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A SINGLE TECHNOLOGY ASSESSMENT:

Transcutaneous non-invasive vagus nerve stimulation (gammaCore) for the treatment of cluster headache

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Norwegian title Transkutan vagusnervestimulering i behandling av klasehodepine (gammaCore): hurtig metodevurdering

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Key messages

Cluster headache is a relatively rare but extremely painful condition. It is part of a group of conditions known as trigeminal autonomic cephalalgias (TACs). Cluster headache involves recurrent attacks of severe, unilateral pain. Attacks occur in periods (clusters) of several weeks and may last from 15 to 180 minutes at a rate of one every other day to eight per day. GammaCore is a handheld medical device stimulating the vagus nerve with electrical impulses. According to the submitter, gammaCore can reduce the need for acute treatment with oxygen or triptans associated with attacks.

Effectiveness and safety: One study comparing gammaCore to standard treatment shows that prophylactic use of gammaCore may improve quality of life, reduce attack frequency, and reduce the use of abortive medication among patients with chronic cluster headache. Two studies comparing gammaCore versus sham in the treatment of ongoing attacks show that gammaCore may have limited impact on patients with chronic cluster headache, but patients with episodic cluster headache probably experience higher likelihood of achieving pain-free status at 15 min and reduced pain intensity.

The included studies reported few adverse events, and no serious adverse events have been reported since the introduction on the European market. However, the manufacturer warns that gammaCore's safety and efficacy has not been evaluated for patients with cardiological disorders.

Severity: Absolute shortfall for patients with chronic cluster headache is 7.03 QALYs. The figure for patients with episodic cluster headache has not been estimated but is likely to be somewhat lower.

Economic analysis: Based on the submitters economic model gammaCore plus standard of care are dominant over standard of care alone, i.e. the costs are lower and the benefits are higher. The submitted budget impact analysis estimates that the number of patients using gammaCore will grow from 0 to 325 over the next five years if gammaCore is adopted, resulting in a cost saving of NOK 7,140,000 at year five.

NIPH considers the economic analysis to be reasonable for patients with chronic cluster headache, but there are important uncertainties with respect to its relevance for those with episodic cluster headache.

Title:
Transcutaneous non-invasive vagus nerve stimulation (gammaCore) for the treatment of cluster headache: A single technology assessment.

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Executive summary (English)

Background

Cluster headache (CH) is a relatively rare, but extremely painful condition. It is part of a group of conditions known as trigeminal autonomic cephalalgias (TACs). CH involves recurrent attacks of severe, unilateral pain. The lifetime prevalence of CH is estimated to 0.5 to 1 per 1000 inhabitants, which for the Norwegian population means that between 2 500 and 5 000 may be diagnosed with the disease.

The attacks occur in periods (clusters) of several weeks and may last from 15 to 180 minutes at a rate of one every other day to eight per day. There are two types of cluster headache: episodic (eCH) and chronic (cCH), though patients may switch between the two variants. Episodic CH typically involves series of attacks that occur at certain times of the year, while cCH involves attacks throughout the year.

GammaCore is a handheld medical device used for non-invasive vagus nerve stimulation (nVNS) with electrical impulses. According to the submitter, use of gammaCore can reduce the need for acute treatment with oxygen or triptans associated with attacks. The submitter believes that gammaCore may be used by patients who do not benefit from existing preventive treatment, either because they are refractory or because they experience adverse events. At year five, this amounts to 325 patients who respond positively to gammaCore per year.

Objective

The aim of this single technology assessment is to assess effect, safety and health economics based on the submitted documentation from electroCore, the manufacturer of gammaCore.

Method

This report is based on an evaluation of the documentation provided by the submitter. The submission file states that the following databases were searched for clinical trials on the 30. March 2022: Medline, Embase, Medline (R) In-Process, and Cochrane Library. ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) were searched for ongoing or unpublished studies. Searches were meant to update the searches reported in a submission file to the National Institute for Health and Care Excellence (NICE) from 2019. The submitter used the following PICO in the selection of clinical effect and safety studies:

Inclusion criteria	
Population	Cluster headache
Interventions	nVNS
Outcomes	All outcomes
Study design	Clinical trials
Language	English
Publication dates	1. January 2005- 30. March 2022
Exclusion criteria	
Study design	Post hoc analyses, non-primary study publications, mechanistic studies, reviews
Publication dates	Prior to 1. January 2005

Results

Effectiveness and safety

One study focusing on attack prevention for patients with cCH compared nVNS plus standard of care versus standard care alone. The study showed that prophylactic use of nVNS may reduce the attack frequency by almost four per week, reduce the need of abortive medication and improve quality of life by almost 0.2 points on EQ-5D-3L.

Two studies examined the effectiveness of nVNS in treating ongoing attacks by comparing nVNS versus sham. For patients with eCH, nVNS probably improves the number of patients who respond at 15 min to the first attack, probably improves the number of patients who are pain free status at 15 min, probably improves the sustained response rate, and may reduce the pain intensity by almost one point on a five-point Likert scale after 15 min. Patients with cCH experience less benefits from nVNS in the treatment of ongoing attacks than patient with eCH, and it seems like using nVNS in the acute phase may have little or no impact on response rates and pain intensity for patients with cCH.

GammaCore has been approved for the European market since 2011 and in the US since 2018 to treat cluster headaches. No serious adverse events have been reported since being on the European market in Medicines and Healthcare products Regulatory Agency database (MHRA), and only one event report in Manufacturer and User Facility Device Experience database (MAUDE, FDA, USA). The included studies reported few adverse events, and those reported were temporary and infrequent. However, there is very limited safety and efficacy data related to patients with cardiological histories, and the 'instructions for use' includes warnings stating this.

Health economics

The submitter's health economic analysis was a Markov model in which preventative use of gammaCore together with standard of care was compared to standard of care alone for patients with chronic cluster headache. The model duration was one year, and the consequences for attack frequency, costs and quality of life were estimated. The result of the deterministic base-case analysis found that gammaCore plus standard of care was dominant (i.e. lower costs and higher benefits) over standard of care alone. The total cost of gammaCore plus standard of care was estimated to be NOK 29,494, whereas total cost of standard of care alone was estimated to be NOK 32,355, the corresponding QALYs were 0.525 and 0.441.

The most uncertain variables were the cost of oxygen and the probability of response to gammaCore. The submitter will offer gammaCore free of charge for the first 93 days to reduce the impact of uncertainties in the probability of response, and the model assumes that only responders will continue treatment beyond this period.

The budget impact analysis includes both cCH and eCH and assumes that the number of patients responding to gammaCore each year will grow from 0 to 325 over the next five years if gammaCore is adopted. Due to the expected reduction in the use of acute treatment, a cost saving of NOK 7,140,000 is projected at year 5.

Discussion

Few treatments are available for patients with cluster headache, though they may benefit from drugs such as verapamil and lithium. Triptans and oxygen may offer relief in the acute phase, but the latter is cumbersome to use and may result in patient isolation.

NIPH recognizes that cluster headache is a relatively rare disease and that it is challenging to undertake clinical trials in this field. It seems that current guidelines in preventive treatment for cluster headache tend to be based on off-label therapies supported by a small number of randomized, controlled clinical trials.

The submitter developed a health economic model based on data from patients with cCH. The submitter assumes that eCH can be included in the model, asserting that evidence regarding preventative effectiveness can be generalized from cCH to eCH. This assumption is not documented, implying that the economic benefits of gammaCore for eCH remain uncertain. Given that gammaCore seems to be effective in treating ongoing attacks in patients with eCH, it is possible that it can involve cost savings, but evidence is lacking. If gammaCore is publicly financed, the submitter proposes that a consultant neurologist should decide if the patient should continue to use the device or not every three months.

Conclusion

Our assessment of the submitted documentation is that gammaCore may provide benefits to some patients in terms of fewer attacks and more rapid pain relief. For patients with cCH the benefits of gammaCore seem to be associated with prophylactic use, whereas patients with eCH probably benefit from treatment in the acute phase.

If gammaCore is offered alongside standard of care subject to 93 days free use, it may generate cost savings to the Norwegian health care system. NIPH considers the economic analysis to be reasonable for patients with cCH, but there are important uncertainties with respect to its relevance for those with eCH.

Hovedbudskap

Klasehodepine er en relativt sjelden, men ekstremt smertefull tilstand. Det er en del av en gruppe tilstander kjent som trigeminus autonome cephalalgier. Klasehodepine involverer tilbakevendende og alvorlige smerteanfall. Anfallene varer typisk 15 – 180 min og opptrer periodevis med frekvens mellom åtte per dag og ett anfall annenhver dag. GammaCore er et håndholdt medisinsk utstyr som stimulerer vagusnerven med elektriske impulser. Ifølge innsender kan gammaCore redusere behovet for akuttbehandling med oksygen eller triptaner.

Effekt og sikkerhet: Én studie sammenligner gammaCore med standardbehandling og viser at gammaCore muligens kan forebygge anfall og bidra til redusert bruk av medisiner og økt livskvalitet blant pasienter med kronisk klasehodepine. To studier sammenligner gammaCore med sham og viser at pasienter med kronisk klasehodepine muligens har begrenset effekt av å bruke gammaCore i behandlingen av pågående anfall. Pasienter med episodisk klasehodepine responderer trolig bedre på behandling i akuttfase, og for disse kan gammaCore trolig bidra til redusert smerteintensitet og at flere oppnår smertefrihet i løpet av 15 minutter.

Studiene rapporterer få bivirkninger, og ingen alvorlige bivirkninger er rapportert etter at gammaCore ble introdusert på det europeiske markedet. Produsenten advarer om at gammaCores sikkerhet og effekt ikke har blitt evaluert for pasienter med kardiologiske lidelser.

Alvorlighet: Absolutt prognosetap for pasienter som lider av kronisk klasehodepine er 7,03 kvalitetsjusterte leveår (QALY). APT for episodisk klasehodepine er ikke beregnet, men er sannsynligvis noe lavere.

Økonomisk analyse: Basert på innsenderens økonomiske modell er gammaCore pluss standard behandling dominerende over standardbehandling alene, dvs. at kostnadene er lavere og nytten høyere for pasienter med kronisk klasehodepine. Innsender anslår at antall årlige pasienter vil øke fra 0 til 325 i løpet av de neste fem årene dersom gammaCore blir tatt i bruk, og resultere i en besparelse på 7 140 000 kroner i år fem.

FHI vurderer den økonomiske analysen som rimelig for pasienter med kronisk klasehodepine. Det er imidlertid usikkerhet med hensyn til relevansen for de med episodisk klasehodepine.

Tittel:
Transkutan vagusnervestimulering ved klasehodepine (gammaCore): en hurtig metodevurdering

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Publikasjonstype:
Hurtig metodevurdering basert på innsendt dokumentasjonspakke

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Svarer ikke på alt:
Ingen vurdering av organisatoriske, juridiske eller etiske forhold

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Hvem står bak denne publikasjonen?
Folkehelseinstituttet har levert rapporten på oppdrag fra Bestillerforum for nye metoder

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Litteratursøk
Innsender utførte siste søk 30.03.2022

Eksterne fagfeller:
Knut Hagen, Professor Nevrologi NTNU, Faglig leder Norsk kvalitetsregister for alvorlige primære hodepiner, Medisinskfaglig rådgiver Klinisk Forskningsenhet Midt-Norge, St. Olav Hospital

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Sammendrag

Bakgrunn

Klasehodepine er en relativt sjelden, men ekstremt smertefull tilstand. Den er en del av en gruppe tilstander kjent som trigeminus autonome cephalalgier. Klasehodepine innebærer tilbakevendende anfall av alvorlig, ensidig smerte. Livstidsprevalensen av klasehodepine er anslått til å være mellom 0,5 og 1 per 1000 innbyggere, noe som betyr at mellom 2 500 og 5 000 mennesker sannsynligvis har fått diagnosen i Norge.

Anfallene forekommer i perioder (klaser) på flere uker. Anfallene kan typisk vare fra 15 til 180 minutter med en frekvens på én annenhver dag til åtte per dag. Det finnes to typer klasehodepine, episodisk og kronisk, men pasienter kan veksle mellom de to formene. Episodisk klasehodepine innebærer serier av anfall som oppstår på bestemte tider av året, mens den kroniske varianten gjerne medfører anfall gjennom hele året.

GammaCore er et håndholdt medisinsk utstyr for ikke-invasiv stimulering av vagusnerven (nVNS) med elektriske impulser. Ifølge innsender kan gammaCore redusere behovet for akuttbehandling med oksygen eller triptaner ved anfall. Innsender mener også at gammaCore kan brukes av pasienter som ikke har nytte av eksisterende forebyggende behandling, enten fordi de er refraktære eller fordi de opplever sterke bivirkninger. Pasientgrunnlaget utgjør i størrelsesorden 325 pasienter per år.

Mål

Målet med denne hurtige metodevurderingen er å vurdere effekt, sikkerhet og helseøkonomi basert på innsendt dokumentasjonspakke fra electroCore.

Metode

Denne rapporten er en vurdering av dokumentasjon som er innsendt av produsent. I henhold til dokumentasjonspakken ble følgende databaser søkt 30. mars 2022: Medline, Embase, Medline (R) In-Process og Cochrane Library. Det ble søkt etter upubliserte studier i ClinicalTrials.gov og World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). Søkene var ment å oppdatere søkene som ble benyttet i en dokumentasjonspakke som ble sendt til National Institute For Health And Care Excellence (NICE) i 2019. Innsender brukte følgende seleksjonskriterier (PICO) for studier om klinisk effekt og sikkerhet:

Inklusjonskriterier	
Populasjon	Klasehodepine
Intervensjoner	nVNS
Utfall	Alle utfall
Studiedesign	Kliniske
Språkbegrensninger	Engelsk
Publiseringsdatoer	1. januar 2005 - 30. mars 2022
Eksklusjonskriterier	
Studiedesign	Post hoc-analyser, ikke-primære studiepublikasjoner, mekaniske studier, oversikter
Publiseringsdatoer	Før 1. januar 2005

Resultat

Effekt og sikkerhet

Én studie, som fokuserte på forebygging av anfall, sammenlignet nVNS pluss standardbehandling versus standardbehandling alene for pasienter med kronisk klasehodepine. Studien viste at nVNS muligens kan redusere antall anfall med nesten fire per uke, redusere behovet for medikamentell behandling og forbedre livskvalitet med nesten 0,2 poeng på EQ-5D-3L.

To studier undersøkte effekt av nVNS i behandlingen av pågående anfall ved å sammenligne nVNS versus sham. For pasienter med episodisk klasehodepine kan nVNS trolig forbedre andel pasienter som responderer i løpet av 15 minutter, andel som blir smertefri i løpet av 15 min og andel med vedvarende respons. Blant pasienter med episodisk klasehodepine kan nVNS muligens også redusere smerteintensitet med nesten ett poeng på en fempunkts Likert-skala. Pasienter med kronisk klasehodepine ser ut til å ha mindre effekt av nVNS i behandling av pågående anfall enn pasienter med episodisk klasehodepine, det vil si at bruk av nVNS i akuttfasen muligens har liten eller ingen effekt på responsrater og smerteintensitet hos pasienter med kronisk klasehodepine.

De identifiserte studiene rapporterte få bivirkninger. I bivirkningsdatabasen til MHRA er det ikke rapportert alvorlige bivirkninger siden gammaCore ble introdusert på det europeiske markedet, og det foreligger bare én hendelsesrapport i MAUDE. Det foreligger begrenset med sikkerhetsdata knyttet til pasienter med kardiologisk historie, og bruksanvisningen inneholder en advarsel om dette.

Helseøkonomi

Innsenderens helseøkonomiske analyse var en Markov-modell der forebyggende bruk av gammaCore pluss standardbehandling ble sammenlignet med standardbehandling alene for pasienter med kronisk klasehodepine. Modellens tidshorisont var ett år, og konsekvensene for anfallsfrekvens, kostnader og livskvalitet ble estimert. Den deterministiske hovedanalysen viste at gammaCore pluss standardbehandling dom-inerte, dvs. at det hadde lavere kostnader og høyere gevinster enn standard alene. Totalkostnaden for gammaCore pluss standardbehandling ble estimert til 29 494 kroner, sammenlignet med 32 355 kroner for standardbehandling alene. QALY-verdiene var henholdsvis 0,525 og 0,441 i basecase-analysen.

De mest usikre variablene var oksygenkostnaden og sannsynligheten for behandlingsrespons basert på responsratedefinisjonen. Innsender vil tilby gammaCore gratis de første 93 dagene for å redusere betydningen av usikkerhet i sannsynlighet for respons, og modellen forutsetter at kun pasienter med opplevd effekt fortsetter behandlingen utover denne perioden.

Budsjettkonsekvensanalysen omfatter både pasienter med kronisk og episodisk klasehodepine, og forutsetter at antall pasienter som årlig vil respondere på behandling vil øke fra 0 til 325 i løpet av de neste fem årene hvis gammaCore blir introdusert. Grunnet forventninger om redusert bruk av akuttbehandling er det anslått en kostnadsbesparelse på 7 140 000 kroner ved år fem.

Diskusjon

Det er et begrenset utvalg av behandlinger tilgjengelig for pasienter med klasehodepine, selv om de kan ha nytte av legemidler som verapamil og litium. Triptaner og oksygen kan gi en viss lindring i den akutte fasen, men sistnevnte er tungvint å bruke og kan føre til pasientisolasjon. Folkehelseinstituttet erkjenner at klasehodepine er en relativt sjelden sykdom og at det er utfordrende å gjennomføre kliniske studier på dette feltet. Det kan virke som at retningslinjer for forebygging av klasehodepine ofte er basert på off-label behandling understøttet av et lite antall randomiserte kontrollerte studier.

Innsender har utviklet en helseøkonomisk modell som er tilpasset til norsk klinisk praksis og som er basert på pasienter med kronisk klasehodepine. Innsender forutsetter at denne modellen også gjelder pasienter med episodisk klasehodepine, det vil si at antakelsen om en forebyggende effekt kan generaliseres fra kronisk til episodisk klasehodepine. Denne forutsetningen er ikke dokumentert, noe som innebærer at de antatte økonomiske gevinstene knyttet til pasienter med episodisk klasehodepine forblir usikre. Gitt at pasienter med episodisk klasehodepine ser ut til å ha effekt av gammaCore i behandlingen av pågående anfall er det mulig at en innføring kan innebære kostnadsbesparelser også for denne gruppen, men dette er ikke dokumentert av innsenderen. Dersom gammaCore blir offentlig finansiert, foreslår innsenderen at videre bruk av utstyret bør revurderes av nevrolog hver tredje måned.

