data sources are unavailable. However, the method assumes that the cost increase between categories is linear, which may not always be the case. The hospital stays, complications, comorbidities, and differential treatment intensities can all contribute to significant cost variations that are not captured through simple linear extrapolation.

Due to the absence of cost data specific for Norway, NOMA does not make any adjustment to the costs for BMI and BMI Z-score used in the submitters economic model.

The costs are converted from EUR to NOK using recent exchange rates to ensure that the data remains relevant to the Norwegian context.

NOMA's conclusion on costs associated with health states in the model

NOMA accepts the submitter's use of Danish data as a reasonable proxy in this context for estimating the Norwegian healthcare costs related to BMI categories, given the absence of specific Norwegian data. While acknowledging the limitations of linear extrapolation for the BMI category of 25 to <30 kg/m², this method is considered acceptable in the absence of direct data.

3.7.5 Monitoring and follow-up

Submitted documentation

Costs related to monitoring and follow-up were included in the submitted model. These costs are not further described or fully evaluated, as NOMA considers them to have limited impact on the outcome of the analysis.

NOMA's assessment

NOMA uses the applicant's approach and assumptions regarding the estimation of costs associated with monitoring and follow-up. NOMA has not validated the assumptions as they are considered to have limited impact on the outcome of the analysis.

NOMA's conclusion on monitoring and follow-up costs

NOMA uses the applicant's approach and assumptions regarding the estimation of costs associated with monitoring and follow-up. NOMA has not validated the assumptions as they are considered to have limited impact on the outcome of the analysis.

3.7.6 Other Costs

Submitted documentation

Rhythm Pharmaceuticals' submission includes an analysis based on an extended health service perspective, which incorporates indirect costs related to both the patient and carer's time associated with treatment, as well as transportation costs for travel to and from healthcare appointments. The patient and carer's hourly rates, as well as the transportation costs, are outlined in Table 25. Additionally, the indirect costs are calculated based on the number of healthcare professional visits and the proportion of patients and carers who incur these costs. It is assumed that 100% of patients and 50% of carers will incur indirect costs, with each healthcare visit estimated to take one hour.

Table 25. Overview of unit cost for indirect costs in Norway

Cost Item	Unit cost (NOK)	Description	Source
Patients (Hourly rate)	514	Hourly rate including wages, taxes, and social costs	Enhetskostnadsdatabase, 2022 (34)
Carers (Hourly rate)	514	Hourly rate including wages, taxes, and social costs	Enhetskostnadsdatabase, 2022 (34)
Transportation costs	1,502	Round trip patient travel costs	Enhetskostnadsdatabase, 2022 (34)

Rhythm Pharmaceuticals estimated the prevalence of comorbidities using a model that accounts for BMI/BMI Z-score categories, age, and the early onset of obesity, given the lack of published data on BBS patients. The submitted cost-effectiveness analysis included five comorbidities: sleep apnoea, osteoarthritis, non-alcoholic steatohepatitis, type 2 diabetes, and cardiovascular events.

NOMA's assessment

NOMA accepts the inclusion of caregiver costs in the analysis, as it aligns with an extended health care perspective and is considered relevant due to the administration of setmelanotide. Given the training and involvement required for caregivers in supporting patients with their treatment regimen, it is reasonable to include these costs. Furthermore, the inclusion of such indirect costs provides a more comprehensive view of the total burden of the treatment, including those associated with the patient's care. The costs are sourced from Unit Cost Database in Norway and is considered appropriate for the analysis.

NOMA does not accept the submitted approach for costs of comorbidities as these are assumed to already be accounted for through the costs related to the BMI-categories. According to the Danish study used for obtaining the BMI-specific costs, healthcare costs related to 11 predefined comorbidities (type-2 diabetes, dyslipidaemia, hip and knee osteoarthritis, obstructive sleep apnoea, asthma, hypertension, chronic kidney disease, atrial fibrillation, unstable angina, heart failure and myocardial infarction) were already included in the estimate (33).

NOMA's conclusion on other costs

NOMA accepts the submitted approach undertaken by the submitter and does not make any adjustment to the assumptions pertaining to the indirect costs for patient time, transportation and carers.

NOMA does not accept the submitted approach for the associated costs of comorbidities; therefore, they are excluded from its main analysis for both the BSC and setmelanotide arm.

4. Analysis results

4.1 Cost-per-QALY analysis

Results are presented based on the maximum AUP excluding VAT for all medications included in the analysis.

4.1.1 The company's base analysis

Table 26. Cost per Quality-Adjusted Life Year (QALY) Gained and per Life Year Gained in the Company's Base Analysis. Based on Maximum AUP Excluding VAT. Per Patient. Discounted Figures.

	Setmelanotide	BSC	Difference
Total costs (NOK)	40,000,001	2,690,533	37,309,468
Total QALYs Total Life-years	7.49 20.28	0.17 19.66	7.32 0.62
Incremental Cost (NOK) per QALY Gained Incremental Cost (NOK) per Life Year Gained			**5,094,047** **60,144,100**

4.1.2 NOMA’s main analysis

Based on NOMA's assessments in the above chapters, NOMA has conducted its own main analysis. The assumptions are the same as in Rhythm pharmaceuticals’ analysis, except for the following:

- The baseline distribution of hyperphagia is adjusted to 25% mild, 50% moderate and 25% severe, as compared to 100% severe for all patients in the base-case. This adjustment only effects the results of the scenario analysis.
- The impact of hyperphagia on QALYs, calculated using the multiplicative approach with utility multipliers, has been excluded due to insufficient clinical evidence demonstrating that setmelanotide improves hyperphagia.
- The treatment initiation in the intervention arm is changed from 60% pediatric and 40% adult patients to 32% pediatric and 68% adult patients in accordance with the Norwegian patient population.
- The response evaluation time frame is adjusted to 1 year in the first cycle as compared to 14-weeks.
- Caregiver burden utilities are excluded from the analysis as their inclusion led to negative QALY outcomes in the BSC arm. As noted earlier in the report, the documentation requirements have not been met.
- The costs and utility decrements of comorbidities are excluded, as they are assumed to be accounted for by BMI-specific utility weights and cost.

Table 27 presents the effects of the various changes made by NOMA, based on Rhythm Pharmaceutical's base case analysis. The effect of each change is shown individually, as well as the cumulative effect of the changes in assumptions, ranked according to the magnitude of their impact on the ICER. The cumulative effect reflects how the assumptions interact with each other, either

amplifying or counteracting one another. Thus, the cumulative effect represents the combined impact of the assumptions, applied sequentially, leading to the estimation of the ICER in the main analysis.