Konklusjon

Vår vurdering av den innsendte dokumentasjonen er at gammaCore kan gi fordeler i form av færre anfall og raskere smertelindring. Pasienter med kronisk klasehodepine har muligens størst nytte av å bruke gammaCore til å forebygge anfall, mens pasienter med episodisk klasehodepine har dokumentert nytte av å bruke gammaCore i den akutte fasen.

Dersom gammaCore tilbys som tillegg til dagens standardbehandling, og gitt at produsenten tilbyr 93 dagers gratis bruk, kan innføring av gammaCore gi kostnadsbesparelser for det norske helsevesenet. FHI vurderer den økonomiske analysen som rimelig for pasienter med kronisk klasehodepine, men det er viktige usikkerhetsmomenter knyttet til den økonomiske analysen for dem med episodisk klasehodepine.

Preface

The Division for Health Services at the Norwegian Institute of Public Health was commissioned by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a single health technology assessment of gammaCore in addition to standard of care for cluster headache patients in Norway. In a single-technology assessment, the technology (a pharmaceutical or a device) is assessed based on documentation submitted by the company owning the technology, or their representatives. The submission used in this single technology assessment of the gammaCore system was submitted by electroCore Inc. The HTA unit of the Norwegian Institute of Public Health (NIPH) received and evaluated the submitted documentation, with regard to effect and safety (important clinical outcomes), resource use and assumptions made in the analysis and models submitted by the manufacturer. NIPH does not develop separate health economic models within the scope of a single technology assessment. If applicable, NIPH can obtain additional information from the manufacturer or independently retrieve updated information to make own calculations of relative effect, costs, cost-effectiveness, severity and budgetary consequences.

Project group: Fawaz Tariq Chaudhry (Health Economist), Alexandra Herborg Cornelius Poulsson (Senior Advisor), Hanna Eikås Klem (Senior Advisor), Gunn Eva Næss (Information Specialist), Monica Gomez Castaneda (Health Economist), Espen Movik (Health Economist), Kjetil Gundro Brurberg (Department Director)**.**

Clinical experts: Knut Hagen, Professor Neurology NTNU, Academic leader of Norwegian quality register for severe primary headaches, Medical advisor Clinical Research Unit Mid-Norway, St. Olavs and Bendik Winsvold, Senior Researcher, Consultant neurologist, Department of Neurology and Department of Research and Development Department, Division of Clinical Neuroscience, Oslo University Hospital.

Patients' representatives: Representative from Hodepine Norge

Conflict of interest: Authors and experts involved in this report state they have no conflict of interest to declare.

Kåre Birger Hagen *Director of Reviews and Health Technology Assessments*	Kjetil G. Brurberg *Department director*	Espen Movik *Project coordinator*

Background

Cluster headache (CH), is a relatively rare but extremely painful condition (1). It is part of a group of conditions known as trigeminal autonomic cephalalgias (TACs). CH involves recurrent attacks of severe, unilateral pain, which is orbital, supraorbital, temporal or in any combination of these sites (2). The pain is associated with ipsilateral conjunctival injection (red eye), lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or restlessness or agitation (2). The intense pain is said to be worse than both passing a kidney stone and giving birth, and is often referred to as the suicide headache (1).

The annual incidence of CH in Norway is estimated to be 3.0 per 100 000, i.e. 114 new CH patients per year. The lifetime prevalence is estimated to range from 0.5 to 1 per 1000 inhabitants, which means that between 2 500 and 5 000 people may be diagnosed with CH (1). Previously, 80% of patients with the condition were male, but CH are now increasingly also diagnosed among females with recent data from Norway showing 59.5% male population (3). The attacks occur in periods (clusters) of several weeks (1). The attacks may last from 15 to 180 minutes at a rate of one every other day to 8 per day (4).

There are two types of cluster headache: episodic (eCH) and chronic (cCH), though patients may often switch between the two variants. ECH involves series of attacks that occur at certain times of the year, often in the autumn and spring, may last for several weeks or months and then disappear for months or years. CCH is almost continuous with attacks throughout the year, though some may experience intermittent, short breaks. Approximately 80-90 % of patients have the episodic form (5).

The technology: the description and use

The following is copied directly from the submission file:

"*gammaCore is a Class IIa therapeutic medical device. The treatment modality delivered by gammaCore is non-invasive vagus nerve stimulation, nVNS, (also: transcutaneous vagus nerve stimulation, tVNS). gammaCore has a valid CE Mark titled 'Acute and/or prophylactic treatment of primary headache (migraine, cluster headache, and hemicrania continua) and medication overuse headache in adults. Furthermore, gammaCore received FDA clearance for the preventive use in CH and the acute treatment of eCH and migraine.*"

The NICE report for vagus nerve stimulation states that:
"*gammaCore delivers electrical stimulation, is a non-invasive vagus nerve stimulator used to treat and prevent cluster headaches. It is self-administered by the person or their carer. After applying conductive gel, gammaCore is held against the neck (over the cervical branch of the vagus nerve) and delivers a small electric current for about 2 minutes. This stimulation should be repeated 3times. The device is small and portable. gammaCore requires RFID (radio frequency identification) card activation...)(6).*

Additional communication with electroCore provided further details on the electrical stimulation provided by the device: *gammaCore produces a low-voltage electric signal consisting of five 5,000-Hz pulses that are repeated at a rate of 25 Hz. The waveform of the gammaCore pulse is approximately a sine wave with a peak voltage limited to 24 Volts when placed on the skin and a maximum output current of 60mA (7).*

The technology: How does it work

This section is copied directly from the submission file:
"Vagus nerve stimulation therapy was pioneered in the 1980's. The original vagus nerve stimulators required an invasive surgical procedure to implant a medical device comprised of a battery pack inserted into the chest wall and stimulating electrodes which were tunnelled up to the cervical region of the vagus nerve, where they are wrapped around the nerve bundle. gammaCore is the first ever non-invasive vagus nerve stimulator allowing a patient to safely, self-administer treatment without the need for expensive and often risky surgical procedures.

gammaCore activates the vagus nerve – which plays an important role in regulating pain – with patented, gentle electrical stimulation. nVNS with gammaCore is believed to help block the pain signals that cause migraine and cluster attacks (8-12)."

Regulatory status and market access

GammaCore received CE marking under MDD 93/42/EEC in 2011 for the gammaCore and alphaCore Series, the device is categorized as class IIa under device code MDD code 1103 and their certificate (13) is currently valid to 26.05.2024 for the following indications (14):

- Preventive treatment of cluster headache
- Acute treatment of cluster headache
- Preventive treatment of migraine headache
- Acute treatment of migraine headache

It is contraindicated for:

- Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
- Patients with metallic device such as a stent, bone plate or bone screw implanted at or near their neck

- Patients who are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., mobile phone)

Patients should not use gammaCore:

- While driving, operating machinery, or during any activity that may put patient at risk of injury
- Near microwave machines, magnetic resonance imaging, radio frequency surgical, or computer-aided tomography machines
- In an explosive atmosphere or in the presence of flammable gas mixtures
- If patient has an open wound, rash, infection, swelling, cut, sore, drug patch, or surgical scar(s) on the neck at the treatment location
- If patient has wet skin, is in the water, or just stepped out of the water (eg, shower, bath, pool)

Warning:

- The long-term effects of the chronic use of gammaCore have not been evaluated.
- Safety and efficacy of gammaCore have not been evaluated in the following patients or situations.
- Patients with uncontrolled hypertension, hypotension, bradycardia, or tachycardia
- Patients with a history of baseline cardiac disease or atherosclerotic cardiovascular disease, including congestive heart failure, known severe coronary artery disease, or recent myocardial infarction (within 5 years)
- Patients with a history of abnormal baseline ECG, prolonged QT interval or arrhythmia
- Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)
- Pediatric patients (less than 12 years of age)
- Pregnant women
- Patients with active cancer or cancer in remission
- Patients with an abnormal cervical anatomy
- Patients with a history of brain tumor, aneurysm, bleed or head trauma
- Patients with a history of syncope or seizures
- Contact your doctor if your symptoms continue or worsen.
- Treatment is intended to be given (administered) as directed by a doctor. A doctor or electroCore Customer Service must provide training in the proper use of gammaCore.

gammaCore has FDA clearances in the United States for the following indications:

- Acute treatment of episodic cluster headache
- Prevention of cluster headache
- Acute treatment of migraine
- Preventive treatment in migraine
- Migraine in adolescents

The most common side effects associated with gammaCore (reported by more than 1% of patients who participated in gammaCore studies) include:

- Application site discomfort

- Application site irritation/redness
- Local pain, face/head/neck area (including toothache)
- Muscle twitching and/or contractions, face/head/neck area (including facial droop and/or lip pull)
- Headache/migraine
- Dizziness
- Tingling, pricking, or a feeling of "pins and needles" on the skin where the device is applied (paresthesia/dysesthesia)

These side effects typically resolve immediately after the stimulation is complete.

In the US, the Food and Drug Administration (FDA) provided clearance for adjunctive use of gammaCore for the preventive treatment of cluster headache in November 2018, *'making gammaCore the first and only therapy available for the prevention of cluster headache'* (2). GammaCore was FDA cleared for the relief of pain associated with migraine in 2018 and eCH in 2017 (2). In February 2021, the FDA granted a label expansion of gammaCore nVNS to include the acute and preventive treatment of migraine in adolescents between 12 and 17 years of age.

In September 2021 the company received Section 510(k) clearance from the United States Food and Drug Administration (FDA) of the company's submission to expand the label of gammaCore nVNS to include the treatment of Paroxysmal Hemicrania (PH) and Hemicrania Continua (HC) in adults. GammaCore is available for patients to privately purchase following authorisation by an appropriate named, registered healthcare professional.

Description of the context of use

This section is copied directly from the submission file

The target condition and the health technology's position in clinical practice

There is currently no prospect of a curative treatment for cluster headache. The attainable goal of treatment is total attack cessation or suppression of the headache until the next episode. A more conservative and realistic goal is to shorten the cluster period in eCH and to reduce the severity/frequency in both eCH and cCH.

The Norwegian Electronic Medical Handbook's clinical guidelines on headache states that oxygen or triptans should be used for acute treatment of CH (15). These treatments can be effective at relieving pain within 15-30 minutes. A cluster period can be terminated with oral steroids, and blockade of the greater occipital nerve may be used as transitional therapy. Oral steroids (e.g. prednisolone) can be used only for a short time because of side effects. The use of verapamil and anticonvulsants for CH is outside their marketing authorisation. Furthermore, verapamil requires gradual titration to minimise the risk of third-degree atrioventricular block, and close ECG monitoring should be offered during this titration. The use of these prophylactic medicines is not supported by a formal clinical evidence base, and their use is completely empirical. When other

treatments fail lithium, occipital nerve blocks and sphenopalatine ganglion stimulation therapy via a surgical procedure may be considered.

Expert advice indicates that many people with cluster headache do not get enough pain relief with current treatment options, which are often limited by side effects and contraindications. gammaCore is intended for use by people with cluster headache for whom standard treatment has been unsuccessful or in people who cannot use other prescribed treatments. If used, it is most likely to be introduced before more invasive procedures or treatment with lithium are considered. gammaCore is most likely to be authorized by neurologists who specialise in headache management. People using gammaCore will need brief training. Once trained, people with cluster headache can use gammaCore in any setting.

Most CH patients are treated on an outpatient basis. Only in justified exceptional cases an inpatient admission usually in specialized headache / migraine clinics takes place. Reasonable exceptions include:

- *Failure of prophylactic therapy*
- *Refractory CH patients who are unresponsive to either approved or standardized off-label therapies*
- *Atypical CH cases*

Patients with a new onset of CH symptoms are also often admitted to the hospital because the symptoms usually appear at night, and they initially feel very threatening for these patients.

The therapy of CH is divided into acute attack treatment and prophylactic long-term treatment. Most therapies are based on practical experience and anecdote since there are only a few controlled studies on the respective therapy options. For these reasons, CH therapy is very individual and not very standardized. The process of finding an efficacious therapy for cCH is difficult and often requires a combination of medications and an experienced doctor. In these cases, a referral to a specialized headache outpatient clinic / certified headache and facial pain expert is usually necessary.

gammaCore can be used as both prophylactic and acute treatments. When gammaCore is used as a prophylactic therapy, verapamil and the associated ECG monitoring during verapamil titration may no longer be needed. This ECG monitoring typically takes place in primary care facilities so will reduce this GP/community nursing team appointment pressure. Hospital outpatient appointments, accident and emergency (A&E) attendance, and telephone consultation may also be reduced as a consequence of improved prophylactic control of CH. Prophylactic use of gammaCore has been shown to significantly decrease the use of both triptans and oxygen during acute attacks, allowing economic and quality of life benefits to be realised for payers and patients, respectively (16). The limitations associated with home-based oxygen cylinders from environmental, safety, and delivery logistics perspectives may also be removed.

Prior to the availability of gammaCore, many patients with treatment-refractory CH may have been referred to a tertiary centre, where a complex invasive surgical procedure may have been

undertaken to achieve treatment success. gammaCore can eliminate a significant number of these unnecessary, expensive interventions.

If gammaCore is adopted in Norway, the current pathway of care for CH patients would not change. The availability of gammaCore would provide clinicians and patients with an authorised, clinically proven, non-pharmacological treatment option that could be easily used by patients as both a prophylactic and acute therapy. Its intended place in therapy would most likely be where standard care treatments for cluster headache are ineffective, not tolerated, contraindicated, or for those seeking a non-pharmacological treatment option.

A study by Fischera et al. investigated the prevalence of cluster headache and reported that 1 year prevalence rates ranged from 0.003% to 0.15%. The pooled analysis suggested a 1 year worldwide prevalence of 0.05% (17) (6)."

Patient Population

The diagnosis of CH is made according to the criteria of the International Classification of Headache Disorders, 3rd edition (18). According to these criteria, CH cases have the following characteristics (19):

- *a. At least 5 attacks that meet criteria b–d*
- *b. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain attacks lasting 15 to 180 minutes if left untreated*
- *c. One or both of the following points is/are fulfilled:*
    1. *At least one of the following symptoms or signs, each ipsilateral to the headache:*
        - *i. conjunctival injection and/or lacrimation*
        - *ii. nasal congestion and/or rhinorrhea*
        - *iii. eyelid edema*
        - *iv. sweating in the area of the forehead or face*
        - *v. miosis and/or ptosis*
    2. *Physical restlessness or agitation*
- *d. Attack frequency ranges from one attack every other day to eight per day*
- *e. Not better explained by another ICHD-3 diagnosis.*

In addition to the criteria mentioned, there must not be any pathological findings for a confirmed CH diagnosis (The International Classification of Headache Disorders: 3rd edition)(18).

The diagnosis of CH consists of a detailed anamnesis and a clinical-neurological examination. The diagnostic differentiation from other primary headaches and facial pain, such as trigeminal neuralgia, persistent idiopathic facial pain, cervicogenic headache and, above all, paroxysmal hemicrania (higher frequency of attacks with shorter duration of attacks and obligatory response to indomethacin) is of great importance, since the associated symptoms are similar.

A cerebral MRI is usually performed to confirm absence of any pathological findings, often performed in conjunction with an additional angiography to rule out any vascular pathologies (19). Particularly in older patients, intracranial masses close to the midline, which can be frontal, occipital or in the cerebellum, should be ruled out. These masses include tumors (especially pituitary tumors), arterio-venous malformations, and also cerebral infarction or inflammatory plaques (19). For this purpose, an MRI and, if necessary, a CT scan of the skull base can be performed.

The target population for nVNS using gammaCore can be generically referred to as refractory CH patients. The term "refractory" refers to patients in whom approved therapies are ineffective or contraindicated. Since the established standard care in the case of CH often consists of off-label therapies, the affected target population is defined as adult (≥18 years) CH patients (eCH and cCH),

1. *where standard conservative therapies are ineffective, not tolerated, or contraindicated, or*
2. *where standard therapies are associated with significant losses in quality of life due to significant and/or disproportionate adverse effects.*

Established standard therapies are divided into preventive and acute therapies. If patients do not respond to an established preventive therapy, they are only left with the use of appropriate acute medications, of which the daily cumulative maximum dose is limited and which also cause high costs. Therefore, nVNS should not only be limited to the patient groups mentioned under 1. and 2., but could also be used as a therapy option in broader CH patient groups, given the advantageous safety profile of nVNS (see section 6.5, Safety).

Self-application of the nVNS requires manual dexterity as well as the ability to follow instructions. nVNS is not indicated for use in patients with a cochlear implant or pacemaker and has neither been evaluated in pregnant or breastfeeding women, nor in underage patients (<18 years).

The annual Norwegian prevalence of CH was conservatively estimated at 0.048%, shown in Table 1 Table 1*, with a male to female ratio of approximately 1.47:1(3) . Another population-based study in a small geographical area in Norway, found a lifetime prevalence of 0.38% CH, but only two out of 7 cases had consulted a physician (20). Studies conducted in other Eurpoean countries report incidences of CH of 7 to 119 cases per 100,000 and year (19;21;22). On this basis, the number of affected patients in Norway is estimated at around 4,300 patients of whom around 15-25% do not receive any effective treatment, since conservative therapies are either ineffective or contraindicated (6;23).*

Our clinical expert has emphasised that the lifetime prevalence in Norway has been found to be 0.38% for CH (20), but only two of seven cases had consulted a physician, and thereby the maximum number of CH patients in Norway is estimated to be 4,300 (23), which is an overestimation.

This gives an estimated number of patients between 640 - 1,070 who are suitable for treatment for CH with nVNS. Of these patients - in whom conservative therapies are either ineffective, contraindicated or associated with disproportionate side effects - up to 50% will benefit from nVNS

therapy such that they wish to continue nVNS treatment beyond 3 months. These estimates result in a total collective of max. 320 to 585 CH patients who would use the nVNS in the long term at the expense of the Norwegian healthcare system shown in Table 2.

Table 1: *Incidence and prevalence of Cluster Headache in Norway & globally*

	Current year	**Source**
Incidence in Norway	3.0 per 100,000	Crespi et al., 2022
Prevalence in Norway*	48.6 per 100,000	Crespi et al., 2022
Global 1-year prevalence	50 per 100,000	Fischera et al., 2008

*Prevalence was measured over an 8-year period (2008-2016), so the numbers are not per year.