Table 27. Individual impact on ICER of the changes made by NOMA in Rhythm pharmaceutical's base analysis, which are included in NOMA's main analysis. Based on maximum AUP excluding VAT. Per patient. Discounted figures.

Assumption	Rhythm's base-case	NOMAs main analysis	Justified in Section	ICER (± changes) (NOK)	Cumulative effect*
ICER in Rhythm Pharmaceuticals' base-case analysis				5,094,047	
Distribution of patients	Paediatric: 60% Adult: 40%	Paediatric: 32% Adult: 68%	3.3.4	4,979,020 (- 115,027)	4,979,020 (- 115,027)
Treatment response evaluation initial cycle	14-weeks	1-year	3.4.3	5,138,576 (+ 44,529)	5,052,192 (-41,855)
Comorbidities	included	excluded	3.6.3	5,732,077 (+ 638,030)	5,629,031 (+534,984)
Caregiver burden	included	excluded	3.6.3	6,707,483 (+ 1,613,436)	8,169,476 (+3,075,429)
Distribution of hyperphagia severity for patients in the BSC	100% severe	25% mild, 50% moderate, 25% severe	3.2	7,446,549 (+2,352,502)	15,906,236 (+10,812,189)
Utility multiplier for hyperphagia	BSC: 0.38 Setmelanotide: 0.91	BSC: 1 Setmelanotide: 1 No effect assumed	3.3.4	11,617,054 (+ 6,523,007)	60,559,608 (+55,465,561)

*The cumulative effect sequentially incorporates the impact of each assumption, as presented in the table above, to calculate an ICER that gradually aligns with NOMA's main analysis estimate. The impact of adjusting each assumption gradually is assessed under the assumption of other things constant. The change in ICER is compared against the base-case values.

Results from NOMA's main analysis:

The results from the health economic model must be interpreted with great caution due to key uncertainties: limited generalizability to Norwegian practice, lack of long-term data, overestimated response rates, exclusion of hyperphagia effects, non-BBS-specific utility values, reliance on Danish registry cost data for BMI, and unvalidated assumptions on hyperphagia, BMI changes due to hyperphagia, and discontinuation rates, all impacting the ICER.

Table 28. Cost per gained quality-adjusted life year (QALY) and gained life year in NOMA's main analysis based on maximum AUP excluding VAT. Per patient. Discounted figures.

	Setmelanotide plus BSC	BSC	Difference
Total Costs (NOK)	32,937,814	1,404,432	31,533,383
Total QALYs Total Life-years	12.75 19.33	12.23 18.85	0.52 0.47
Incremental cost (NOK) per QALY gained Incremental cost (NOK) per life-year gained			**60,559,608** **66,485,892**

4.1.3 Uncertainty analyses

Scenario analyses

NOMA aims to shed light on the uncertainties related to the assumptions in the cost-effectiveness analysis that may influence the decision on whether or not to implement setmelanotide.

Table 29 presents various scenarios related to NOMA's main analysis and their impact on the ICER and AS. These scenarios represent alternative, reasonably possible variations of relevant assumptions.

Table 29. Scenario analysis for NOMAs main analysis based on maximum AUP without VAT.

	Parameter/ assumption	NOMA's main analysis	Scenario-analysis	ICER (NOK)	AS* (QALY)
Result of NOMA's main analysis				60,559,608	29.70
1	Hyperphagia Utility Multiplier	Excluded for impact on QALYs	Included, assuming baseline distribution of 100% patients with severe hyperphagia	8,169,476	46.59
2	Baseline distribution of hyperphagia	25% mild, 50% moderate, 25% severe (utility multiplier is excluded and does not affect the ICER).	25% mild, 50% moderate, 25% severe with hyperphagia utility multiplier (assuming a 2-level decrease in severity from severe to mild for responders)	15,906,236	38.63
3	Treatment effect on hyperphagia	Excluded	1-level decrease in hyperphagia severity from the baseline distribution of patients as assumed in scenario 2.	19,416,046	38.63
4	Decrease in BMI Z score class	2 levels for paediatric patients without effect of hyperphagia	1 level for paediatric patients without effect of hyperphagia	83,463,904	29.70
5	Distribution of paediatric and adult patients	32% paediatric and 68% adults	80% paediatric and 20% adults	54,177,755	30.90
6	Dosage Paediatric patients and Adults	Paediatric Dose Year 1: 2.46 mg Paediatric Dose Year 2+: 2.5 mg Adult Dose Year 1: 2.77 mg Adult Dose Year 2+: 2.8 mg	Paediatric Dose Year 1: 2.96 mg Paediatric Dose Year 2+: 3 mg Adult Dose Year 1: 2.94 mg Adult Dose Year 2+: 3 mg Based on Norwegian settings and iteration period adjustments	66,516,921	29.70

7	Treatment Discontinuation	1% yearly after one year	3% yearly after one year	71,245,898	29.70

AS: Absolute shortfall; *AS for the primary condition used in the scenario analysis is based on the weights for the paediatric and adults' population for the remaining QALYs at mean age of diagnosis. AS for sequela is provided in 4.2.

Description of scenario analysis:

The paragraphs below discuss the individual scenarios presented in Table 29 in detail:

1. Inclusion of hyperphagia for the effect on patients HRQoL: This scenario examines the impact of hyperphagia on QALYs in the economic model, unlike NOMA's main analysis, which excluded it due to limited clinical evidence. Here, NOMA keeps the baseline distribution of hyperphagia severity as proposed by Rhythm Pharmaceuticals (i.e., 100% severe for the BSC arm). Other assumptions remain unchanged, with all patients with severe hyperphagia assumed to improve to mild hyperphagia with treatment at a 100% probability. The scenario focuses on changes in HRQoL as reflected in QALYs gains due to improved hyperphagia. Thus, the change is driven by QALYs, with costs unaffected. The assumption of severe hyperphagia for BBS patients with obesity and hyperphagia is based on the submitter's estimates. Scenario results (Table 29) show a significant ICER reduction, as treatment reduces hyperphagia severity and enhances patient outcomes. This leads to a high absolute shortfall (AS) value compared to NOMA's main analysis, as hyperphagia impacts patients' QoL for managing extreme hunger. The QALY gains from the intervention lowers the ICER substantially, from NOK 60.56 million per QALY to NOK 8.17 million per QALY for BBS patients, assuming all start with severe hyperphagia. However, the results of this scenario are highly implausible due to the lack of validated metrics for measuring hyperphagia. Therefore, the scenario results offer only a general indication of the likely direction of impact on the ICER if hyperphagia assumptions are included in the health economic model.

2. Reducing hyperphagia severity distribution at baseline: This scenario builds on scenario 1 but adjusts the baseline distribution of hyperphagia severity to see how a less extreme assumption impacts the ICER if patients' baseline severity is lower in the absence of treatment. Given that BSC and lifestyle interventions (like dietary changes) have varied tolerability among patients in managing hunger, this scenario tests a less skewed severity distribution to avoid overestimating ICER impacts. Due to uncertainty around hyperphagia utility multipliers based on hunger scores, NOMA adjusts the baseline to 25% mild, 50% moderate, and 25% severe hyperphagia. NOMA maintains the assumption of a two-level decrease, so all patients with severe hyperphagia transition to mild with 100% probability. Scenario results (Table 29) show that ICER nearly doubles compared to scenario 1 and reduces the AS since fewer baseline patients experience extreme hunger.

3. One level decrease in hyperphagia from the baseline: This scenario considers one level decrease in hyperphagia severity from the baseline based on the distribution of patients adjusted by NOMA to 25% mild, 50% moderate and 25% severe. The one level decrease reduces the treatment effect of the intervention with regards to managing hyperphagia and accounts for further uncertainty around overestimating its impact on ICER. The results of the scenario analysis (Table 29), increases by some degree due to the loss of additional QALYs due to decrease in treatment effectiveness. However, this adjustment has no implication on the baseline characteristics of the patients, so the AS remains unchanged.

4. One level decrease in BMI Z score for paediatric patients: NOMA, main analysis was based on a two-level class change in the baseline for patients receiving treatment with

setmelanotide, whereas this scenario explores the impact of one level class change for paediatric patients in their Z score. NOMA excludes hyperphagia from this scenario as to assess the sensitivity of ICER for reduction in treatment effect solely based on BMI that is clinically supported. Scenario analysis results (Table 29) show a significant increase in ICER from the main analysis to NOK 83.4 million per QALY, while the AS remains unchanged as compared to the main analysis as baseline characteristics are assumed to be the same as NOMAs main analysis.

5. Increased proportion of early treatment initiation: NOMA changes the distribution of paediatric (32%) and adults' (68%) patients assumed in the main analysis for BBS to a higher percentage of paediatric patients (80%) and lower percentage of adult patients (20%). The results of the scenario (Table 29) lead to decrease in ICER from the main analysis and increases the AS, in absence of hyperphagia severity.

6. Dosage Based on Norwegian Clinical Practice for setmelanotide: In this scenario, NOMA adjusts the dosage of setmelanotide to align with the recommended guidelines in the SmPC, which specifies dosage increases over several weeks for both adults and paediatric patients, presented below:

   For adults and adolescents (ages 16 to 17):
   Weeks 1-2: 2 mg once daily
   Week 3 and onward: Increase to 3 mg once daily if the 2 mg dose is well tolerated

   For paediatric patients (ages 6 to <16):
   Week 1: 1 mg once daily
   Week 2: Increase to 2 mg once daily if the 1 mg dose is well tolerated
   Week 3 and onward: Increase to 3 mg once daily if the 2 mg dose is well tolerated

   This adjustment allows the dosage in the model to more closely reflect clinical practice, which may affect both the cost-effectiveness analysis and ICER due to potential changes in drug costs. By dosing patients gradually according to the criteria, NOMA used the iteration approach by the submitter to estimate the average cost for year 1 and for the year 2 onwards. The average dose is presented in Table 14 based on this approach as weekly adjustment were not possible in the model and tolerability of patients is not measured in the current model. The results for the scenario increase the ICER to NOK 66.5 million per QALY million as compared NOK 60.56 million per QALY in the main analysis.

7. Treatment Discontinuation Rate Beyond One Year: In this scenario, the treatment discontinuation rate beyond one year was increased from 1% to 3% to explore the impact on the ICER if more patients discontinued treatment after the first year. The result of this scenario led to an increase in the ICER by approximately NOK 10.6 million, while the AS remained unaffected.

4.2 Severity and absolute shortfall

The benefit and cost criteria should be assessed in relation to the severity of the condition in question. Severity influences whether costs are considered reasonable relative to the treatment's benefit. With high severity, greater resource use is accepted in proportion to the benefit compared to cases of lower severity.

NOMA's submission guidelines states: *"For medicinal products targeting a primary condition, the assessment and calculation should focus on the overall severity of the primary condition and symptoms directly related to the primary condition.*

For medicinal products aimed at symptoms resulting from the primary condition, sequelae, the severity of the sequelae itself must be evaluated and quantified, and not the primary condition. For interventions targeting adverse reactions, it is the severity of the adverse reaction, not the primary condition, that must be evaluated and calculated."

Setmelanotide is only expected to target the obesity and hunger-related aspects of the broad primary condition BBS, and this argues against calculating severity for the primary condition. Moreover, the sequela is not specific for the primary condition and the mechanism of action for the treatment of the sequela is not specific for the patients with the condition in question. However, the sequela and the primary condition are expected to be strongly correlated. Therefore, NOMA has chosen to calculate severity for both the primary condition and the sequela obesity in this case.

NOMA uses a quantitative method to calculate severity for patients treated with best supportive care. Further details can be found in Appendix 4.

The calculation of AS for the primary condition is presented in Table 30. The calculation is based on a weighted average approach that includes the severity of the primary condition (BBS), where the age at treatment start is 6 years for paediatric patients and 20 years for the adult patients. The expected remaining QALY for the average population without the disease is calculated and weighted according to the distribution of paediatric (32%) and adults (68%) patient groups in the main analysis. Likewise, the expected remaining QALYs for each age group with BSC is computed from the model using the same weights for the distribution of patients in the model.

In addition, a scenario analysis is performed for measuring the AS for the primary condition using the same approach as above that includes only paediatric patients, as future treatment may shift toward early intervention for this group. The scenario analysis assumes the mean age of treatment initiation to be 6 years and calculates expected remaining QALYs for the paediatric population in the model.

The AS for BBS patients is significantly influenced by the BMI of the patients, especially due to the relationship between BMI and mortality. Higher BMI and comorbidities typically lead to a higher shortfall in QALYs, driven by both direct health effects (such as reduced life expectancy and complications) and the indirect impact on health-related quality of life. Although comorbidities are not explicitly included in the model, the impact of obesity-related conditions is reflected in the QALYs for BMI-related categories, for both paediatric and adult patients. Additionally, the 0.8 QALY multiplier accounts for non-obesity-related symptoms of BBS. The multiplier serves as an assumption to capture factors not included in the BMI category-based QALY calculations. Excluding the BBS QALY multiplier from the severity calculation would cause the severity to be lower than what is estimated in Table 30 by approximately 6 QALYs if the multiplier effect is considered to be equal to 1, for the main analysis. This multiplier is intended to reflect non-obesity-related symptoms of BBS, but its relevance is based on assumptions rather than direct evidence. Hence, the 0.8 QALY is associated with considerable uncertainty.