Table 2: *Expected future patient numbers using gammaCore based om submission file.*

	2022	**2023**	**2024**	**2025**	**2026**	**2027**
Norwegian patients expected to use the technology*	0	68	137	205	274	325

* Numbers estimated based on technology adoption path in Budget Impact model

Literature search

Information about the search

This section is comprised of information collected from the submission file

PICO Clinical efficacy and safety

P	Cluster headache, excluding non−cluster headache disease states, healthy subjects
I	nVNS excluding treatments other than nVNS
C	• Subcutaneous or nasal spray triptan therapy (acute) • Oxygen therapy (at home), used alone or alongside subcutaneous or nasal spray triptan therapy (acute) • Verapamil (preventive) • Sphenopalatine ganglion nerve stimulators (acute and preventive treatment for chronic cluster headache) • Occipital nerve block (preventive)
O	All outcomes
S	Clinical trials, excluding post hoc analyses, non-primary study publications, mechanistic studies, reviews

Results from the search

According to the submission file (2), Medline, Embase, Medline (R) In-Process, and Cochrane Library databases were searched for all clinical studies of non-invasive vagus nerve stimulation (nVNS) in the treatment and prevention of cluster headaches. The initial search was performed in 2019 for a submission of evidence to the National Institute for Health and Care Excellence (NICE), UK, in the framework of the Medical Technologies Programme (MTP) and updated in 2022. Combining the PRISMA charts the search identified 216 records of which 20 full text articles were assessed. Ten studies were included in the qualitative synthesis, and two studies were reviews that included quantitative synthesis (meta-analysis).

Searches for studies related to safety were conducted separately. The first search was conducted in 2019 and complemented by a second search. The complementary search used identical search strategies and databases. *The Medline, Embase, Medline In-Process, and Cochrane Library databases were searched for all clinical studies that included comprehensive safety evaluations of nVNS in patients with headache conditions or safety studies of nVNS focused on cardiovascular effects, a*

serious adverse event (AE)-related concern associated with other comparators (e.g. subcutaneous sumatriptan, invasive vagus nerve stimulation). A separate PICO was established for the safety searches, this included focus on the following population: *'Headache, non-headache with a focus on cardiovascular adverse outcomes.'*

The two searches covered the period from 1 January 2005 through 30 March 2022. The searches identified 238 records, of which 27 full text articles were assessed for eligibility and 15 studies were included in qualitative synthesis, there were no studies for quantitative synthesis.

Ongoing studies

In the submission ongoing studies were identified by searches performed on 30th and 7th of March 2022. The ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) databases were searched for all clinical studies involving nVNS in the treatment and prevention of cluster headaches. The submission file states: *In the ClinicalTrials.gov search, "cluster headache" was specified for the condition or disease and "vagus nerve stimulation" OR "gammaCore" was specified for the intervention/treatment; no other search limits were defined. In the WHO-ICTRP, search terms were "cluster headache" AND "vagus nerve stimulation" OR "gammaCore," and no other search limits were defined. Conference abstracts and presentations that were excluded from the published study search due to the absence of corresponding published articles were added to the unpublished study search results and are included with this submission.*

For unpublished safety studies the following is stated: *In the ClinicalTrials.gov search, "vagus nerve stimulation" OR "gammaCore" was specified for the intervention/treatment, and "headache" OR "migraine" OR "cardiovascular" was specified for the Other terms field. A search limit was defined to exclude studies with a status of "not yet recruiting," "recruiting," or "enrolling by invitation," as results would be unavailable for such studies. In the WHO-ICTRP, search terms were "headache" OR "migraine" OR "cardiovascular" in the Title field AND "vagus nerve stimulation" OR "gammaCore" in the Intervention field. No other search limits were defined.* Three unpublished safety studies were identified by the submitter.

Comments from NIPH on the search

The literature search was performed with a very limited selection of keywords, especially related to population. The search is poorly documented, and this applies to both subject and text words. It is not possible to reproduce the search as presented in the submission file. Only the health economics search can be run as it is described. The submitter has performed separate searches for effect, safety and health economics, while NIPH would see these as heavily interlinked and would not have separated them.

To confirm whether the search strategies were adequate, NIPH used the Systematic Review Accelerator from Bond University (24). Utilising the studies identified in the submission file as 'seed articles', Systematic Review Accelerator tools aide in the identification of relevant MESH terms. With the MESH terms identified the "SearchRefinery" tool (25) can be used to identify

which critical mesh terms are needed to allow for the identification of all the seed articles at the same time as the number of irrelevant hits are kept as low as possible.

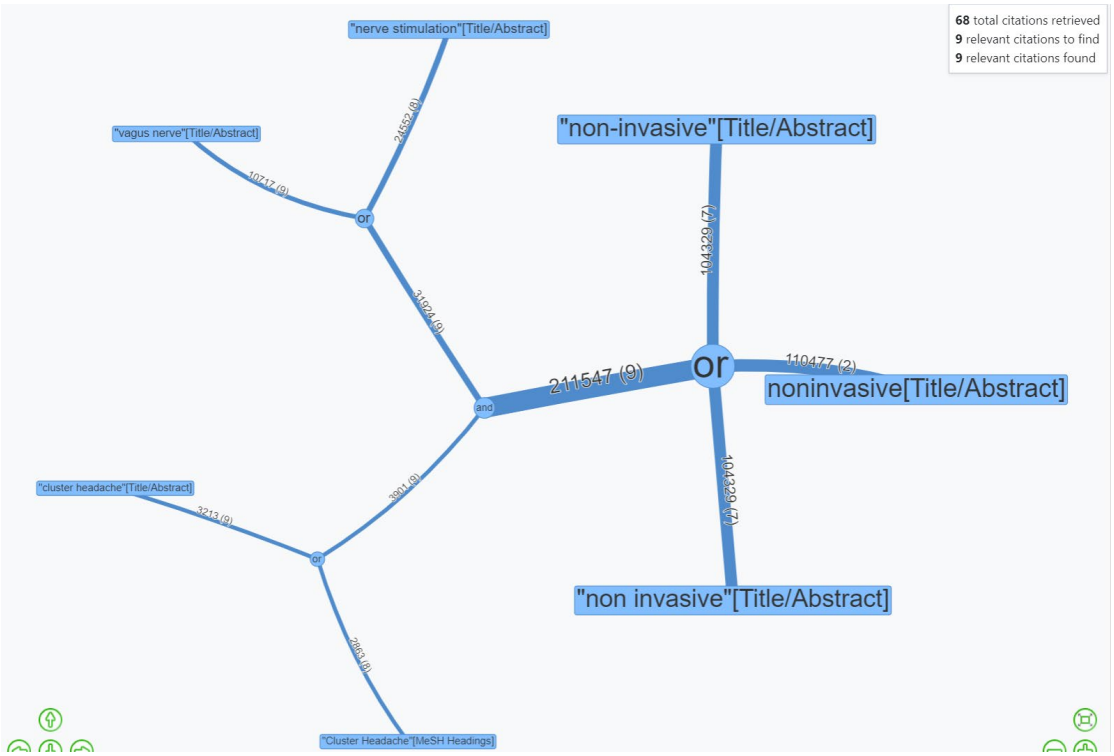


Figure 1: *'SearchRefinery' diagram showing the MESH terms used, and how many hits are found with each term, and their combination to maintain all 9 seed articles.*

Figure 1 shows the number of articles with each term, and the process identified 68 potentially relevant references from the nine RCTs included in the submission. These 68 references were entered into OpenAlex, an openly accessible dataset with more than 250,000,000 scientific objects (26). OpenAlex also includes gray literature such as institutional reports, parliamentary reports and evaluations that are published electronically. Instead of searching for subject words or keywords in titles and abstracts, OpenAlex connects references based on the content and meaning of the text. OpenAlex identified 2274 potentially relevant references.

We used Priority screening which is a ranking algorithm in the software EPPI-Reviewer (27;28) trained by the researchers' decisions about the inclusion and exclusion of references at title and abstract level. Ranking algorithms are trained to recognize relevant data and to rank the remaining data according to the likelihood that they are relevant. References that the algorithm considers more relevant based on the researchers' decisions about inclusion and exclusion are pushed forward in the "queue". In this way, we get a quicker overview of how many references possibly meet the inclusion criteria than if we were to read the references in a random order.

Once selected into 'include title and abstract' or 'exclude' categories, the next step was using the Cochrane RCT classifier in the EPPI reviewer software (27;28). The classifiers are algorithms trained to recognize data with special characteristics and they categorize data according to whether these characteristics are possessed or not. The Cochrane RCT classifier has been built, validated and trained on 280,000 healthcare references, which means that it is able to distinguish

with a high degree of certainty between randomized controlled study designs (RCT) and other study designs (29;30). This classifier classifies the references into two categories "likely to be an RCT" and "unlikely to be an RCT", with 99% certainty (recall) and 0.08% precision (specificity). Cochrane recommends that all systematic reviews of RCTs only consider references classified as "likely to be an RCT", i.e. all studies categorized as "unlikely to be an RCT" can be excluded without manual review.

We identified 12 articles related to RCTs on nVNS for cluster headaches, and an additional 28 articles were identified as background articles, as shown in Appendix 1.2. None of the articles identified were new RCTs about nVNS in the treatment of cluster headaches but reported additional details from RCTs included in the submission file (Appendix 1.0). Our use of machine learning tools showed that the search and selection processes performed by the submitter were not adequately reported.

Clinical effectiveness and safety

In this section we present and assess the evidence on the clinical effectiveness and safety of gammaCore in patients with chronic (cCH) an episodic (eCH) cluster headache. The presented results are based on data from the submission file but supplemented with data extracted from some of the primary articles included in the submission file. We refer to the treatment as gammaCore or non-invasive vagus nerve stimulation (nVNS).

Method

The submitter performed two separate literature searches for safety and effect for all groups of evidence. The submitter presented eligibility criteria in tables and flow charts summarising the selection process. We discovered some discrepancies in the number of references in the flow charts and the studies presented in the submission file. On request the submitter provided a revised flow chart. The submitter did not describe in detail how the screening or the data extraction were carried out.

For some outcomes, the results are based on a re-analysis by de Coo and coworkers rather than the numbers reported in the primary studies. The de Coo re-analysis is not a traditional meta-analysis, but an individual patient data meta-analysis based on the assumption that the two available studies (ACT1 and ACT2) were very similar regarding participant population and treatment protocol. The authors performed study interaction tests to check the tenability of this assumption without finding evidence of treatment-by-study-interactions for any of the outcomes examined. Some heterogeneities between ACT1 and ACT2 can be attributed to the fact that the distribution of eCH versus cCH participants is different in the two studies. This has limited impact on our analysis as we choose to present data for the two subgroups separately.

In our summary we present results from de Coo et al, but we have also done our own complementary analysis based on the available primary studies. Moreover, we have chosen to deviate from the submission file as we think this provides a better match between evidence (effect and safety) and the health economic analysis. In our presentation we make clear distinctions between prophylactic treatment and acute treatment of ongoing attacks. We also separate between the treatment of eCH and cCH, as available evidence suggests there are important subgroup effects that differ between the two types of cluster headache. In the presentation of effect data, we have chosen to focus strictly on patients with cluster headache even though the submission file also includes studies on patients with migraine. For safety outcomes we include all patient categories.

The submitter did not perform GRADE (31) assessments, so we have chosen to grade the evidence on effect and prepare summary of findings tables to structure the data presentation. One reviewer from NIPH performed the GRADE assessments, and another reviewer checked the assessments. The GRADE assessments are presented in the summary of findings tables (Table 7, 8 and 9).

Included reviews

The submission file included two reviews: a systematic review by Lai 2020 (32) and a pooled analysis by de Coo 2019 (8). The review published by Lai and co-workers assesses (32) the effectiveness of nVNS in a mixed population consisting of patients with CH or migraine. Even though there may be some overlap the mechanisms of disease and pain relief, CH and migraine differ clearly in clinical features, response on preventive treatment as well as functional and genetic markers to such a degree that they cannot be viewed as the same population. Based on our clinical expert's opinion, pooling of these patient categories is not appropriate (33;34). We have therefore chosen to focus on studies where patients with cluster headaches are the population, as in the pooled analysis by de Coo (8). However, we present the results on safety from the Lai review, as our clinical experts did not see this as a problem.

Included primary studies

As described in the Methods section, NIPH has chosen to review preventive treatment and treatment of ongoing attacks as two separate research questions. Moreover, NIPH has also chosen to differ between treatment of eCH and cCH. Three RCTs were identified by the submitter (10;11;16), of which two were also included in the pooled analysis by de Coo (8). The submission file also referred to five non-randomized studies. The included studies on clinical effectiveness are listed in Table 3.

Table 3: Complete list of included primary studies

Study, design	**Population (ITT)**	**Intervention** (# participants)	**Comparison** (# participants)
ACT1 (US) RCT Silberstein et al. (11)	eCH (n=101) cCH (n=49)	nVNS (acute) n=60 (eCH-38 / cCH-22)	Sham n=73 (eCH-47 / cCH-26)
ACT2 (EU) RCT Goadsby et al. (10)	eCH (n=27) cCH (n=66)	nVNS (acute) n=48 (eCH-14 / cCH-34)	Sham n=44 (eCH-13 / cCH-31)
PREVA (EU) RCT Gaul et al. (16)	cCH (n=93)	SoC+nVNS (preventive) (n=45)	SoC alone (n=48)
Marin et al. (UK) Retrospective audit of RWD (35)	eCH (n=29) cCH (n=1)	SoC+nVNS (real-world, preventive) (n=30)	SoC alone (n=30)
Nesbitt et al. (UK) Single arm pilot study (36)	eCH (n=8) cCH (n=11)	nVNS (acute and preventive)	N/A
Trimboli et al (UK) Open-label prospective audit in a real-world setting (37)	cCH (n=12), chronic migraine (n=23), hemicrania continua (n=4) , SUNA (n=2)	nVNS (real-world, acute and preventive)	N/A
Mwamburi et al Prospective patient registry (38)	eCH (n=17)	nVNS (acute and pre-ventive)	N/A
Silver et al Retrospective audit of pre-scriptions (39)	CH (n=2092 pre-scriptions)	nVNS	N/A

Table 3 has been adapted from the submission file by NIPH. The Abbreviations: cCH-chronic cluster headache, eCH-episodic cluster headache, nVNS: non invasive vagus nerve stimulation; SoC: standard of care; N/A: not applicable; SUNA: Short-lasting Unilateral Neuralgiform headache Attack; RWD: Real World Data

Risk of bias in included primary studies

The following tables (Table 4-6) are copied from the submission file, with an additional column where NIPH has commented on the appraisal performed. There is one quality assessment table for each randomized trial (ACT1(11), ACT2 (10) and PREVA (16)) for which the submitter assessed the quality using the Cochrane Risk of Bias (RoB) tool (40). The submitter used an adapted check list from Critical Appraisal Skills Programme (CASP) (41) for the remaining studies, but we have chosen not to include these.

Table 4: Critical appraisal of the ACT1 study (adapted from the submission file)

Study name	**ACT1** (11)		
Study question	**Response**	**How is the question addressed in the study?**	**NIPH's comments to the assessment**
Was randomisation carried out appropriately?	Yes	Independent statistician–generated randomisation schedules were used to assign subjects (1:1 allocation) to receive nVNS or sham treatment using a variable block design stratified by study site.	Described on page 1320 in the publication. NIPH agrees with this assessment.
Was the concealment of treatment allocation adequate?	Yes	Devices were labelled with randomisation numbers and allocated to study sites by a third-party distributor according to the randomisation scheme.	Described on page 1320 in the publication. NIPH agrees with this assessment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline characteristics were similar between groups and were consistent with those of a typical CH patient population.	Table 1, page 1323. NIPH agrees with this assessment: The statistical significance between the treatment groups has not been evaluated. The nVNS and sham groups appear similar, as do the demographic and baseline characteristics between these two groups. However, there is difference in the size of the eCH and cCH cohorts, (101 - eCH and 49 – cCH), the study protocol describes the recruitment population as adults diagnosed with cluster headaches with no subgroup differentiation.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A		Described on page 1320 in the publication. NIPH agrees with this assessment.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A		Figure 3 page 1322 in the publication. NIPH's comment: There was a dropout of 19% (n=14) in the nVNS group, and 10.4% (n=8) dropouts in the sham group during the randomized phase. This is not discussed in the article. NIPH's comment: We would assess a greater than 10% dropout to have a potential to

			cause bias, leading to YES or UNCLEAR.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		NIPH's comment: the study protocol was found at clinicaltrials.com. The authors report the primary and secondary outcomes described there. NIPH agrees with this assessment.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Missing data were imputed as failures for response variables and using the last observation carried forward for attack intensity.	Page 1321 in the publication. NIPH agrees with this assessment. However: *imputing missing data as failures* could entail some risk of bias.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.
Abbreviations: CH, cluster headache; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table 5: Critical appraisal of the ACT2 study (adapted from the submission file)

Study name	**ACT2** (10)		
Study question	**Response**	**How is the question addressed in the study?**	**NIPH's comments to the assessment**
Was randomisation carried out appropriately?	Yes	A standard design with a block size of 4 was used to randomly assign subjects (in a 1:1 ratio) to receive treatment with either nVNS or the sham device.	Page 960 in the publication. NIPH agrees with this assessment.
Was the concealment of treatment allocation adequate?	Yes	Each study site received sealed randomisation envelopes imprinted with subject numbers; subjects were enrolled in consecutive order at each site.	Page 960 in the publication. NIPH agrees with this assessment
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The mean duration of attacks and median number of attacks per week during the run-in period were similar between treatment groups.	Table 1 page 962. NIPH agrees with this assessment. NIPH's comment: The statistical significance between the treatment groups has not been evaluated. The nVNS and sham groups appear similar, as do the demographic and baseline characteristics between these two groups. However, there is difference in the size of the eCH and cCH cohorts, (30 - eCH and 101 – cCH), however it is not clear from the study protocol or

			published study if the recruitment was skewed towards cCH.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A		Page 960: *Unblinded trainers provided subjects with the appropriate device, as indicated by their randomization envelope, and training on its use.* NIPH's comment: We would have assessed this as NO.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A		Figure 1 page 963 in the publication. NIPH's comment: There was a drop-out of 10%(n=5) in the nVNS group and 27% (n=14) in the sham group This is not discussed in the article. We would have assessed this as YES or UNCLEAR.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		NIPH's comment: The study protocol was found at clinicaltrials.com. The authors report the primary endpoint and two of the secondary end points. They do not report secondary outcome *Change in Disability From Baseline (Randomization) to 2 Weeks After Baseline* nor *Mean Change of Questionnaire EQ-5D-3L (Euroqol- 5D-3L) From Baseline to After 2 Weeks Treatment.* The end point *adverse effects* in the publication are not described in the protocol. We would have assessed this domain as YES.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Subjects were included in the analyses for all endpoints for which they provided data.	NIPH agrees with this assessment.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.