Table 30. NOMA's Calculation of absolute shortall (calculation from age at treatment start – 6 years for paediatric patients and 20 years for adult patients)

Age	A	Main Analysis	Scenario Analysis
Expected remaining QALYs for the average population without the disease (Undiscounted)	$QALYs_A$	56.9	65.6
Expected remaining QALYs with the disease without the new treatment (Undiscounted) (Prognosis)	P_A	27.2	34.2
Number of lost QALYs due to disease (absolute shortfall)	**AS**	**29.7**	**31.4**

NOMA adjusted the absolute shortfall to account for the severity of BBS patients, excluding the non-obesity factor. This adjustment estimates the severity impact of obesity alone and reflects the expected remaining QALYs for both paediatric and adult patients. The expected remaining weighted QALYs for both groups, excluding non-obesity factors, are estimated to be 34 QALYs.

The severity attributable to obesity, the sequela influenced by treatment, is calculated as the difference between the expected remaining QALYs for the average population without the disease and the expected remaining weighted QALYs for both groups, excluding non-obesity factors (56.9 – 34 = 22.9 QALYs). Thus, the severity of the obesity sequela is estimated as a loss of 22.9 QALYs.

NOMA considers that the estimated severity of the sequela is highly uncertain due to several factors, including sensitivity to the distribution of patients across BMI categories, considerable influence by excess mortality rates for the obese patients in the submitted model, as well as technical limitations in the modelling framework that affect the validity of severity estimates .Changes in the BMI-distribution of patients in both paediatric and adult groups could result in a different estimate of the absolute shortfall attributable to the sequela.

For comparison, NOMA estimated that obesity treated with the current standard of care (lifestyle interventions alone), had an AS between 2 and 6 QALYs in the STA of Wegovy (semaglutide) as an adjunct to lifestyle interventions for weight management in individuals with a BMI ≥ 40 kg/m² or a BMI ≥ 35 kg/m² with at least one weight-related comorbidity (35).

The difference in estimated AS may to some extent be explained by a lower age at diagnosis and earlier onset of obesity in patients with BBS. Still, an AS of 22.9 is regarded as unrealistically high and suggests that the prognosis in BBS-patients treated with BSC is modelled too pessimistically in the model submitted by Rhythm Pharmaceuticals.

Lastly due to the lack of valid data on hyperphagia, severity for this aspect of the syndrome, could not be calculated although it is expected to be targeted by setmelanotide to an unknown extent.

In summary, NOMA has estimated that BBS treated with BSC has an absolute shortfall of about 30 QALY's for the primary condition, BBS. Severity for the sequela obesity, that is targeted by setmelanotide, could not be reliably calculated in the submitted model but was less than 10 in a previous single technology assessment.

The impact of treatment on overall survival and quality of life should be interpreted with caution, given the potential limitations of the underlying assumptions.

4.3 Assessment of guiding criteria for very small patient groups with extremely severe conditions

The Priority-setting White Paper allows for the acceptance of a lower evidence level and a higher level of resource use compared to other interventions for medicines intended for very small patient groups with extremely severe conditions (36;37). There are three guiding criteria for assessing whether the medication is intended for the treatment of a particularly small patient group with a very severe condition:

1. **Very small patient group:**
   a. Fewer than approx. 1 patient per 100 000 inhabitants affected on a global basis per medicine (prevalence on a global basis)
   b) Fewer than approx. 50 patients in Norway per medicine (steady state prevalence in Norway)

2. **Extremely severe condition:**
   The severity of a condition is measured using the concept of absolute shortfall, i.e., how many quality-adjusted life years patients in the relevant group will lose on average by the absence of the medicinal product under evaluation. For a condition to be considered extremely severe, an absolute shortfall should be equivalent to a minimum loss of around 30 quality-adjusted life years.

3. **Considerable expected benefit:**
   The following indicative criterion applies to considerable expected benefit: The expected benefit of the treatment in question is considerable and leads to a gain of at least 2 quality-adjusted life years compared to standard treatment.

All three of these guiding criteria are, as a rule, to be met.

BBS is a rare disorder with an estimated prevalence between 1 in 250,000 and 1 in 160,000 among individuals of European descent (1). It is estimated that there are approximately 63 patients with BBS in Norway, as of 2024. Importantly, setmelanotide is already approved for treatment of other rare disorders (e.g., loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency). Moreover, according to ClinicalTrials, more indications may be underway (38). NOMA assess that criterion 1 regarding a very small patient group is most likely not met.

Calculations of severity have been performed in the submitted model from Rhythm Pharmaceuticals, based on the assumptions in NOMA's analysis. According to available sources on prognosis with current treatment, this indicates an absolute prognosis loss of about 30 QALY’s for the primary condition. Severity for the sequela obesity, targeted by setmelanotide, could not be reliably calculated in the submitted model. Absolute shortfall calculated for obesity in a previous single technology assessment was less than 10 QALYs. The severity for hyperphagia could not be calculated although it is expected to be targeted by setmelanotide to an unknown extent. NOMA assesses criterion 2 regarding extremely severe condition to be met for the primary condition BBS, but regarding the sequela of obesity not to be met.

In NOMA’s main analysis it is estimated that patients treated with setmelanotide in addition to BSC, on average, gain 0.52 QALYs. NOMA assesses that criterion 3 regarding considerable expected benefit is not met.

4.4 NOMA’s assessment of analysis results

In the main analysis, the additional cost for setmelanotide compared to BSC, based on the maximum AUP excluding VAT, is approximately:

NOK 60.5 million per gained QALY
NOK 66.5 million per gained year of life

NOMA has conducted scenario analyses to shed light on the uncertainties related to the main analysis.

Alternative scenarios tested by NOMA, excluding hyperphagia, that led to significant changes in the ICER were found to be the distribution of patients between paediatric and adult groups for treatment initiation. A shift in the proportion from 32% paediatric patients to 80% paediatric patients decreased the ICER by approximately NOK 6 million. Conversely, a change in the BMI Z-score class for paediatric patients from a two-class change to a one-class change increased the ICER by approximately NOK 22 million. Lastly change in treatment discontinuation rate from 1% to 3% beyond one-year increased ICER by about NOK 10.7 million.

The scenario analysis highlights the potential variance in the ICER especially due to the inclusion of hyperphagia severity on the QoL of patients with BBS. However, NOMA's scenario analysis is unable to validate the assumptions made regarding utility multipliers and the distribution of patients suffering from severe hyperphagia at baseline. Therefore, the results of the scenario analysis with respect to hyperphagia need to be interpreted with caution due to limitations concerning the clinical evidence for hyperphagia in the current analysis. While it provides with an understanding of the impact on the ICER, as hyperphagia may have clinical significance but results are implausibly low compared to the main analysis.

The scenario analysis primarily helps to understand the impact on the ICER based on changes to some of the assumptions made by the submitter in the base case. It highlights the variation in results compared to NOMA's main analysis, which focuses on outcomes supported by clinical evidence, such as BMI changes, treatment discontinuation rates, changes in patient distribution, or level of class change for responders in the paediatric BMI Z-score category.

Additionally, there is significant uncertainty regarding the estimated AS (absolute shortfall). The variation in the absolute shortfall observed in the scenario analysis is primarily driven by the secondary conditions, namely obesity and in some scenarios hyperphagia, although the latter is deemed implausible due to lack of clinical evidence. The lack of evidence on hyperphagia remains a significant limitation of the current analysis. Moreover, the main analysis calculation of the absolute shortfall due to sequela, influenced by the treatment is considerably influenced by distribution of patients in the BMI categories, and the estimate is greatly influenced by the uncertain mortality rates for the obese patients within the BMI categories.

NOMA considers that there is significant uncertainty related to the documentation. Significant uncertainty regarding documentation and calculation methods should, all else being equal, lead to lower priority, cf. the Priority-setting White Paper (36).

5. Budget calculations

5.1 Estimate of the number of patients eligible for treatment with Imcivree for Bardet-Biedl syndrome in Norway

According to a medical expert consulted by NOMA, there are 63 patients with BBS including 20 under 18 years of age in Norway, according to the registry at The Centre for rare disorders. Some of these patients will be younger than six years old, and not eligible for treatment with Imcivree according to the approved indication. However, not all patients are included in the registry and the true overall prevalence in Norway is likely to be higher. Of those with a clinical diagnosis of BBS, the prevalence of genetic confirmation is expected to be very high and was not accounted for in the estimate.Therefore, NOMA based further calculations on an estimate of 63 patients.

NOMA is not aware of any publicly available sources on the prevalence of obesity in patients with BBS in Norway. Based on input from a medical expert, the prevalence expected to be close to 100%. Accordingly, NOMA has applied an arbitrary prevalence of 90%, resulting in 57 eligible patients.

NOMA estimates a higher number than Rhythm Pharmaceuticals, who assumes 20 eligible patients. Their estimate was based on a prevalence of 55 patients, 72-92% obese, 80% without chronic renal failure, 95% of patients above six years of age, and 60% with severe hyperphagia. According to the Imcivree SmPC, dose adjustments are necessary in patients with severe renal failure (not mild to moderate), and it should not be administered to patients with terminal renal failure. The prevalence of terminal renal failure in obese BBS-patients in Norway is unknown but is expected to be low and was not accounted for in NOMAs estimate. Moreover, severe hyperphagia in patients is not a requirement for treatment with Imcivree according to the SmPC and was not included in NOMAs estimate of eligible patients.

Rhythm Pharmaceuticals assumes that 10% of eligible patients will receive Imcivree in year 1, increasing 100% in year 5. They also assume that a proportion of 30% will discontinue treatment in the first year of treatment due to lack of efficacy (aligned with the average response rate for paediatric and adult patients observed in the pivotal trial), and a discontinuation rate of 1% associated in year two and onwards.

As there are currently no available approved treatments for obesity in BBS, NOMA expects that Imcivree will be rapidly adopted in the eligible patient population with a 50% uptake in year 1 and 100% in year 2 and onward. As described in chapter 3.4, NOMA assumes that evaluation of treatment efficacy in clinical practice take place after approximately 1 year of treatment and applies a 30% discontinuation rate at the end of year 1 and 1% annual discontinuation rate thereafter.

NOMA has not accounted for an increase in number of BBS patients due to population growth or increased awareness due to new available treatment, if Imcivree is introduced. A small increase in incidence may occur but is expected to be offset by treatment discontinuation, keeping the eligible patient count stable.

Based on this, NOMA assumes that 39 patients will be eligible for treatment with Imcivree in year 5 (Table 31). The estimate is subject to uncertainty due to limited data on the characteristics of patients with BBS in Norway and depends on adherence in clinical practice to discontinuing treatment who do not respond.

Table 31. The number of patients over the first five years as assumed in NOMA's budget estimates

	År 1	År 2	År 3	År 4	År 5
Annual number of patients expected to be treated with Imcivree if it is introduced	29	49	40	39	39
Annual number of patients expected to be treated with BSC if Imcivree is introduced*	57	57	57	57	57
Annual number of patients expected to be treated with BSC if Imcivree is NOT introduced*	57	57	57	57	57

*Imcivree is expected to be add-on to BSC not influencing the number receiving BSC.

5.2 Estimated drug expenditure per patient

NOMA has extracted costs per patient per year for the first five years from the health economic model representing NOMA's main analysis. The costs include value-added tax (VAT) and are undiscounted.

The regional health authorities are reimbursed for VAT on pharmaceuticals. However, in budget calculations, pharmaceutical prices are used inclusive of VAT, ensuring that budget calculations are conducted in the same manner regardless of where the financing responsibility lies (National Insurance or specialist healthcare services).

Table 32. Pharmaceutical costs per patient for Imcivree and BSC. Maximum AUP, including VAT. Undiscounted.

	År 1	År 2	År 3	År 4	År 5
Imcivree (Setmelanotide) Paediatric	3,405,019	3,456,982	3,456,982	3,456,982	3,456,982
Imcivree (Setmelanotide) Adult	3,832,252	3,871,819	3,871,819	3,871,819	3,871,819
BSC	0	0	0	0	0

5.3 Budget consequences

The budget consequences are divided into three categories:

- Pharmaceutical costs for the specialist healthcare services
- Total costs for the specialist healthcare services
- Total costs in the health and care services

In the top point listed above, only the direct pharmaceutical costs for Imcivree and BSC are included in the analysis. NOMA chooses to calculate only the pharmaceutical costs for the specialist healthcare services in this case because we believe that the effects beyond pharmaceutical costs will not have significant budgetary importance.