Abbreviations: N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table 6: Critical appraisal of the PREVA study (from the submission file)

Study name	**PREVA** (16)		
Study question	**Response**	**How is the question addressed in the study?**	**NIPH's comments to the assessment**
Was randomisation carried out appropriately?	Yes	Subjects were randomly assigned (1:1 allocation) using a standard block design to receive either SoC plus nVNS or SoC alone.	Page 535 in the publication. NIPH agrees with this assessment
Was the concealment of treatment allocation adequate?	N/A	Open-label study	NIPH does not agree with this assessment due as it is open-label and the inherent bias this can lead to.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Disease characteristics at baseline were similar between treatment groups.	Table 1 page 538 in the publication. NIPH's comment: The statistical significance between the treatment groups has not been evaluated. The groups appear similar
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Possible placebo response to nVNS	NIPH's comment: we agree with the assessment of this domain, but the submitter has not discussed the likely impact on the risk of bias (for each outcome).
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A		Figure 1 page 536 in the publication. NIPH' s comment: The dropouts appear similar across the groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		NIPH' s comment: We would have assessed this domain as YES. Page 536: secondary outcomes not listed in the protocol: *≥50% response rate (i.e. proportion of participants with ≥50% reduction in mean number of CH attacks per week), abortive medication use and duration and intensity of CH attacks that were acutely treated with nVNS.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Missing data were imputed to *no change* for reduction in the number of CH attacks or to *no response* for response rate.	Page 537: *The reduction in the number of CH attacks per week from baseline to the randomised phase (primary end point) was assessed in the ITT population, for which missing data were imputed to 0 (i.e. no change; designated as treatment failures).* NIPH agrees with this assessment.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.
Abbreviations: CH, cluster headache; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

NIPH's comments on risk of bias assessment

Overall, we have evaluated that the submitter's risk of bias assessment for the studies presented above does not adhere to Cochrane's RoB guidance (40). There are a number of places where the submitter has assessed the risk of bias to be 'low' while we would evaluate it to 'high'. This means that we have more concerns than the submitter when it comes to the impact of RoB on the overall certainty of evidence.

The submitter assessed the quality of five of the non-randomized studies using Critical Appraisal Skills Programme (CASP)(41): "Making sense of evidence - 12 questions to help you make sense of a cohort study". That is, the tables describing the risk of bias in the Mwamburi (38) and Silver (39) studies have the text *Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.* The domains in the tables, however, are the CASP domains. The CASP checklists were designed to be used as educational pedagogic tools, as part of a workshop setting. NIPH think that the ROBINS I checklist would have been a better choice for assessing the five studies. The submitter has also omitted several domains in the CASP cohort checklist, without explaining the possible rationale for this decision. The domains not included in the submitter's checklist are:

1. Did the study address a clearly focused issue?
6. (b) Was the follow up of subjects long enough?
7. What are the results of this study?
9. Do you believe the results?
10. Can the results be applied to the local population?
11. Do the results of this study fit with other available evidence?
12. What are the implications of this study for practice?

In the instructions on how to use the CASP checklist for cohort studies, the two first questions are described as screening questions, and the answer should be "yes" to both in order for the checklist to be continued. As the submitter has omitted screening question 1 along with six other domains, we find the assessments very deficient, and it is futile to comment further upon these assessments.

All the RCTs which are included by the submitter were sponsored by the submitter and therefore contain an inherent bias, and this must be taken into account when evaluating the studies. The reviewers from NIPH have not assessed the risk of bias appraisals done by the submitter of the studies included in the safety part of the submission file. Five of the thirteen studies included were already assessed for RoB in the Effect Section and the remaining studies were not assessed as the only outcome under consideration was safety.

Acute phase treatment: Effect of gammaCore versus sham or standard of care

The submission file includes several analysis and figures, many of which are from published articles and are redrawn by the submitter. In the following, we present figures from the submission, and figures that the NIPH have generated in Review Manager (RevMan)(42). As the submission was intended to focus on cluster headache, we have chosen to report results from the studies that included patients with cluster headache, and have not included results for patients with migraine. The reported results are either derived directly from the aforementioned primary studies or from the pooled analyses published by de Coo et al. (8).

Proportion of participants responding at 15 minutes for the first attack

The dossier included a plot similar to figure 1 in de Coo (7). The analyses were based on individual patient data and showed that across ACT1 and ACT2, 20 of 52 participants (38.5%) with eCH in the vVNS group responded at 15 min for the first treated attack. The corresponding number in the sham group was seven out of 60 (11.7%). A similar difference in effect was not seen among participants with cCH where 14 og 56 participants (25.0%) in the vVNS group and 17 of 57 participant (29.8 %) in the sham group experienced effect.

NIPH comments: Participants who responded at 15 min for the first treated attack was reported as an outcome in two of the included RCTs: ACT1 (11) and ACT2 (10). The two trials were pooled in an analysis by de Coo and co-workers (8). The data shows that a statistically significant proportion of eCH participants had effect from the first nVNS treatment in the ACT 1 study (32), in ACT 2 (32) there were fewer eCH participants, however the pooled data from both studies shows that the treatment had a significant effect for participants with eCH. In the article by de Coo et al. the pooled estimate for all cluster headache patients was reported as odd ratio (OR) 1.72 (95% confidence interval (CI) 0.93 to 3.17). The primary analysis included both patients with eCH and cCH, but the subgroup analysis suggested a significant subgroup effect with a higher response rate associated with eCH (OR 4.67; 95% CI 1.77 to 12.32) than cCH (OR 0.74; 95% CI 0.32 to 1.72). The GRADE assessment for these outcomes can be found in Table 7 and Table 8.

Proportion of all treated attacks that achieved pain-free status at 15 minutes

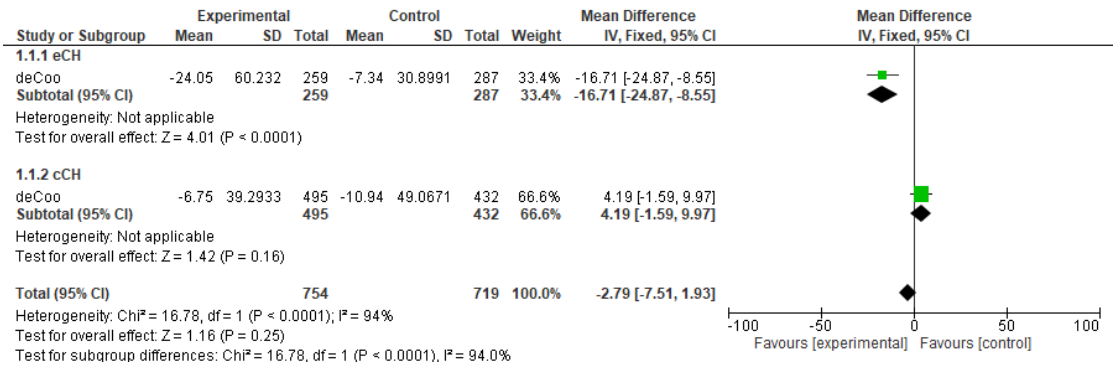


Figure 2: *Proportion of all treated attacks that achieved pain-free status at 15 minutes. The numbers are taken from de Coo et al. (8) and show the mean difference have been converted by the NIPH. cCH: chronic cluster headache; CH: cluster headache; CI: confidence interval; eCH: episodic cluster headache; nVNS: non-invasive vagus nerve stimulation.*

NIPH's meta-analysis in figure 2, shows the mean difference of the pooled data from ACT 1 and ACT 2 for the intervention vs the sham, where nVNS is estimated to have an effect on the eCH participants, with a relatively wide confidence interval (mean difference of -16.7 (95% CI -24.9 to -8.6, p<0.0001), however this was not shown for cCH participants, or overall where the mean difference was -2.8 (95% CI -7.5 to 1.9, p=0.25). The GRADE assessment for this outcome can be found in Table 7 and Table 8.

Changes in pain intensity after 15 minutes

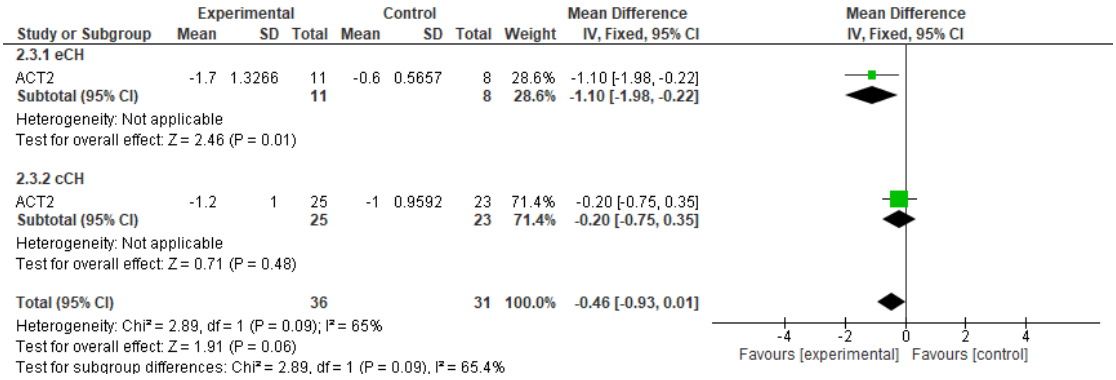


Figure 3: *Changes in pain intensity after 15 minutes. The numbers from ACT 2 (10) are calculated by NIPH.*

The analysis in figure 3 is based on data from ACT2 and shows changes in pain intensity, measured on a five-point Likert scale, after 15 minutes. The intervention is not shown to have a clear effect across eCH and cCH, with a mean difference of -0.46 (95% CI -0.93 to 0.01, p=0.06). The plot does however show an effect for nVNS for the eCH group alone with a mean difference of of -1.10 (95% CI -1.98 to -0.22, p=0.01). The GRADE assessment for these outcomes can be found in Table 7 and Table 8.

Response rate

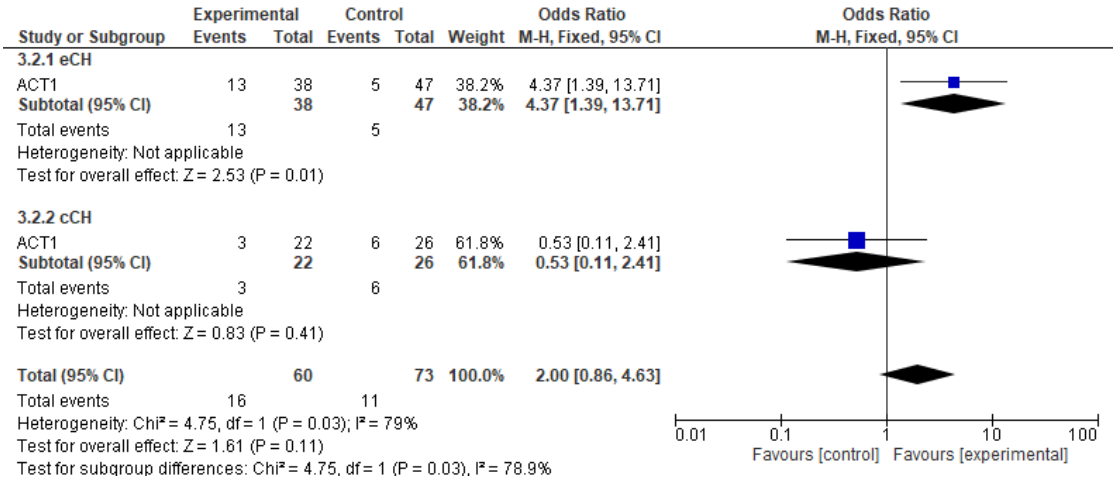


Figure 4: *The response rate for eCH and cCH. The numbers from ACT1 (11) are calculated by NIPH.*

The analysis for response rate in figure 4 is based on data from ACT 1. There is no clear overall effect (i.e. across eCH and cCH) with an odds ratio of 2.00 (95% CI 0.86 to 4.63, p=0.11). There

was however a statistically significant effect in favour of nVNS in the eCH subgroup, with an odds ratio of 4.37 (95% CI 1.39-13.71, p=0.01). GRADE assessment for this outcome can be found in Table 7.

Sustained response

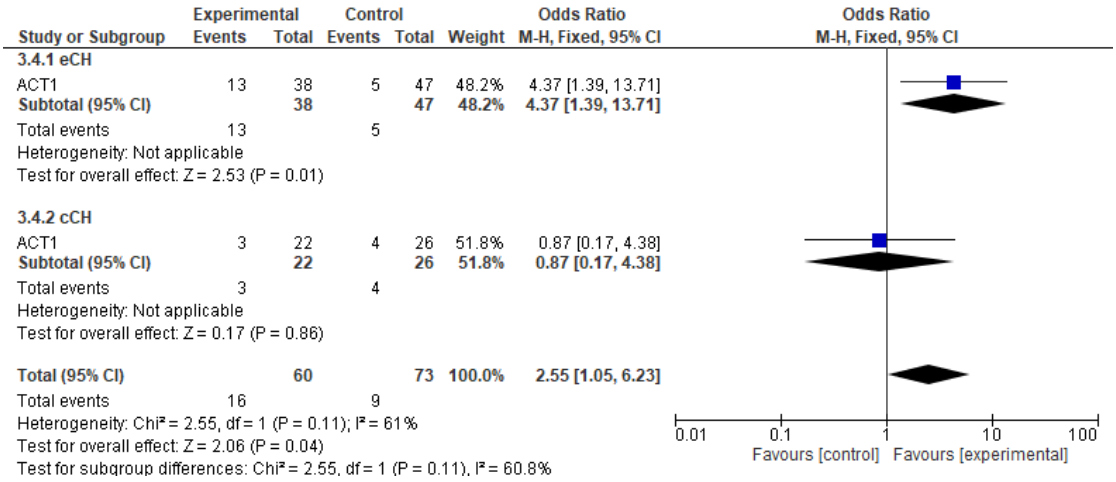


Figure 5: *Sustained response. The numbers from ACT1 (11) are calculated by NIPH.*

The analysis for sustained response is based on data from ACT1 (Figure 5), and shows there is an effect of nVNS with an odds ratio of 2.55 (95% CI 1.05 to 6.23, p=0.04) for the combined eCH and cCH groups. There was also a clear effect shown for nVNS for the eCH subgroup, with an odds ratio of 4.37 (95% CI 1.39-13.71, p=0.01). GRADE assessment for these outcomes can be found in Table 7 and Table 8.

Prophylactic treatment: Effect of gammaCore versus sham or standard of care

Data presented in this section is based on outcomes reported in the PREVA study (15). PREVA only recruited participants with cCH, and hence, no data is provided for the eCH subgroup.

Attack frequency

PREVA (16) measured and reported the number of attacks per week and showed that patients in the nVNS group had a greater reduction in the number of attacks per week than patients in the control group with a mean difference -3.9 (95% CI -7.2 to -0.5). See Table 9 for GRADE assessment.

≥50% response rates

PREVA (16) reported the proportion of patients with ≥50% reduction in mean number of CH attacks per week. The authors reported more responses in the nVNS group (40%, 18 of 45) than in the control group (8.3%, 4 of 48). This corresponds to an OR of 7.33 (95% CI 2.24 to 23.98), which indicates a large effect in favour of nVNS. See Table 9 for GRADE assessments.

Abortive medication use

PREVA (16) reported abortive medication use. During the randomised phase, a 57% decrease in the frequency of abortive medication use was noted in the SoC plus nVNS group. This corresponds to a reduction of -15 percentage points (95% CI: -22.8, -7.2; $p < 0.001$). For patient in the control group the corresponding reduction was -2 percentage points (95% CI -9.8, 5.4; p=0.59). The change in abortive medication use was therefore larger in the SoC plus nVNS than in the SoC alone group (MD -13 percentage points, 95% CI -24 to -2; p=0.02). See Table 9 for GRADE assessments.

Quality of life

PREVA (16) measured and reported quality of life among patients with cCH following the use of nVNS. Quality of life was assessed using the EQ-5D-3L scale (43), and the results were clearly in favour of nVNS. The change in the SoC group was -0.049 points, and the change in the intervention group was 0.194 points higher (95% CI 0.054 to 0.334). This difference is higher than the suggested minimal important difference of 0.074 points and can therefore be considered clinically meaningful. See Table 9 for GRADE assessments.

Satisfaction with the device

CH patient satisfaction using nVNS was evaluated in ACT1/PREVA. The proportion of patients who were extremely satisfied, very satisfied or satisfied with the treatment were 38.3% for ACT 1 and more than 50% in PREVA. This corresponds to an OR of 1.35 (95 % CI 0.66 to 2.77) for ACT1. This outcome was not graded.

Use of nVNS as abortive therapy

The PREVA study (16) also reported that during the randomised phase 93.8% (45/48) of participants assigned to nVNS + SoC acutely treated more than 1 CH attack with nVNS. This also occurred during the unblinded phase of trial where 68.2% (30/44) of the SoC plus nVNS group and 83.3% (40/48) of the control group treated more than 1 CH attack with nVNS in the two-week period. It should be noted that there was no control group for this. This outcome was not graded.

GammaCore in the included real-world evidence (audits)

The studies by Nesbitt et al. (36), Silver et al. (39), Marin et al. (35), Mwamburi et al. (38) were audits of real-world clinical experience, thus they were not RCTs and no intention-to-treat analyses was performed. The Nesbitt et al. (36) study evaluated eCH and cCH patients. The submitter states: *Further formal evidence synthesis is impractical because of the heterogeneity and inconsistent quality among the remaining PREVA (16), Marin et al. (35) Nesbitt et al. (36)(…) studies of nVNS in cluster headache*. As we do not have a complete risk of bias assessment for these studies, the NIPH cannot evaluate the quality of the aforementioned studies, other than state that these study designs do not allow for the interpretation of causality between treatment and effect, as would be possible in blinded RCTs.