5.3.1 Budget consequences for the pharmaceutical budget of the specialist healthcare services

The budget consequences are based on undiscounted costs and include value-added tax (VAT). NOMA has assumed the number of patients as shown in Table 31, while the pharmaceutical costs per patient are as shown in Table 32.

The estimated budget impacts of the implementation of the method are presented in Table 33.

Table 33. Expected budget impact on the pharmaceutical budget of the specialist healthcare services for Imcivree for the treatment of BBS (NOK, maximum AUP including VAT).

	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Imcivree is introduced	105,322,806	179,917,280	148,443,003	146,958,573	145,488,988
Imcivree is not introduced	0	0	0	0	0
Budget impact of recommendation	105,322,806	179,917,280	148,443,003	146,958,573	145,488,988

Conclusion on the pharmaceutical budget of the specialist healthcare services

The total budget impacts are estimated to be approximately NOK 145 million in the fifth budget year (and estimated to be highest in year 2 approximately NOK 180 million), based on the maximum AUP including VAT. The budget calculations are uncertain and simplified and will depend on the number of patients who end up receiving the treatment.

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Appendix 1: Supplementary results

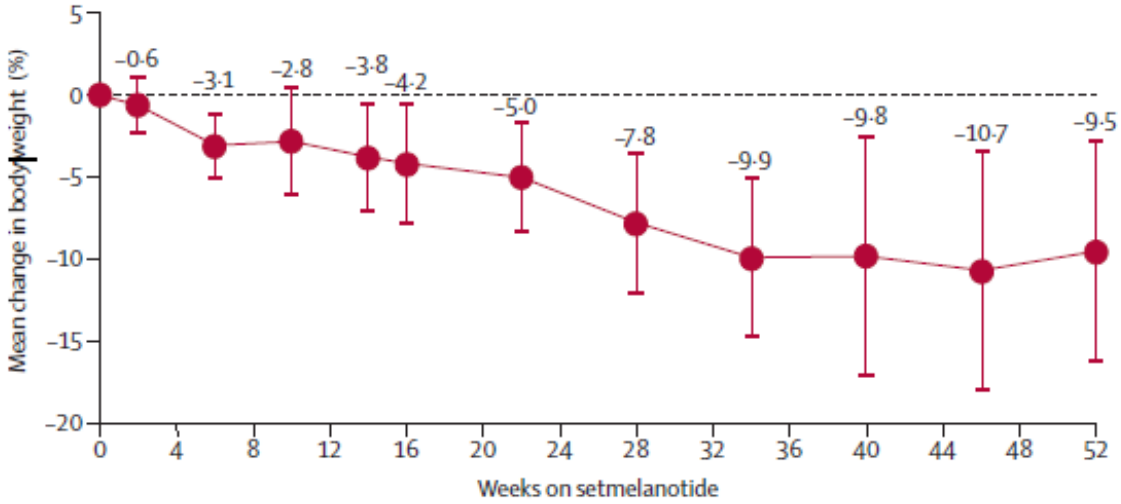

Figure 5. Mean change in body weight from active-treatment baseline in patients aged ≥18 years (study RM-493-023, pivotal patient FAS). Source: Rhythm Pharmaceuticals

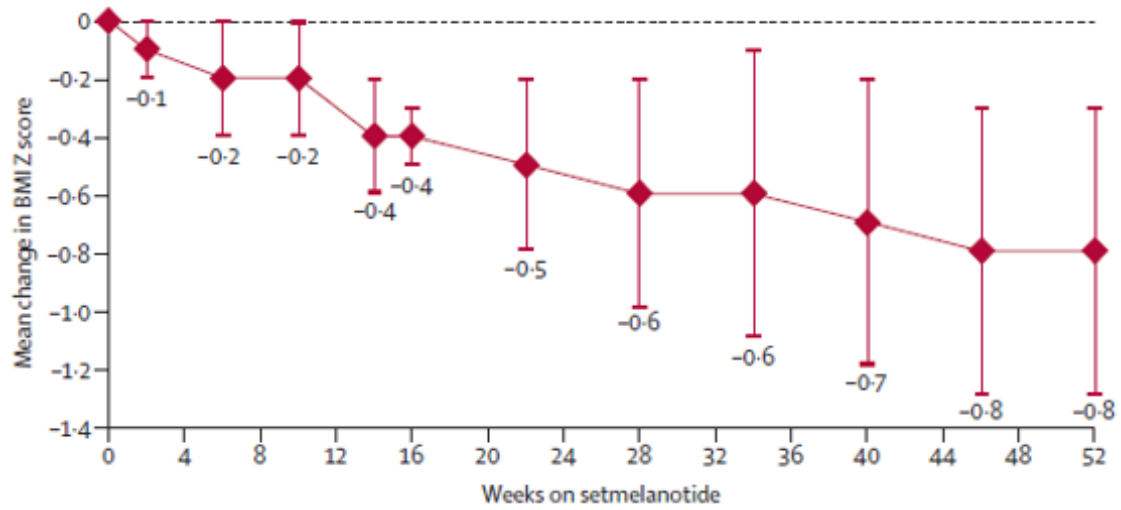

Figure 6. Mean change in BMI Z-score from active treatment baseline in BBS patients <18 years (study RM-493-023, pivotal patient FAS). Source: Rhythm Pharmaceuticals

Appendix 2: Documentation of quality of life

Table 34. General provision of quality-of-life documentation, provided by Rhythm Pharmaceuticals, compared against NOMA's guidelines/requirements for clinical quality of life documentation

Requirements for documentation according to NOMA's guidelines.	**Submitted by Rhythm Pharmaceuticals?**
An overview of the number of participants who responded to the study's measurement tool(s) (compliance rates at each measurement point for each treatment arm), including reasons for non-compliance and any differences between respondents and non-respondents, should be provided.	Partly
Handling of missing data, including a description of any patterns, underlying assumptions, and methods for imputation, should be documented.	No

Table 35. General provision of quality-of-life documentation, provided by Rhythm Pharmaceuticals, compared against NOMA's guidelines/requirements for describing how clinical quality of life data has been integrated into the health economic model

Requirements for documentation according to NOMA's guidelines.	**Submitted by Rhythm Pharmaceuticals?**
The choice of statistical model for the quality-of-life analyses (e.g., regression model) should be described, including the full model equation with justifications for the selection of variables and the correlation structure.	No
Assumptions for the statistical model used in the quality-of-life analyses (e.g., homoscedasticity, normality of residuals, independence in non-hierarchical models, linear relationships between predictors and outcomes) should be described.	No

Appendix 3: Description of the vignette study assessing the utilities associated with hyperphagia

OBJECTIVES
Patients with rare forms of monogenic or syndromic diseases of obesity often present with early-onset severe obesity and hyperphagia, characterized by an extreme, persistent, unsatisfied drive to consume food. Persistent hyperphagia-associated behaviours can lead to marked negative impact on the lives of patients. While utility values associated with obesity are available in published literature, no studies have estimated utilities associated with hyperphagia and impacts on patients' quality of life beyond obesity. The purpose of this study was to estimate health state utilities associated with various levels of hyperphagia.

METHODS
In time trade-off (TTO) interviews, participants from the United Kingdom general population valued four health state vignettes drafted from literature review and input from clinicians who treat patients with hyperphagia. Health states described patients with no hyperphagia, as well as mild, moderate, and severe hyperphagia. A composite TTO (cTTO) approach was followed, with health states perceived to be better than dead valued via conventional trade-off methods and health states perceived to be worse than dead valued with a lead-time procedure.

RESULTS
A total of 215 participants completed interviews (39.5% male; mean [range] age 39.1 [18-76] years). Mean (SD) utilities were 0.98 (0.02) for no hyperphagia, 0.91 (0.10) for mild hyperphagia, 0.70 (0.30) for moderate hyperphagia, and 0.22 (0.59) for severe hyperphagia. When compared to the health state with no hyperphagia, disutilities (i.e., utility decreases) were -0.08 for mild hyperphagia, -0.28 for moderate hyperphagia, and -0.77 for severe hyperphagia.
Using a conservative alternative, accepted methodology, whereby any negative utility scores from responders for any of the health states were set to zero, a utility multiplier of 0.98 was derived for no hyperphagia, 0.91 for mild hyperphagia, 0.72 for moderate hyperphagia and 0.38 for severe hyperphagia.

CONCLUSIONS
This novel research showed greater severity of hyperphagia is associated with lower health state utilities, underscoring the need for effective treatments that address the substantial quality-of-life impact of severe hyperphagia. These results could additionally be useful in economic evaluations for assessing benefits of treatments for hyperphagia.

Source: Rhythm Pharmaceuticals

Appendix 4: Severity calculations

NOMA uses a quantitative method to grade severity based on the current treatment with best supportive care. NOMA's calculations are based on absolute shortfall (AS). AS is the average health loss measured in undiscounted quality-adjusted life years (QALYs) as a result of the disease/condition without the new treatment.

The calculation of absolute prognostic loss is done in steps:

1) First, the average age at the start of treatment for the relevant Norwegian patient group under consideration for the new treatment is defined. This age is denoted as A. The sources for age include the Clinical Registry Investigating BBS (CRIBBS) database for paediatric patients[5] and the RM-493-023 study for adult patients[6].
2) The average number of expected remaining QALYs (undiscounted) is calculated for the general population with the same age as the average age of the patient group. This is referred to as $QALYs_A$. We have used mortality data for the Norwegian population from Statistics Norway (2022) to calculate the expected remaining life expectancy for different ages[7]. This is combined with age-specific quality of life data for an average population to calculate the quality-adjusted remaining life expectancy for different ages. We have used Norwegian age-specific quality of life data for an average population, along with British population-based EQ-5D valuation tariffs, based on Stavem et al. (2018)[8]. The table below shows the expected remaining quality-adjusted life years (QALYs) by age for the general population and is based on the sources mentioned above.
3) The average prognosis for the relevant Norwegian patient group is calculated. The prognosis is the expected remaining QALYs (undiscounted) for the patient group under the current standard treatment. We refer to this as P_A. The prognosis is based on simulations of treatment with the comparator in the health economic model used in this assessment.
4) The absolute shortfall (AS) is the difference between the expected number of remaining QALYs for the general population of the same age (point 2) and the expected number of remaining QALYs for the patient group under the current standard treatment (point 3)
5) $AS = QALYs_A - P_A$

Expected remaining QALYs in the general population
The table below shows the expected remaining QALYs and (health-related) quality of life weights by age for the general population. The expected remaining QALYs are based on mortality data for the Norwegian population from Statistics Norway[7] and the age-specific quality of life weights in the right column.

NOMA has updated the quality-of-life weights[9] for the general population using the recently published normative data by Stavem et al.[8]. The population sample is representative of all of Norway, and the data is more recent than the previously used normative data from Sweden[10], however, the number of

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respondents is lower. The new quality of life weights are, as before, valued using population-based EQ-5D tariffs (UK)[11].

The Norwegian normative data cover the age group from 19 to 97. The quality-of-life weights (values in parentheses) for the age groups 19–50 years have been taken directly from Stavem et al.[12] divided into the age groups 19–30 (0.906), 31–40 (0.870), and 41–50 (0.846). The age groups 51–70[13] (0.811) and 71–80 (0.808) are calculated using a weighted average[14] of raw data from Stavem et al.[15]. For the age group over 80 years, we use raw data from Stavem et al., which provide a weight of 0.730. A steeper decline in quality of life after the age of 80, compared to the decline between 50 and 80 years, is supported by findings from the Tromsø Study (T7, unpublished) and health-related quality of life studies from Europe[16]. NOMA assumes, as before, a slightly higher quality of life in the age group 0 to 19 years and applies the same adjustment (0.02) to calculate this (0.926).

[11] Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997;35(11):1095-108.

[12] Stavem K, Augestad LA, Kristiansen IS, Rand K. General population norms for the EQ-5D-3 L in Norway: comparison of postal and web surveys. Health and quality of life outcomes. 2018;16(1):204.

[13] In Stavem *et al* the quality-of-life weights in the 51–60 age group are lower than those in the 61–70 group. Similar fluctuations have not been observed in other studies. Therefore, NOMA has smoothed these quality-of-life weights by creating a weighted average for the entire group.

[14] In the raw data, quality-of-life weights are calculated in 5-year intervals, with the average weighted according to the proportion of respondents in each age group.

[15] Stavem-personal communication

[16] Janssen MF, Szende A, Cabases J, Ramos-Goni JM, Vilagut G, Konig HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. The European journal of health economics : HEPAC : health economics in prevention and care. 2019;20(2):205-16.

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Mangen MJ, Bolkenbaas M, Huijts SM, van Werkhoven CH, Bonten MJ, de Wit GA. Quality of life in community-dwelling Dutch elderly measured by EQ-5D-3L. Health and quality of life outcomes. 2017;15(1):3.