The study by Nesbitt et al. (36) collected patient-estimated efficacy data by systematic inquiry during follow-up appointments up to a period of 52 weeks of continuous use. There were 11 chronic and 8 episodic patients. The results reported were: *Fifteen patients reported an overall improvement in their condition, with 4 reporting no change, providing a mean overall estimated improvement of 48%. Of all attacks treated, 47% were aborted within an average of 11 ± 1 minutes of commencing stimulation. Ten patients reduced their acute use of high-flow oxygen by 55%, with 9 reducing triptan use by 48%. Prophylactic use of the device resulted in a substantial reduction in estimated mean attack frequency from 4.5/24 hours to 2.6/24 hours (p < 0.0005) posttreatment.*

The study by Silver et al. (39) is a retrospective review of prescribing in England, collecting data regarding gammaCore prescriptions and refills from 1 April 2019 to 31 December 2020 in patents with cluster headache. The results reported were: *In total, 52 NHS sites submitted 2092 prescriptions for gammaCore devices, including 655 for new starters. Among new starters, 46.3% received ≥1 refill and 30.9% received ≥2 refills. Those who started using gammaCore after its inclusion in the Innovation and Technology Payment programme received up to seven refills during the data collection period, representing 21 months of therapy.*

The study by Marin et al. (35) retrospectively analysed data from 30 patients with CH (29 chronic, 1 episodic). *The mean (SD) CH attack frequency decreased from 26.6 (17.1) attacks/wk. before initiation of nVNS therapy to 9.5 (11.0) attacks/wk. (P < 0.01) afterward. Mean (SD) attack duration decreased from 51.9 (36.7) minutes to 29.4 (28.5) minutes (P < 0.01), and mean (SD) attack severity (rated on a 10-point scale) decreased from 7.8 (2.3) to 6.0 (2.6) (P < 0.01). Use of abortive treatments also decreased. Favourable changes in the use of preventive medication were also observed. No serious device-related adverse events were reported.*

From the submission file, Marin et al. (35) shows patients who used gammaCore treatment over a period of 3-6 months. Data was collected from interviews and patient diaries, physicians' notes. The data shows the gammaCore treatment significantly reduced the number of attacks per week, duration and severity compared to SoC in this limited pool of patients who responded to initial treatment.

The Mwamburi study (38) is a gammaCore Patient Registry, designed to provide insights on the use of gammaCore and prescription patterns in the real-world setting and to characterize respective benefits and challenges during the acute treatment of episodic cluster headache. *Of the 192 cluster headache attacks reported, gammaCore was used in 116 (60%) attacks. Within this group, the mean pain score at the start of the attacks was 2.7, the mean number of stimulations used was 3.6, and the pain score after 30 minutes was 1.3. At 30 minutes, the pain of 81 (70%) attacks was reduced to none (27%) or mild (43%) (a pain score of 0 or 1) and in 94 (81%) attacks, patients experienced a reduction of at least 1 point in the pain score.*

Safety – Adverse events

The submitter performed two separate literature searches on safety and screening process resulted in 15 included safety studies, three from the search ending in 2019 and 12 from the most recent search ending in March 2022, as described in the Literature search Section. The submitter also searched for, and included, three unpublished safety studies. The search was performed with 'cardiovascular' as a search term, because the submitter wanted to focus on those effects. This is not how the NIPH would perform a search as this may exclude other safety issues, also including cardiovascular, if the term has not been used precisely. Their search omitted to find a systematic review on "Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans" by Redgrave et al. which identified 51 articles reporting transcutaneous VNS treatment harms (44). This review however is not limited to stimulation applied to the neck, but also covers auricular and cervical branches of the vagus nerve. Appendix 2 - SAFETY – ADVERSE EVENTS provides tables with a more detailed overview of the adverse events that have been reported in literature.

One of the studies the submitter has highlighted is Rubenstein et al. (45), a conference abstract for a clinical trial with 30 asthma patients who's ECG (electrocardiogram) was monitored during nVNS. The findings showed both premature atrial or ventricular contractions occurred in 17% (n=5) of patients during or after stimulation, a benign sinus arrhythmia occurred in 37% (n=11) of patients, where 14% (n=4) had previously had benign sinus arrythmia at baseline. However, the authors concluded that this "had no clinically meaningful effect on cardiovascular function, as the abnormal ECG events were transient and benign." The clinical trials described under the Acute phase treatment: Effect of gammaCore versus sham or standard of care Section had cardiovascular history described as exclusion criteria. In addition, the instructions for use for the gammaCore device state that patients with pacemakers and other active implantable devices are contraindicated (14). In addition, amongst other warnings the following is stated under long-term effects of the chronic use of gammaCore, where it is stated that safety and efficacy have not been evaluated for the following conditions (14):

- Patients with uncontrolled hypertension, hypotension, bradycardia, or tachycardia
- Patients with a history of baseline cardiac disease or atherosclerotic cardiovascular disease,
- including congestive heart failure, known severe coronary artery disease, or recent
- myocardial infarction (within 5 years)
- Patients with a history of abnormal baseline ECG, prolonged QT interval or arrhythmia
- Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)

It is important that the physicians prescribing gammaCore devices are aware of any contra-indications and warnings provided in the Instructions for Use (14), especially those related to cardiological conditions. As mentioned, in the majority of studies all patients with cardiological histories were excluded leading to very limited safety data for these conditions.

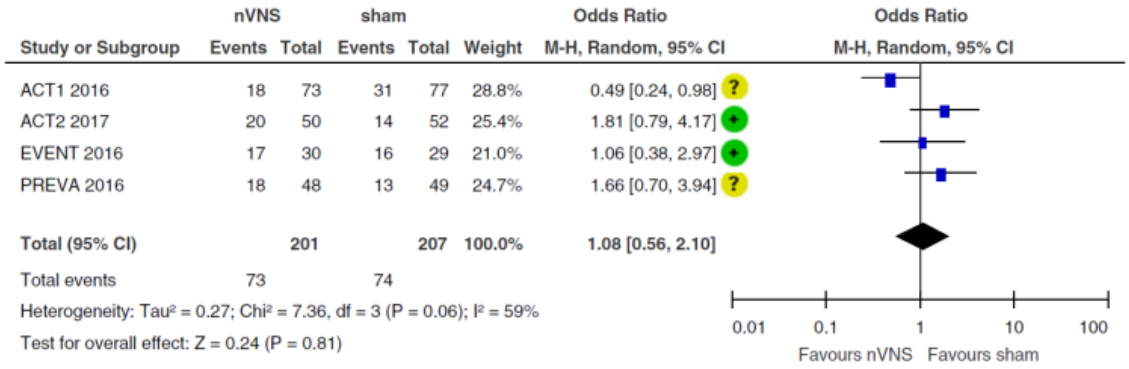


Figure 6: *Forest plot of adverse events from the submission file (2) adapted from Lai et al (32). From the submission file. "Four studies mentioned adverse events. There were no significant differences in adverse events between the nVNS group and control group (OR, 1.084; 95% CI, 0.56~2.10; p = 0.81; I2 = 59%)".*

For the forest plot from Lai et al. (32) adapted as figure 6, it is stated that: *"Our meta-analysis showed that nVNS is safe and well tolerated. Adverse events in our studies were mild or moderate, such as skin irritation, pain at the application site, musculoskeletal disorders (headaches, and oropharyngeal and back pain), facial/neck twitching, nasopharyngitis, and dizziness. The most common side effects reported in a previous meta-analysis (51) were local skin irritation from electrode placement (240 participants, 18.2%), headaches (3.6%), and nasopharyngitis (1.7%); in addition, 2.6% participants dropped out due to side effects."*

It must however be noted that the stimulation through vagus nerve has been shown in the clinical trials ACT 1 and ACT 2 to not only lead to adverse events with the gammaCore device, but also through the sham devices (10;11). In these trials adverse effects such as burning and tingling (paranesthesia), and skin irritation at the site of application were observed both with the sham and gammaCore device (46). The study by Schroeder et al. suggests that the sham used in these trials also had an unintended stimulating effect, modulated the trigeminal-autonomic reflex.

Redgrave et al. identified 51 studies where different devices including gammaCore stimulate the vagus nerve, in addition the site of stimulation varied. The studies comprised of a total of 1322 human subjects receiving tVNS. *The most common side effects were: local skin irritation from electrode placement (240 participants, 18.2%), headache (47, 3.6%) and nasopharyngitis (23, 1.7%). Whilst heterogeneity in overall side effect event rates between studies was not accounted for by the frequency (Hz) or pulse width (ms) of stimulation, a minority (35 participants (2.6%)) dropped out of studies due to side effects. Overall, 30 SAE occurred but only 3 were assessed by the relevant researchers to be possibly caused by tVNS.*

Adverse events registered in MAUDE or MHRA database

As described in the submission file the MHRA did not have any registered adverse events in their database (47), since the device has been on the European market. Through the FDA MAUDE database (48) there is one event reported in 2018: *The event was described as the experience of neck twitching, lymph node and neck swelling, and numbing and inability to move the left arm. These symptoms presented approximately 5 minutes after the patient's sixth nVNS stimulation. The patient went to the emergency department. The manufacturer was unable to gather additional information from the patient or the patient's doctor's office (because of no response from the patient).* The database searches were verified on the 23.01.2023 by NIPH and no more incidents have been reported.

NIPH Comments: The safety data from registries and published articles all show only a few severe adverse events. The remaining device related adverse events are mostly related to contact reactions and the electrical stimulation to the muscles surrounding the application site. In addition, since the device was brought to the European market there have been no reported adverse events in the MAUDE or MHRA databases. As mentioned, it is important that the physicians prescribing gammaCore devices are aware of the warnings provided in the Instructions for Use (14), related to cardiological conditions.

Assessment of the certainty of the evidence

We used the Grade framework (49) to assess the certainty of the evidence provided in the submission file from the selected RCTs (ACT 1, ACT 2, PREVA) and the pooled analysis by de Coo et al. (8). We have not graded the evidence from the other studies.

The GRADE assessments are presented as a part of Summary of Findings tables shown in Table 7, Table 8, and Table 9. The summary of finding tables don't include all outcomes reported in the primary studies but are selected to provide an overview of various effects that will follow from offering the intervention within the health services.

Table 7: *Summary of Findings nVNS compared to sham as acute treatment in episodic cluster headache*

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with sham	**Risk with nVNS**			
Proportion of participants who responded at 15 min for the first treated attack	117 per 1 000	**381 per 1 000** (189 to 619)	**OR 4.67** (1.77 to 12.32)	112 (2 RCTs)	⨁⨁⨁◯ Moderate[a]
Proportion of all treated attacks that achieved pain- free status at 15 min	The mean proportion of all treated attacks that achieved pain- free status at 15 min was **7.34**	MD **16.71 higher** (24.87 higher to 8.55 higher)	-	546 (2 RCTs)	⨁⨁⨁◯ Moderate[a]
Changes in pain intensity after 15 minutes	The mean changes in pain intensity after 15 minutes was **-0.6**	MD **1.1 lower** (1.98 lower to 0.22 lower)	-	19 (1 RCT)	⨁⨁◯◯ Low[a,b]
Response rate	106 per 1 000	**342 per 1 000** (142 to 620)	**OR 4.37** (1.39 to 13.71)	85 (1 RCT)	⨁⨁⨁◯ Moderate[b]
Sustained response	106 per 1 000	**342 per 1 000** (142 to 620)	**OR 4.37** (1.39 to 13.71)	85 (1 RCT)	⨁⨁⨁◯ Moderate[b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. The ACT2 study has high risk of bias
b. Only one study included in the analysis

Table 8: *Summary of Findings nVNS compared to sham as acute treatment in chronic cluster headache*

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with sham	**Risk with nVNS**			
Proportion of participants who responded at 15 min for the first treated attack	298 per 1 000	**239 per 1 000** (120 to 422)	**OR 0.74** (0.32 to 1.72)	113 (2 RCTs)	⨁⨁◯◯ Low[a,b]
Proportion of all treated attacks that achieved pain- free status at 15 min	The mean proportion of all treated attacks that achieved pain- free status at 15 min was **10.94**	MD **4.19 higher** (1.59 higher to 9.97 lower)	-	927 (2 RCTs)	⨁⨁◯◯ Low[a,b]
Changes in pain intensity after 15 minutes	The mean changes in pain intensity after 15 minutes was **-1**	MD **0.2 lower** (0.75 lower to 0.35 higher)	-	48 (2 RCTs)	⨁⨁◯◯ Low[a,b,c]
Response rate	231 per 1 000	**137 per 1 000** (32 to 420)	**OR 0.53** (0.11 to 2.41)	48 (1 RCT)	⨁⨁◯◯ Low[b,c]
Sustained response	154 per 1 000	**137 per 1 000** (30 to 443)	**OR 0.87** (0.17 to 4.38)	48 (1 RCT)	⨁⨁◯◯ Low[b,c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. The ACT2 study has high risk of bias
b. The CI crosses the line of null effect
c. Only one study included in the analysis

Table 9: *Summary of Findings nVNS+SoC vs. SoC alone for prevention in chronic cluster headache*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with SoC alone	**Risk with nVNS + SoC**			
Attack frequency [attacks per week]	The change in attack frequency was **-2.1**	The change was **3.9 lower**(7.2 lower to 0.5 lower)	-	93 (1 RCT)	⊕⊕◯◯ Low[a,b]
Participants experiencing ≥50 % treatment response	83 per 1 000	**400 per 1 000** (169 to 686)	**OR 7.33** (2.24 to 23.98)	93 (1 RCT)	⊕⊕◯◯ Low[a,b]
Abortive medication use	The change in use of abortive medication was -2 percentage points	The change was **13 points lower** (24 lower to 2 lower)	-	93 (1 RCT)	⊕⊕◯◯ Low[a,b]
Quality of life assessed with: EQ-5D-3L	The change in QoL was -0.049. points	The change was **0.194 points higher** (0.054 higher to 0.334 higher)	-	93 (1 RCT)	⊕⊕◯◯ Low[a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Participants not blinded and several outcomes are not listed in the protocol
b. Only one study included in the analysis

The main findings of the evidence graded by NIPH are:

nVNS compared to sham as acute treatment in episodic cluster headache:

- Probably improves the proportion of patients who respond within 15 min after the first attack.
- Probably improves the proportion of all treated attacks that achieve pain-free status within 15 min.
- Probably improves the overall response rate.
- Probably improves the overall sustained response rate.
- May lead to a one point reduction in pain intensity after 15 min on a 5-point Likert scale.

nVNS compared to sham as acute treatment in chronic cluster headache:

- May make little or no difference to response rate and sustained response rate.
- May make little or no difference in pain-free status or change in pain intensity.

nVNS + SoC compared to SoC alone for prevention in chronic cluster headache:

- May lead to a reduction of almost four attacks per week (result in almost four attacks less in the intervention group)
- May result in a reduction of abortive medication use that is 15 percent point larger t
- May improve the quality of life, assessed with EQ-5D-3L

- 40% of patients in the nVNS group may experience more than a 50% reduction in the mean number of attacks per week.

Health economic evaluation

METHOD

Methods for evaluating submitted cost-effectiveness models

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard treatment using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. To make comparisons across different treatment modalities and multiple health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life years (QALYs), a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as:

(Cost_Intervention - Cost_Comparator) / (QALY_Intervention - QALY_Comparator)

There is no single correct way to build economic models estimating the cost-effectiveness of a specific health intervention. Modelling requires consulting with clinical experts to gain understanding of expected disease progression, and to determine the relevant treatment population, comparators, health outcomes and adverse events connected to treatment. This information informs the basic model structure and determines which clinical effect data are most important to retrieve in the systematic literature search. Once the model structure is in place, systematic searches and evidence grading are used to assess the model input parameter and relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include sufficient details to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Evaluation of health economic model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in the model have adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analyses to determine the degree and sources of uncertainty in the model results;

and whether the model displays external and internal validity. Checklists are available to help researchers systematically examine these issues.

We proceed by first describing the health economic model used in the manufacture's submission and the results generated by the model. We then provide our evaluation of the model, focusing on the following issues: model structure, choice of model parameters, use of appropriate sensitivity and/or scenario analyses to examine the extent of uncertainty in model results, and relevance of the model for the Norwegian context.

Previously published cost-effectiveness analyses presented in the submission

This section is copied directly from submission:

We did not identify any full-text reports of models or cost studies in Norway. Four high-quality economic evaluations that were reported in seven publications (Table 10). All were cost-utility models with a payer perspective, two for gammaCore, comprising a Markov chain Monte Carlo simulation model of chronic cluster headache in Germany and the UK (50) and a decision tree model of episodic cluster headache in the USA (51). The third was a decision tree model of sphenopalatine ganglion (SPG) stimulation in chronic cluster headache in Germany (52).

Table 10: *Cost effectiveness studies*

	Studies			
Parameters	**(Morris et al., 2016)**	**(Mwamburi et al., 2017)**	**(Jan B. Pietzsch et al., 2015)**	**(Bulsei et al., 2021)(53)**
Study objective	To assess whether non-invasive vagus nerve stimulation (nVNS, gammaCore) is a cost-effective treatment option compared with the current standard practice (SoC) for chronic cluster headache in Germany.	To conduct a cost-effectiveness analysis of gammaCore adjunct to SoC compared with SoC alone for the treatment of acute pain associated with episodic cluster headache attacks in the USA.	To assess the cost-effectiveness of sphenopalatine ganglion (SPG) stimulation compared with medical management in Germany.	To evaluate the cost-effectiveness of Occipital Nerve Stimulation (ONS) compared to conventional treatment in refractory cCH patients in France.

The models all compared the main intervention with acute use standard of care (triptans and/or oxygen) and had health states based on whether the patient responded or not to treatment. However, response was defined differently in the three models. In the German/UK gammaCore model, response was defined as having a greater than 50% reduction in cluster headache attacks per week (50). The USA gammaCore model defined response as having 50% or more of attacks that responded to gammaCore and included a "Failure" health state where 0% of attacks responded

within 15 minutes. In this model, non-responders were defined as having 1 to <50% of attacks responding or improved but still needing rescue medication (51). In the SPG model, the costs and QALYs were modelled for the intervention and control groups assuming a 31% reduction in attack frequency with the intervention (54).

The two gammaCore models had a time horizon of 1 year and therefore did not apply a discount rate. The SPG model had a time horizon of 5 years and applied a 3% discount rate. Efficacy data and utility values were taken from relevant RCTs, but only one model also used cost and resource use data from the same RCT (50), the others basing this on other published cost studies and expert opinion.