Tabell A 1: The expected remaining QALYs and quality of life weights in the general population

Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV
0	70,98	0,926	**36**	38,85	0,870	**72**	11,68	0,808
1	70,19	0,926	**37**	38,01	0,870	**73**	11,05	0,808
2	69,29	0,926	**38**	37,16	0,870	**74**	10,44	0,808
3	68,37	0,926	**39**	36,32	0,870	**75**	9,83	0,808
4	67,45	0,926	**40**	35,48	0,870	**76**	9,24	0,808
5	66,54	0,926	**41**	34,65	0,846	**77**	8,66	0,808
6	65,62	0,926	**42**	33,84	0,846	**78**	8,09	0,808
7	64,70	0,926	**43**	33,03	0,846	**79**	7,53	0,808
8	63,78	0,926	**44**	32,22	0,846	**80**	6,99	0,808
9	62,86	0,926	**45**	31,40	0,846	**81**	6,48	0,730
10	61,94	0,926	**46**	30,60	0,846	**82**	6,05	0,730
11	61,01	0,926	**47**	29,79	0,846	**83**	5,62	0,730
12	60,09	0,926	**48**	28,98	0,846	**84**	5,21	0,730
13	59,17	0,926	**49**	28,18	0,846	**85**	4,83	0,730
14	58,25	0,926	**50**	27,37	0,846	**86**	4,45	0,730
15	57,33	0,926	**51**	26,59	0,811	**87**	4,11	0,730
16	56,41	0,926	**52**	25,82	0,811	**88**	3,78	0,730
17	55,50	0,926	**53**	25,07	0,811	**89**	3,47	0,730
18	54,59	0,926	**54**	24,32	0,811	**90**	3,19	0,730
19	53,70	0,906	**55**	23,57	0,811	**91**	2,93	0,730
20	52,81	0,906	**56**	22,82	0,811	**92**	2,68	0,730
21	51,92	0,906	**57**	22,08	0,811	**93**	2,47	0,730
22	51,04	0,906	**58**	21,34	0,811	**94**	2,29	0,730
23	50,15	0,906	**59**	20,60	0,811	**95**	2,10	0,730
24	49,27	0,906	**60**	19,88	0,811	**96**	1,94	0,730
25	48,38	0,906	**61**	19,15	0,811	**97**	1,83	0,730
26	47,50	0,906	**62**	18,43	0,811	**98**	1,71	0,730
27	46,61	0,906	**63**	17,72	0,811	**99**	1,55	0,730

28	45,72	0,906	**64**	17,02	0,811	**100**	1,41	0,730
29	44,83	0,906	**65**	16,32	0,811	**101**	1,30	0,730
30	43,95	0,906	**66**	15,64	0,811	**102**	1,29	0,730
31	43,08	0,870	**67**	14,96	0,811	**103**	1,19	0,730
32	42,24	0,870	**68**	14,29	0,811	**104**	1,09	0,730
33	41,39	0,870	**69**	13,62	0,811	**105**	0,87	0,730
34	40,54	0,870	**70**	12,97	0,811	**106**	0,37	0,730
35	39,70	0,870	**71**	12,31	0,808			

Appendix 5: Comments from the manufacturer (Rhythm Pharmaceuticals)

Attn: Norwegian Medical Products Agency (NoMA)

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

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

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

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

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

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

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

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

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

2. Exclusion on modeling effect of Imcivree® on hyperphagia

We acknowledge NoMA's rationale for excluding the modelling effect of Imcivree® on hyperphagia from their main analysis due to the lack of specific hyperphagia data, and the measure of hunger instead. Nevertheless, this approach significantly underestimates Imcivree's therapeutic benefits. The targeted mechanism of action on the MC4R pathway, identified as the primary root of hyperphagia, joined with clinical experiences and testimonials from patients and their families, shows that reduction in hyperphagia is essential for patients to achieve the weight loss documented in clinical trials and is felt by patients within days of therapy initiation. Hyperphagia also returns almost immediately in case of therapy interruption.

Such evidence and insights underpin our emphasis on a response-based model, with responders to treatment experiencing a considerable reduction in hyperphagia levels, as this would be necessary to drive a clinically meaningful improvement in their BMI/BMI Z-score. Therefore, we request that NoMA reconsiders the broader therapeutic benefits of Imcivree® beyond measurable weight-related outcomes. The impact of Imcivree® on hyperphagia has been recognized by most HTA bodies, including NICE, GBA, HAS and AIFA.

3. Lack of "considerable" benefit

A direct effect of the exclusion of hyperphagia from the model is a significant reduction in the number quality-adjusted life years gained with therapy compared to standard treatment.

NoMA estimates that patients treated with setmelanotide gain 0.52 QALYs. BBS is a rare and disabling genetic disorder with multiple clinical features, exacerbated by the obesity resulting from hyperphagia [1,2] This condition severely affects patients' quality of life, daily functioning, and mental health, resulting in a significant burden that negatively impacts the lives of both patients and their caregivers [3]. It is also widely recognized that obesity is associated multiple related complications and an increase in mortality [4], with the risks being even greater in cases of early-onset obesity [5,6,7]. In this context, 0.52 QALYs dramatically underestimates the value of IMCIVREE for patients expressed by patients themselves, their caregivers and treating physicians.

4. Exclusion of modeling effect of Imcivree® on caregiver burden

As shown by Ervin et al [8] hyperphagia has a strong negative effect on patients and caregivers, and treatment with setmelanotide improves several dimensions of QoL. Caregivers of patients living with obesity and BBS as well as all family members are negatively affected by the presence of hyperphagia and obesity in their personal, social and professional life. This affects all family members and excluding this effect results in a model that is profoundly disconnect from the reality of the disease in real life.

5. Lack of Plausibility of utility values

In its report NoMA comments on the lack of plausibility of the utility values used in the company based case (page 58 first line). These utility values are indeed very low. As already discussed, BBS is a rare and disabling genetic disorder with multiple clinical features, exacerbated by the obesity resulting from hyperphagia [1,2] This condition severely affects patients' quality of life, daily functioning, and mental health, resulting in a significant burden that negatively impacts the lives of both patients and their caregivers [3]. Utilities values are a combination of three things:

- The effect of hyperphagia as measured in the Vignette study. The study was independently conducted and was published in a peer reviewed journal, and this is the only source of published data on hyperphagia disutility
- The impact on obesity on comorbidities. It is now clearly established that early onset is a severe disease that significantly increase the risk of morbidities and reduces life expectancy

- The impact of the disease on caregivers as discussed earlier

Rhythm cannot discuss the plausibility of the resulting utilities, but would like to stress that those simply reflect available published data.

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