All three models found that the intervention dominated standard of care, with probabilistic and deterministic sensitivity analyses or scenarios generally also demonstrating that the intervention was cost-effective at willingness to pay thresholds of €20,000 (50) or $25,000 (51). The UK gammaCore model was summarised very briefly as a local adaptation of the German model, and found an ICER of £166.12/QALY gained, with 47% of simulations demonstrating cost savings for gammaCore compared with standard of care (50).

The complementing hand-search identified one more cost-effectiveness analysis (53), representing a before-and-after economic study, with data collected prospectively in a nation-wide registry in France. The study compared occipital nerve stimulation (ONS) with a surgically implanted device to conventional treatment in refractory cCH patients. Due to the ONS registry data collection protocol, data were collected over a short period of three months prior and after to the ONS device implantation. Data for conventional treatment was assumed to be the same as during the 3 months prior to ONS device implantation and carried forward over the analysis time frame. Endpoints to assess ONS efficacy were weekly cluster headache attack frequency and health-related quality of life. The analysis was conducted from the French healthcare perspective, and two different time horizons were applied: 3 months and 1 year. Costs and effectiveness (measured in QALYs) were not discounted due to the short time horizon. The ICER of the ONS strategy in the 3 months analysis was €109,676/QALY gained, indicating an 80% chance that the ONS strategy is cost-effective at a WTP threshold of €122,000/QALY gained. The ICER of the ONS strategy in the 1-year analysis was €-4846/QALY gained, the probabilistic sensitivity analysis indicated an 80% chance, hat the ONS strategy is dominant (cost-saving).

The eleven cost analyses identified by the systematic review, were as follows:

3 were database analyses of direct costs associated with cluster headache in the USA ((55); (56); (57)), one of which also reported indirect costs (57);

1 was a database analysis of direct and indirect costs associated with episodic and chronic cluster headache in Germany (19);

2 reported cost savings and reduction in medication costs following SPG stimulator implantation for chronic cluster headache in Germany (52) and the UK (only available as a conference abstract) (58);

1 reported costs of different types of oxygen cylinders across the USA as treatment for chronic cluster headache (59);

3 reported costs associated with occipital nerve stimulation for chronic cluster headache, including 2 in Germany, (60), (61) and one conference abstract in the UK (62);

1 reported reduction in medication costs after hypothalamic stimulation for chronic cluster headache in Italy (63).

These cost analyses found that the direct costs of cluster headache were at least double those of control patients, and were driven by outpatient visits, inpatient admission and medication costs. Chronic cluster headache incurred greater costs than episodic attacks. Costs of medication, in particular subcutaneous triptans, were substantially reduced after nerve or hypothalamic stimulation, with the reduction in some cases being enough to compensate for the implantation costs of the device. Indirect costs due to absenteeism and short-term disability were reported to be approximately 25% to 50% of the direct costs associated with cluster headache.

The complementing hand search identified 2 more relevant cost analyses: An Italian and a Danish cost analysis aiming to quantify the total direct and indirect cost of eCH and cCH over a cluster period (64), and annually (65). These analyses identified the same main cost drivers compared to the previous cost analyses, although on a different absolute cost level, given the different time horizons and jurisdictions the analyses were focusing on.

Rationale for the cost-utility model

From the submission file:

The preventative use of gammaCore added to patients' existing standard of care (SoC) therapies, significantly reduced attack frequency compared with SoC alone in multiple studies, including a randomised controlled study in chronic cluster headache (cCH).

Significant efficacy of gammaCore for acute pain relief was demonstrated for patients with episodic cluster headache (eCH) in sham-controlled trials, with additional abortive benefits on attack severity and duration seen across studies. Reduction in attack frequency was reflected in a reduced use of abortive medication (high-flow oxygen and triptans) in the PREVA study and a real-world observational study conducted in the UK (35), hereafter referred to as the "Marin study.

If used, gammaCore is most likely to be introduced before more invasive procedures or treatment with lithium are considered, at least in some countries, e.g., the United Kingdom (6). The rationale for undertaking a cost utility analysis is to demonstrate that use of gammaCore in CH alongside standard of care reduces use of abortive medication to a level that offsets any acquisition and ongoing costs of gammaCore, translating into cost savings and a beneficial cost-effectiveness ratio to the Norwegian health care system.

NIPH comments:
The submitter performed a cost utility assessment based on the Drummond criteria (66).

Population, intervention, and comparator in the cost-effectiveness model

From the submission file:

A cost utility analysis was performed to demonstrate the use of gammaCore alongside Standard of care (SoC) for patients with cluster headaches above the age of 18 for whom standard of care is ineffective or contraindicated (16). If used, gammaCore is most likely to be introduced before more invasive procedures or treatment with lithium are considered.

The cost utility model compares the use of gammaCore plus SoC abortive medicine (subcutaneous or nasal spray triptan therapy and/or oxygen) vs. SoC abortive medicine alone from the Norwegian health care perspective with a time horizon of 1-year. The model captures the reduced use of abortive therapy when gammaCore is used preventatively. GammaCore is most likely to be introduced before more invasive procedures or treatment with lithium are considered(6). The rationale for undertaking a cost utility analysis is to demonstrate that use of gammaCore in CH alongside standard of care reduces use of abortive medication to a level that offsets the costs of gammaCore, translating into cost savings and a beneficial cost-effectiveness ratio to the Norwegian health care system.

The gammaCore device was supplied with 3-months' worth of doses including acute treatment on top of preventative treatment. (30 doses/day). For the Norwegian context the scope of SoC included abortive medicine (subcutaneous or nasal spray triptan therapy and/or oxygen). However, the model did not consider the use of verapamil for patients that use gammaCore in either the preventive or acute settings on the basis of low evidence[1] (35). The use of occipital nerve block was used during pregnancy according to NICE guidelines in 2012, however, no later guidelines for use of this in refractory CH were identified and is unknown in such patients. Therefore, it was excluded from the analysis.

NIPH Comments:

The present model from a Norwegian health care perspective was a replication of the model used by Morris et al. (2016) for a cost effectiveness analysis conducted (50) from the German statuary health insurance perspective. The German model was based on a study of patients with chronic cluster headache and assessed the use of gammaCore in addition to SoC compared to standard of care alone.

We found the objective of the submitted study to be relevant for the cCH patients in the Norwegian setting. The other cost - effectiveness studies presented earlier in the document were not directly comparable such as the one for eCH patients (51), however the Appendix (Table A 5)

[1] From the submission: "*Patients in the PREVA trial were not permitted to reduce SoC prophylactic medicine use and only 8 of 30 patients recruited in the Marin UK observational study were taking verapamil, of which 2 discontinued use (35).*

refers to episodic model structure and assumptions in contrast with the current chronic model. The other two studies mentioned earlier in the report were excluded for comparison as they did not include gammaCore their analysis. However, both cost models considered the cost of the treatment with acute use of SoC (including triptans and oxygen).

Model structure

From the submission file:

The cost utility analysis was performed using the Markov model adapted from Morris et al., 2016. The initial cost model assumptions and results were reviewed by the National Institute of Excellence (NICE) in the UK (67) and the model was extended to include QALYs assessed in the PREVA study using EQ-5D-3L (16).

Markov Health States

A two state Markov model was developed that included patients aged 43 diagnosed with chronic cluster headache (EU), following a cycle length of 1 month for a 1-year time horizon. The patients entered the model based on probability of response (A) and probability of no response (1-A). For the base case, response was defined as a ≥50% reduction from baseline in the number of cluster headache (CH) attacks for the randomized period. The probability of response is maintained for the base case.

The following other scenarios were included for the Markov model for including the probability of response loss ($1-B_t$):

1. *Constant rate of response loss.*
2. *Diminishing rate of response loss.*
3. *No intial response in the SoC arm.*

The model captures two health states, ***responder*** *and* ***non-responder.*** *Use of gammaCore (in the gammaCore plus SoC arm only) is captured in both health states during the 3-month evaluation period. After 3-months, non-responders discontinue treatment in 3-month blocks.*

Health States

Responder

The responder health state represents the patients who achieve a defined minimum percentage reduction in attack frequency from baseline, ≥50% in the base case. Abortive medication use (intranasal zolmitriptan, intranasal sumatriptan, subcutaneous sumatriptan, and inhaled oxygen) is captured in this health state, with use being lower than the non-responder health state. At each 3-month period assessment for gammaCore this state includes a small number of patients who have lost response since the last assessment and continue to use gammaCore until they are assessed for response at the start of the next 3-month prescription period, at which point they discontinue.

Non-responder

The non-responder health state represents the patients who did not achieve the defined minimum percentage reduction in attack frequency from baseline. Abortive medication use (intranasal zolmitriptan, intranasal sumatriptan, subcutaneous sumatriptan, and inhaled oxygen) is captured in this health state but is higher than the responder health-state.

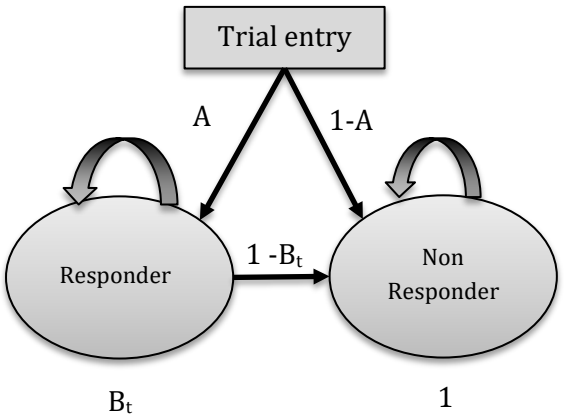


Figure 7: *Model Schematic*

The model in schematic form, Markov states and transitions between health states are presented in Figure 7. The patients are initially allocated between two Markov health states based on the base case probability for response. The patients can then progress from responders' health state (B_t) to non-responder based on rate of response loss ($1-B_t$). The remaining patients would stay in the responder's health state. Patients in the non-responder's health state would remain in this permanent health state and in every cycle new patient losing response to treatment would be added to this health state. The model does not consider mortality due to the short time horizon (1-year). The model outcome was reported in terms of cost and effect (QALYs).

Patient group analysis

The cost utility analysis considered that gammaCore in a patient population aged 43 (median age in the PREVA trial, (16)) with chronic cluster headache, whereas the population of scope are patients over 18 years. The ACT 1 and ACT2 ((10),(11)) trial provide insignificant evidence to support gammaCore as monotherapy for patients when used acutely for chronic cluster headaches (cCH). The Marin UK observational study also included patients that used gammaCore acutely. The patients experiencing eCH were excluded from the cost utility analysis as studies were not powered to detect differential effects between the two subgroups (35). As the gammaCore device will be supplied with sufficient doses to permit acute use on top of preventative doses per 3-month period (up to 30 doses/day), there would be no additional costs for acute use by patients already using gammaCore preventatively, and any further reduction in abortive medication use would be an upside not captured in the model.

Main Model Assumptions

- *In the base case, treatment response is defined as ≥50% reduction from baseline in the number of CH attacks per week.*

- *Response rates to gammaCore in PREVA are generalisable to those of patients eligible for gammaCore.*

- *Starting age of the analysed patient population is 43 years, corresponding to the PREVA study.*

- *Beyond 1 month, responders in the SoC group are assumed to be non-responders.*

- *Patients are reassessed every 3 months for ongoing response and non-responders in the gammaCore plus SoC group discontinue prophylactic treatment with gammaCore but continue use of abortive treatments. Discontinuation occurs in 3-month blocks in line with prescriptions for a gammaCore refill.*

- *After 3-months the non-responders in gammaCore plus SoC revert to medication use in the SoC arms of PREVA trial.*

- *The use of abortive medication conditional on responder status is assumed to remain constant.*

- *Prophylactic medicines are therefore not included in the cost utility analysis as equal use of these in both arms would cancel out. This is a conservative assumption given that there is some indication of reduced use from the Marin study.*

- *Response loss scenarios were explored by fitting an exponential survival curve function to data from patients in the nVNS and SoC group on the basis of their response statuses at the end of the randomised phase and at the end of the extension phase.*

- *In the base case analysis, responders from the gammaCore plus SoC group throughout the extension phase of PREVA were assumed to maintain this response until the end of the model time horizon (1 year). However, there is an initial loss of response after 1 month of treatment as reflected in the PREVA trial, but after the 2nd month patients retain their response.*

- *Resource use in the gammaCore plus SoC group, conditional on response status, was assumed to remain the same from the randomised phase to the end of the 1-year time horizon. Resource use in the SoC only group was aslo assumed to remain the same to the end of 1-year time horizon.*

- *In the post-hoc analysis of medication use based on the responder status, use neither consistently increased nor decreased between the randomised and extension phases.*

Model parameters

Submitted clinical efficacy data from the submission file:

Model parameter estimates were derived from data on the reduction in attack frequency and the use of abortive medications from the randomised and extension phases of PREVA (16). In the base case, treatment response was defined as ≥50 % reduction from baseline in the number of CH attacks per week, by comparing matched data of attack frequency during the run-in and randomised phases of PREVA. The probability of being a responder was calculated on an ITT basis, with patients not providing matched attack frequency data imputed as non-responders.

A post-hoc analysis of abortive medication use from the last 14 days of the PREVA randomised phase was used to assess health care resource utilisation in the gammaCore arm, conditional on responder status. As not all patients with matched responder data had matched abortive medication data available, the abortive medication use was obtained from a subset of the patients who provided response data. Abortive medication use (triptans and oxygen) in the gammaCore arm was extracted from matched patient data stratified into responders and non-responders according to whether they achieved a minimum reduction in attack frequency (>50% in the base case) during the randomised phase.

In the gammaCore arm, medication use in patients identified as responders was used to inform abortive medication use in the responder health state. During the first 3 months of treatment, the evaluation period during which both responder and non-responders are using gammaCore, medication use for non-responders was obtained from patients identified as non-responders from the randomised phase of PREVA (matched data only). After the initial 3 months, non-responders were assumed to discontinue gammaCore and revert to the level of medication use in the SoC arm of the PREVA trial. In a sensitivity analysis, after the initial 3 months, non-responders were assumed to revert back to their medication use observed at baseline (collected during the run-in period of PREVA).

In the SoC arm, the probability of being a responder in the first month was assumed to be as reported in the ITT analysis of the PREVA trial (based on a ≥50% reduction in attack frequency). Responders in the SoC arm were assumed to revert to non-responder status after the first month. Conservatively, medication use in the responder state of the SoC arm was assumed to be the same as the medication use for responders in the gammaCore arm (for the 50% responder definition only, as only one response definition is relevant and necessary for the SoC arm). Medication use in the non-responder health state of the SoC arm was the mean use in the SoC arm of PREVA reported during the randomised phase (16).

A further sensitivity analysis was conducted assuming that no patients in the SoC arm were responders in the first month (i.e., medication use was the mean reported in the SoC arm during the randomised period of PREVA for all cycles).

The Model input parameters are provided in Table 11.

Table 11: *Model Input parameters*

		Variable description		Mean value	Lower CI	Upper CI
Probability of response to treatment			Variable names			
	Standard care	Probability of response (50% reduction) - SoC	probrespSC	8%	2%	18%
	GC	Probability of response - gCore	probrespGC	40%	26%	55%
Attack Frequency			Variable names			
	Standard care	Number of attacks-Responder	att_freq_SoC_R	3.77		
	Standard care	Number of attacks-Non-responder	att_freq_SoC_NR	14.60		
Baseline	GC responder	Number of attacks - Baseline. gCore responder	att_freq_GC_R_base	3.77		
	GC non-responder	Number of attacks - Baseline. gCore non responder	att_freq_GC_NR_base	10.68		
Randomised	GC responder	Number of attacks - Rand. gCore responder	att_freq_GC_R_rand	3.77		
	GC non-responder	Number of attacks - Rand. gCore non responder	att_freq_GC_NR_rand	13.71		
Open label	GC responder	Number of attacks - OL gCore responder	att_freq_GC_R_OL	6.50		
	GC non-responder	Number of attacks - OL gCore non responder	att_freq_GC_NR_OL	9.65		
Survival analysis						
Exponential	GC	Prob. of discont. response per month for initial responders	probdiscresp	31%	16%	54%
Resource Use						
	SoC - responder	zolmitriptan doses per 14 days - SoC responder	zolper14SoC_R	0.60	0.10	1.52
		sumatriptan doses per 14 days - Soc responder	sumaper14SoC_R	2.50	1.04	4.59

		oxygen doses per 14 days - SoC responder	oxyper14SoC_R	2.20	0.56	4.94
	SoC - non-responder	zolmitriptan doses per 14 days - SoC non responder	zolper14SC	1.30	0.45	2.59
		sumatriptan doses per 14 days - SoC non responder	sumaper14SoC_NR	7.50	4.88	10.67
		oxygen doses per 14 days - SoC non responder	oxyper14SoC_NR	10.80	6.68	15.90
	GC - responder	zolmitriptan doses per 14 days - gCore responder	zolper14GC_R	0.60	0.10	1.52
		sumatriptan doses per 14 days - gCore responder	sumaper14GC_R	2.50	1.04	4.59
		oxygen doses per 14 days - gCore responder	oxyper14GC_R	2.20	0.56	4.94
	GC - non-responder (on Tx)	zolmitriptan doses per 14 days - gCore non responder (on Tx)	zolper14GC_NR_onTx	2.50	0.32	6.89
		sumatriptan doses per 14 days - gCore non responder (on Tx)	sumaper14GC_NR_onTx	4.10	1.00	9.33
		oxygen doses per 14 days - gCore non responder (on Tx)	oxyper14GC_NR_onTx	11.20	5.45	18.98
	GC - non-responder (off Tx)	zolmitriptan doses per 14 days - gCore non responder (baseline)	zolper14GC_NR_baseline	3.80	0.55	10.13
		sumatriptan doses per 14 days - gCore non responder (baseline)	sumaper14GC_NR_baseline	4.50	2.07	7.85
		oxygen doses per 14 days - gCore non responder (baseline)	oxyper14GC_NR_baseline	18.60	9.35	30.98
		% using triptans at baseline	prop_triptans_base	73%	56%	87%
		% using oxygen at baseline	prop_oxy_base	97%	66%	98%

		% oxygen treatm. that are portable	prop_oxy_port	50%	0%	60%
		% sumatriptan treatm. that are s.c.	prop_suma_sc	87%	66%	98%
Unit costs (NOK)						
Background medication						
		zolmitriptan nasal per unit cost	zolcostPUUK	92.52		
		sumatriptan s.c. per unit cost	sumcostPUUK_sc	147.70		
		sumatriptan nasal per unit cost	sumcostPUUK_nas	88.49		
		oxygen per unit cost - static	oxycostPUUK_static	6.28	5.58	6.98
		oxygen per unit cost - portable	oxycostPUUK_port	8.79	7.81	9.77
gammaCore						
	Norway	gCore first 3 months cost		0		
		gCore cost per 3 months	GCcostPQUK	5,750	4,600	6,900
Health related quality of life						
UK	Standard care	Utility score responder	UKHRQLrespSC	0.72	0.65	0.79
		Utility score non responder	UKHRQLnonrespSC	0.44	0.39	0.48
	GC	Utility score responder	UKHRQLrespGC	0.73	0.65	0.80
		Utility score non responder	UKHRQLnonrespGC	0.44	0.40	0.49

Adverse events

Adverse events (AEs) as reported were generally benign, with no AEs requiring hospitalisation. In the UK Marin study, no serious device-related AEs were reported during gammaCore therapy (35). Observed AEs in this patient cohort included redness and muscle soreness at the stimulation site, which were also reported in previous randomised clinical trials. Consistent with these previous studies, AEs were mild and transient and were typically reported early in the evaluation period, when the use of gammaCore was relatively novel. It is anticipated that reported AEs would be largely self-managed and would not incur any NHS costs. Therefore, no costs related to AEs were included in the model.

Submitted cost data

The costs for the cost utility analysis were considered from a Norwegian healthcare perspective that include all direct and indirect medical cost.

Clinical management of cluster headache in Norway

The comparator in the cost utility analysis is SoC abortive medication use alone, which is prescribed by specialist neurologists in secondary and tertiary care centres, gammaCore would also be provided to patients via this route and training would be provided free by electroCore. Clinical reviews to provide 3-monthly prescriptions of gammaCore would be as per current patient follow-up for SoC medication. The clinical pathway would therefore not change and no change in Norwegian resource use other than SoC abortive medicine use is anticipated. Abortive medicine use is sourced directly from the PREVA trial.

The present analysis was conservative in that it included only the costs associated with use of abortive medications without accounting for other potential sources of cost savings (e.g., reduced preventative medication, reduced frequency of clinic visits, fewer hospitalisations due to adverse events of abortive medication and verapamil). These were not captured during the PREVA and other trials, which were of short duration. The Marin study did not report any hospitalisations (35).

Resource use and measurement

The only change in resource use relevant to the cost utility analysis is the use of abortive medication, which is sourced from the PREVA trial (16).

The cost of a unit of oxygen is uncertain due to the many suppliers and the quantity used per dose. There is a paucity of costing studies available for oxygen. The cost of oxygen treatment was estimated using information from a Norwegian expert in cluster headache. Treatments are assumed to last 20 minutes and consume 240 to 300L of oxygen per treatment assuming a 12-15L/min flow rate. A patient with cluster headache is assumed to consume between 65,51 and 151,057 litres per year, at a mean cost of 6.28 NOK per treatment.

Portable oxygen refills, which are smaller and more frequent, are assumed to cost 40% more. A cost/L of oxygen was calculated using this information, ranging from 0.02 NOK to 0.03 NOK per litre.

In the PREVA trial, patients at baseline used 14.6 oxygen treatments over 2 weeks. Using the standard error of 2.27 for number of treatments and the assumption of 240-300L per treatment led to consumption estimates of 65,515 to 151,057L per cCH patient per year. Considering together the lower to upper estimates of cost/1,000L and the lower and upper estimates of litres of oxygen consumed led to unit cost estimates of 5.58-6.98 NOK per treatment for static supplies and 7.81-9.77 NOK per treatment for portable supplies.

These costs include only provision of oxygen refills and not rental or assessment fees which remain constant regardless of the amount of oxygen consumed.

In the PREVA trial only subcutaneous sumatriptan was used whereas two patients in the Marin study used nasal sumatriptan. In order to make the model more generalisable, a proportion of the patients (2 out of 15 sumatriptan patients; 13%) were assumed to use nasal sumatriptan.

Cost of standard of care

Comparator's costs consist of medication costs for abortive medication use and were obtained from Norwegian Medicine Agency (68). The cost of oxygen therapy is uncertain due to the many suppliers and the quantity used per dose. There is a paucity of costing studies available for oxygen. The cost of oxygen treatment was estimated using information from a Norwegian expert in cluster headache.

*Treatments are assumed to last 20 minutes and consume 240 to 300L of oxygen per treatment assuming a 12-15L/min flow rate. Cost of a refill of 50L of compressed oxygen (1L compressed O2 = 860L O2 gas) are assumed to be 1,000 NOK. Portable oxygen refills, which are smaller and more frequent, are assumed to cost 40% more. The mean cost/treatment of oxygen was calculated using this information, and ranges from 6.28 NOK (static use) to 8.79 NOK (portable use) per treatment (Table 13*Table 13: Cost per treatment/patient associated with SoC in the model*).*

Cost of intervention and technology

The gammaCore device, conductive gel consumables, and first 93-day activation card are provided free of charge. This allows the effectiveness of the treatment in individual users to be assessed before further treatment is bought. If the trial is successful, further treatment (through new activation cards) costs 5,750 NOK for 93 days of use (exclusive of VAT, Table 12)."

Other cost assumptions

The costs of preventive medications were not counted as one of the sources for cost savings (e.g., reduced preventive treatment, reduced frequency of clinic visits, fewer hospitalizations due to adverse events of abortive medication or verapamil). Such costs were also not captured in the PREVA and other similar trials, due to short duration of these trials. The Marin Study also did not report any hospitalizations (as mentioned earlier).

***Table 12:** Cost per treatment/patient associated with gammaCore in the model.*

Items	Value	Source
Price of the technology per treatment/patient	5,750 NOK for 93 days of use (exclusive of VAT) after the first 3 months.	electroCore

Table 13: *Cost per treatment/patient associated with SoC in the model*

Items	Cost/unit	Source
zolmitriptan 5mg/0.1ml nasal spray	92.52 NOK	https://www.legemiddelsok.no/
sumatriptan 6mg/0.5ml subcutaneous inj	147.70 NOK	https://www.legemiddelsok.no/
sumatriptan 10mg/0.1ml nasal spray	88.49 NOK	https://www.legemiddelsok.no/
sumatriptan tablet per unit cost	13.98 NOK	https://www.legemiddelsok.no/
oxygen per unit cost - static	6.28 NOK	Using expert opinion and PREVA trial
oxygen per unit cost - Portable	8.79 NOK	Using expert opinion and PREVA trial

NIPH Comments:

Based on the submitted data we performed a careful evaluation of the most imperative variables such as the response rate, attack frequency, costs and QALY's assumption in the health economic model for chronic cluster patients.

We found these assumptions to be relevant for the chronic patient's analysis based on the PREVA study (16). The submitter had used the UK EQ-5D index data from PREVA by using ordinary least squares to control for various imbalances between arms. We carefully assessed the calculations and did not find any inconsistencies among the parameters calculated, especially for the Multivariate normal distribution used for the health state utility value of responder and non-responder among control and the treatment arm. The survival curve fitting seemed a reasonable approach for accounting for probability of discounting response per month using rate to probability conversion using exponential form.

However, it should be worth considering that utilities and health economic parameters for attack frequency for the current model for chronic headaches were based on the PREVA study alone (16).

Moreover, we compared the differences between the model structure, utilities, and probability of response of the episodic model from the USA (51) with the current chronic model. The Appendix (Table A 5) provides the difference in the modelling structure for the episodic compared with the current chronic model.

The costs of the current Markov model were taken from the Norwegian healthcare perspective (68) and uncertainty was accounted for using appropriate gamma distribution and resource use from the PREVA study (16). Most of the uncertainty was around the cost of oxygen (details of which are provided in Appendix 3.2.4). The submitter did not account for patient or travel cost as the treatment can be administered during usual activities for a few minutes twice in the day. Hence, they did not account for any cost saving associated with reduced preventative

medication, reduced frequency of clinic visits, fewer hospitalisations due to adverse events of abortive medication and verapamil (as cited in the submission). We found this assumption to be reasonable.

As argued, there were no studies that reported discontinuation of gammaCore due to severe adverse events during the randomized phase. Hence, the company did not include any costs associated with adverse events in the model. However, we believe that including the cost of adverse events would not have had a significant effect on the cost based on the evidence available (mild to moderate adverse events, (67). Moreover, as patients did not discontinue gammaCore due to these events it would be worth considering that the discomfort may not exceed the benefits of the treatment. Any inconsistencies in the cost would be captured by the sensitivity analysis for cost of gammaCore.

Uncertainty

The base case analysis defines treatment response as a ≥50% reduction in attack frequency vs baseline, according to the PREVA trial definition. However, in the Marin study, submission for an IFR (individual funding request) was discouraged for patients who did not achieve a ≥ 25% decrease in weekly attack frequency, suggesting that the threshold for what is considered a clinically meaningful response may be lower.

The % reduction in weekly attack frequency observed in patients who obtained funding in the Marin study was 64% (9.5 [0–38.5] vs. 26.6 [3.8–77.0] at baseline). To explore alternative definitions of responder, the model considers responder definitions of ≥40%, ≥25%, ≥50%, and ≥65% reduction in attack frequency or more from baseline (additional definitions of ≥30% and ≥60% were explored, but the results were identical to those for ≥25% and ≥65% reduction, respectively).

A further ≥50% reduction in attack frequency scenario was explored which followed the methods used by Morris et al., 2016 (50), whereby mean medication use in the nVNS plus SoC arm during the randomised phase of PREVA informed the responder health states and mean medication use in the SoC arm during the randomised phase of PREVA informed the non-responder health state. The base case applies the medication data from the randomised phase of the SoC arm of PREVA to the gammaCore non-responder health states who have discontinued gammaCore (i.e. following the 3-month evaluation period). Alternative scenarios were explored where the baseline medication use for gammaCore non-responders was applied to the non-responder health states who had discontinued gammaCore. This was done to capture any potential differences in medication use at baseline between responders and non-responders.

The base case analysis assumes an initial loss of response as observed between the randomised and extension phases of PREVA, leading to a single reduction in response after the first 1-month cycle. The rate of this initial loss of response was estimated by fitting an exponential survival curve function to data from patients in the nVNS plus SoC group of the PREVA trial on the basis of their response statuses at the end of the randomised phase and at the end of the extension phase. In the base case, no loss of response to gammaCore after 2 months of treatment (the end of the extension phase of the PREVA trial) was assumed.

Two alternative scenarios were explored regarding loss of response (and subsequent discontinuation of gammaCore):

1. *In the first alternative scenario, the exponential function was used to predict patient response status beyond 1 month (i.e. beyond the randomised phase) assuming a constant monthly rate (~31 %) of response loss throughout the course of the model.*

2. *The second scenario was modelled assuming a diminishing rate of response loss; that is, the rate at which response was lost beyond 1 month (as predicted by the exponential function) was reduced by a fixed percentage (10%) each month.*

The above scenarios were modelled in alternative combinations using multi-way scenario analysis.

A further scenario was modelled in which no patients in the SoC-alone group were assumed to have responded initially, and all other assumptions were the same as in the base case. As this had little effect on the cost estimates, it was carried out as a single scenario keeping other assumptions constant.

One-way sensitivity analyses (OWSA) were carried out on any variables with uncertainty estimates and on total costs as well as the ICER." These comprised primarily the probability of response and use of abortive medication conditional on response from the PREVA study. The cost of a unit of oxygen is uncertain due to the many suppliers and the quantity used per dose. Therefore, this was also included in the OWSA, varying the cost between the highest and lowest estimates of unit cost.

Probabilistic sensitivity analysis (PSA) was undertaken using a Markov chain Monte Carlo simulation. Distributions for each model parameter of interest were estimated in line with best practice. A probabilistic analysis with up to 10,000 simulations for each scenario was conducted, and mean values from this analysis were calculated.

NIPH Comments:

We individually tested assumptions of the alternative scenarios in the model, checking for calculation consistencies and probabilities taken from the PREVA study. We found these assumptions to reflect realistic scenarios with regards to exploring uncertainties associated with response of gammaCore. It is worth noting that the Markov model for cCH patients in the SoC and gammaCore plus SoC allows for initial response to treatment in the first month only. The response for gammaCore plus SoC is higher than that for SoC, therefore results of constant response loss and loss of response with fixed percentage should be considered for evaluating the cost effectiveness of the intervention. The current model applied the baseline medications use of non-responder in the SoC to the non-responders in the intervention arm (gammaCore) for the base-case. The PREVA study had also provided the baseline medications use for the non-responders of gammaCore. The assumptions were tested to assess any variations in the two scenarios producing difference in costs for the intervention arm. Therefore, the baseline use of medication for gammaCore non-responders reduces cost of gammaCore and should be considered when evaluating the result of multi-way scenario analysis.

Furthermore, it is important to understand the definition of response rate for sensitivity analysis. The question of whether a patient is considered a responder (low resource use) or a non-responder (high resource use), is answered by the responder definition/response rate criteria. This parameter describes the necessary minimum mean reduction in weekly attacks to classify as responder. If this value is high (e.g., 65%), the threshold to be considered a responder is equally high because patients will only be responders if they experience a mean reduction of 65% or more in weekly attacks. Therefore, the probability of response to gammaCore will be quite low (e.g., 24%).

Conversely, if the responder definition / response rate criteria is set to a lower threshold (e.g. 25%), the overall model probability of response to gammaCore will be high, because the threshold to be considered a responder is equally low (e.g. a reduction of 25% of weekly attacks is already sufficient to be a responder).

In other words, the responder definition / response rate criteria drive the probability of response to gammaCore: the higher the necessary reduction in weekly attacks, the lower the probability of response to gammaCore. Only responders will trigger reduced consumption of medication. Non-responders will continue to consume baseline amounts of medication as a means of habit and dependence.

The results of the probabilistic sensitivity analysis would seem to provide a better rationale for the mean ICERs, as it was assumed to have tested uncertainty in all parameters using their distributions and scenarios accordingly.

Severity considerations- Absolute shortfall (AS) results

The absolute shortfall (AS) is based on projections about life expectancies from the health economic model. Calculation of AS has been described in more detail in the submission guideline for pharmaceutical reimbursements of the Norwegian Medicines Agency, which is based on the white paper on priority setting, and a Norwegian life table and age adjusted health related quality of life information from a general Swedish population (69). Absolute shortfall is defined as the difference in quality adjusted life expectancies at age (A) without the disease (QALYsA), and prognosis with the disease with current standard care (PA):

AS = QALYsA – PA

In the calculations, undiscounted numbers for QALYsA and PA are used.

From the submission:

The age-spread of the CH population in Norway is uneven. A recent publication found that the mean age of the patient population was 55.8 (+/- 18.9) years but the median age of the patients with CH was 42 years with an interquartile ratio of 20 (3). Based on this data, it is assumed that the average age of the cluster headache population to be treated with gammaCore in Norway is 43 years, which was also the mean age of patients observed in the PREVA study.

NIPH Comments:

The absolute shortfall of 7.03 (Table 14) corresponds to a willingness to pay threshold of NOK 385,000 group 2. The severity calculation for the 1-year time horizon of the model was based on Norwegian medicines agency (NOMA) guidelines (70). However, the submitter decided to use the SoC responder share and initial undiscounted utility values from PREVA to estimate the prognosis based on weighted absolute shortfall. The calculation was in line with NOMA guidelines (70).

Table 14: *Calculation of severity*

Parameter	**Value**	**Source**
median age of CH population (in years)	43	Crespi et al., 2022, CUA model, PREVA study
QALY weights	**Value**	**Source**
SoC, responder	0.722	CUA model (PREVA study)
SoC, non-responder	0.439	CUA model (PREVA study)
SoC (weighted, non-resp.&resp.)	0.665	Calculated
share of responders to SoC	0.800	NICE 2018, Wei et al. 2018 (23) (71)
HSUV of general population at mean age	0.846	Table 7 of NIPH guideline for STAs
Absolute shortfall	**Value**	**Comment**
QALYs (general population)	32.9	number of remaining healthy life years for an average person from the **general population** with the mean age
QALYs (CH patients)	25.868	number of remaining healthy life years for an average person from the **patient population** with the mean age
Number of QALYs lost due to disease (absolute shortfall)	**7.032**	

Results

From the submission:

Table 12: *Deterministic base-case results*

	Total per patient cost (NOK)	QALYs per patient	ICER (NOK)
gammaCore plus SoC	29,494 NOK	0.525	
SoC	32,355 NOK	0.441	
Difference	-2,861 NOK	0.085	-33,803

Table 13: *Summary of costs by category of cost per patient*

Item	Cost gammaCore plus SoC (NOK)	Cost SoC (NOK)	Increment (NOK)
GC cost	4,758		4,758
Sumatriptan	19,951	27,136	-7,185
Zolmitriptan	3,138	3,115	23
Oxygen	1,647	2,104	-457
Total	29,494	32,355	-2,861

Table 14: *Summary of costs by health state per patient*

Health state	Cost gammaCore plus SoC (NOK)	Cost SoC (NOK)	Increment (NOK)
Responder	7,895	76	7,819
Non-Responder	21,599	32,279	-10,680
Total	29,494	32,355	-2,861

NIPH comments:
The result of the deterministic analysis for the base-case found that gammaCore plus SoC was dominant (cost-saving and more effective) over SoC. The estimated total cost of gammaCore plus SoC was NOK 29,494 which was lower than that of SoC alone estimated at NOK 32,355. The total QALYs corresponding to gammaCore plus SoC and SoC were found to be 0.525 QALYs and 0.441 QALYs, respectively.

The results in terms of the incremental cost-effectiveness ratio (ICER) showed that gammaCore plus SoC was dominant (i.e., less costly, and with higher benefit) over SoC with a negative ICER of NOK -33,803 per QALY (*Table 15*), therefore implying cost savings for the Norwegian healthcare system.

The summary of costs presented in *Table 16* found Sumatriptan to be associated with the highest cost savings by using gammaCore with SoC. The health state with highest cost was found to be non-responders in the SoC, whereas the responder health state for gammaCore relatively had a relatively higher cost as compared to SoC responders (which accounted for a small proportion of responders), presented in *Table 17*Table 14.

We believe there are higher costs associated with non-responders in the SoC arm compared to responders in the SoC arm and this may be the result of a large number of refractory patients that may have adopted dependency on these medications.

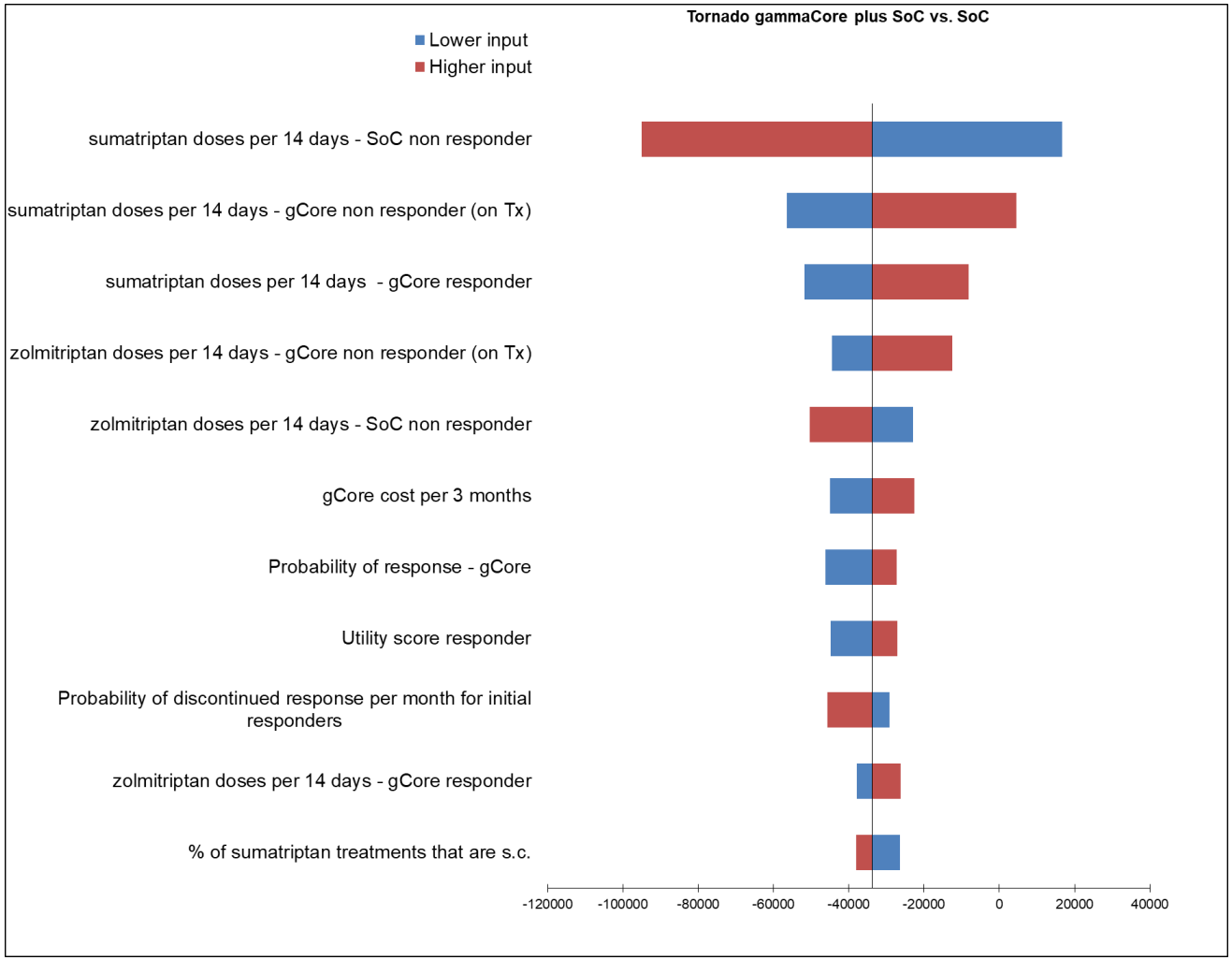


Figure 8: *Tornado Chart of OWSA on total costs*

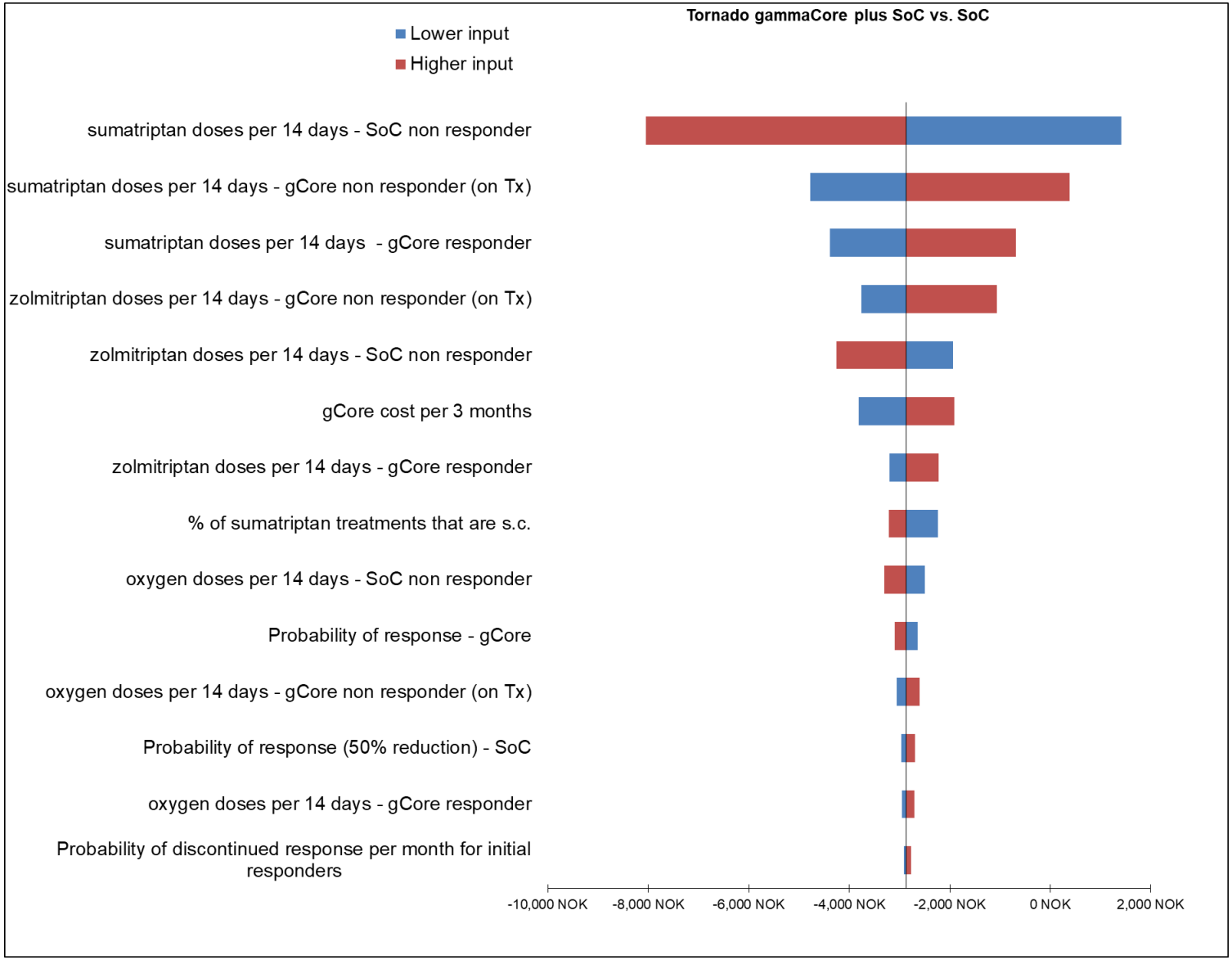


Figure 9: *Tornado Chart of OWSA on ICER*

Two-Way Sensitivity Analysis

Table 15: Results of the TWSA of gammaCore costs and probability of response on total costs

gCore cost per 3 months	Probability of response - gCore											
	0.26	0.29	0.31	0.34	0.37	0.39	0.42	0.44	0.47	0.49	0.52	0.55
4600.00	-3,261.45 NOK	-3,364.75 NOK	-3,468.06 NOK	-3,571.36 NOK	-3,674.67 NOK	-3,777.97 NOK	-3,881.28 NOK	-3,984.58 NOK	-4,087.89 NOK	-4,191.19 NOK	-4,294.49 NOK	-4,397.80 NOK
4809.09	-3,147.52 NOK	-3,239.75 NOK	-3,331.98 NOK	-3,424.21 NOK	-3,516.44 NOK	-3,608.67 NOK	-3,700.90 NOK	-3,793.12 NOK	-3,885.35 NOK	-3,977.58 NOK	-4,069.81 NOK	-4,162.04 NOK
5018.18	-3,033.60 NOK	-3,114.75 NOK	-3,195.90 NOK	-3,277.06 NOK	-3,358.21 NOK	-3,439.36 NOK	-3,520.52 NOK	-3,601.67 NOK	-3,682.82 NOK	-3,763.97 NOK	-3,845.13 NOK	-3,926.28 NOK
5227.27	-2,919.67 NOK	-2,989.75 NOK	-3,059.83 NOK	-3,129.90 NOK	-3,199.98 NOK	-3,270.06 NOK	-3,340.14 NOK	-3,410.21 NOK	-3,480.29 NOK	-3,550.37 NOK	-3,620.44 NOK	-3,690.52 NOK
5436.36	-2,805.75 NOK	-2,864.75 NOK	-2,923.75 NOK	-2,982.75 NOK	-3,041.75 NOK	-3,100.75 NOK	-3,159.75 NOK	-3,218.76 NOK	-3,277.76 NOK	-3,336.76 NOK	-3,395.76 NOK	-3,454.76 NOK
5645.45	-2,691.82 NOK	-2,739.75 NOK	-2,787.67 NOK	-2,835.60 NOK	-2,883.52 NOK	-2,931.45 NOK	-2,979.37 NOK	-3,027.30 NOK	-3,075.23 NOK	-3,123.15 NOK	-3,171.08 NOK	-3,219.00 NOK
5854.55	-2,577.90 NOK	-2,614.75 NOK	-2,651.60 NOK	-2,688.45 NOK	-2,725.30 NOK	-2,762.14 NOK	-2,798.99 NOK	-2,835.84 NOK	-2,872.69 NOK	-2,909.54 NOK	-2,946.39 NOK	-2,983.24 NOK
6063.64	-2,463.97 NOK	-2,489.75 NOK	-2,515.52 NOK	-2,541.29 NOK	-2,567.07 NOK	-2,592.84 NOK	-2,618.61 NOK	-2,644.39 NOK	-2,670.16 NOK	-2,695.94 NOK	-2,721.71 NOK	-2,747.48 NOK
6272.73	-2,350.05 NOK	-2,364.75 NOK	-2,379.44 NOK	-2,394.14 NOK	-2,408.84 NOK	-2,423.54 NOK	-2,438.23 NOK	-2,452.93 NOK	-2,467.63 NOK	-2,482.33 NOK	-2,497.03 NOK	-2,511.72 NOK
6481.82	-2,236.12 NOK	-2,239.74 NOK	-2,243.37 NOK	-2,246.99 NOK	-2,250.61 NOK	-2,254.23 NOK	-2,257.85 NOK	-2,261.48 NOK	-2,265.10 NOK	-2,268.72 NOK	-2,272.34 NOK	-2,275.96 NOK
6690.91	-2,122.20 NOK	-2,114.74 NOK	-2,107.29 NOK	-2,099.84 NOK	-2,092.38 NOK	-2,084.93 NOK	-2,077.47 NOK	-2,070.02 NOK	-2,062.57 NOK	-2,055.11 NOK	-2,047.66 NOK	-2,040.20 NOK
6900.00	-2,008.27 NOK	-1,989.74 NOK	-1,971.21 NOK	-1,952.68 NOK	-1,934.15 NOK	-1,915.62 NOK	-1,897.09 NOK	-1,878.56 NOK	-1,860.03 NOK	-1,841.50 NOK	-1,822.97 NOK	-1,804.44 NOK

Table 16: Results of the TWSA of utility score of gammaCore responders and probability of response on ICER

Utility score responder	Probability of response - gCore											
	0.26	0.29	0.31	0.34	0.37	0.39	0.42	0.44	0.47	0.49	0.52	0.55
0.65	-45848.09	-42729.98	-40088.56	-37822.28	-35856.52	-34135.22	-32615.45	-31263.78	-30053.77	-28964.27	-27978.12	-27081.29
0.66	-45920.91	-42792.22	-40142.49	-37869.54	-35898.35	-34172.56	-32649.04	-31294.19	-30081.47	-28989.64	-28001.46	-27102.86
0.68	-45993.96	-42854.65	-40196.56	-37916.92	-35940.28	-34209.99	-32682.70	-31324.67	-30109.23	-29015.05	-28024.84	-27124.46
0.69	-46067.25	-42917.26	-40250.78	-37964.42	-35982.30	-34247.50	-32716.43	-31355.20	-30137.04	-29040.51	-28048.26	-27146.10
0.70	-46140.77	-42980.05	-40305.14	-38012.03	-36024.43	-34285.09	-32750.23	-31385.80	-30164.90	-29066.01	-28071.72	-27167.78
0.72	-46214.53	-43043.03	-40359.65	-38059.77	-36066.65	-34322.76	-32784.10	-31416.45	-30192.81	-29091.56	-28095.22	-27189.49
0.73	-46288.52	-43106.19	-40414.31	-38107.63	-36108.97	-34360.51	-32818.04	-31447.16	-30220.77	-29117.15	-28118.76	-27211.23
0.74	-46362.75	-43169.53	-40469.12	-38155.61	-36151.40	-34398.35	-32852.04	-31477.94	-30248.78	-29142.79	-28142.34	-27233.01
0.75	-46437.22	-43233.07	-40524.08	-38203.70	-36193.92	-34436.27	-32886.12	-31508.77	-30276.85	-29168.48	-28165.96	-27254.82
0.77	-46511.93	-43296.79	-40579.18	-38251.92	-36236.54	-34474.28	-32920.27	-31539.66	-30304.97	-29194.21	-28189.62	-27276.67
0.78	-46586.88	-43360.69	-40634.44	-38300.26	-36279.26	-34512.37	-32954.50	-31570.62	-30333.14	-29219.98	-28213.31	-27298.55
0.79	-46662.07	-43424.79	-40689.85	-38348.73	-36322.09	-34550.54	-32988.79	-31601.64	-30361.36	-29245.80	-28237.05	-27320.47

NIPH comments:

The results of one-way sensitivity analysis for total costs per patient found that the most imperative variables were resource use of sumatriptan doses for 14 days for SoC non-responders, followed by sumatriptan doses for 14 days for gammaCore responders and then the non-responders. The cost of gammaCore for 3 months moderately impacted the total cost savings (*Figure 8*).

Conversely, the results of one-way sensitivity analysis for the ICER found probability of response of gammaCore to be impactful (*Figure 9*). The probability of response is inversely related to the response rate definition. In other words, a higher response rate criteria leads to more cost savings as interpretated from the results. The ICER was found to be sensitive to other parameters such as the probability of discontinued response per month for gammaCore and the probability of response for SoC.

The results of two-way sensitivity analysis are presented in *Table 18* and *Table 19*. Based on the results we found that all combination for cost changes of gammaCore and probability of response of gammaCore lead to cost savings provided that the other base-case assumptions are kept constant. The cost savings were also associated with respect to utility of responders in the SOC arm and probability of gammaCore.

Table 17: *Base-case results of PSA using 10,000 simulations*

PSA response - Definition	**50%**		
	Total per patient cost (NOK)	**QALYs per patient**	**ICER (NOK)**
gammaCore plus SoC	29,450	0.528	
SoC	31,945	0.443	
Difference	-2,738	0.085	-34,536

82.8% probability that gammaCore is cost saving.

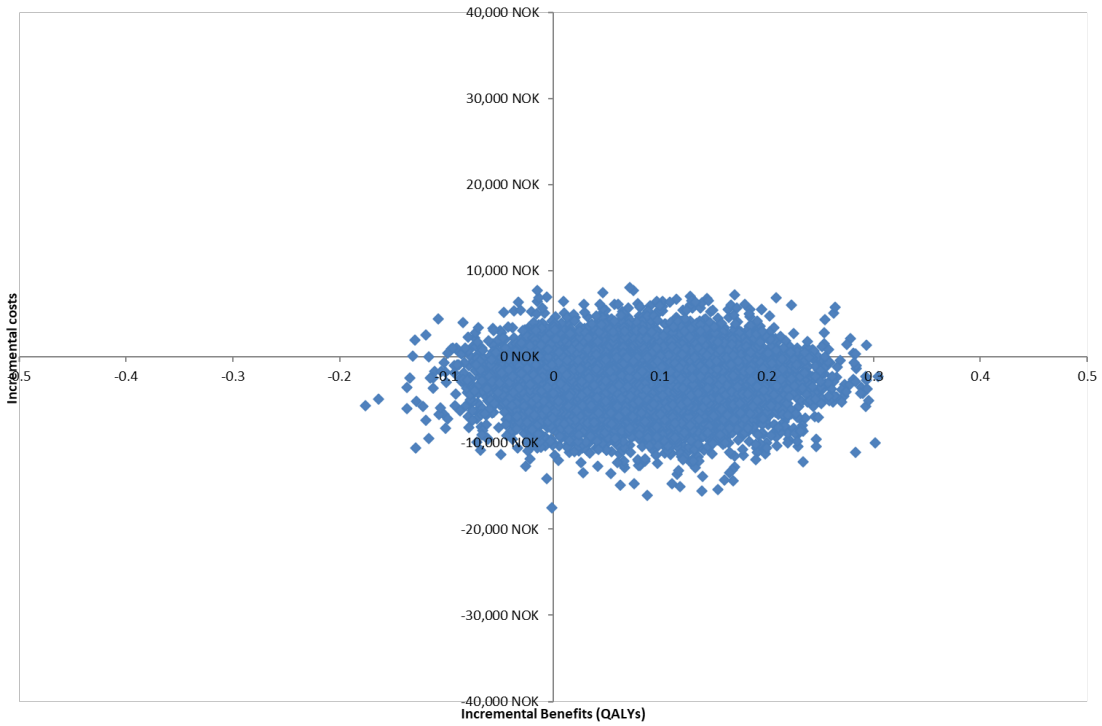


Figure 10: *Cost-effectiveness plane of PSA using 10,000 simulations*

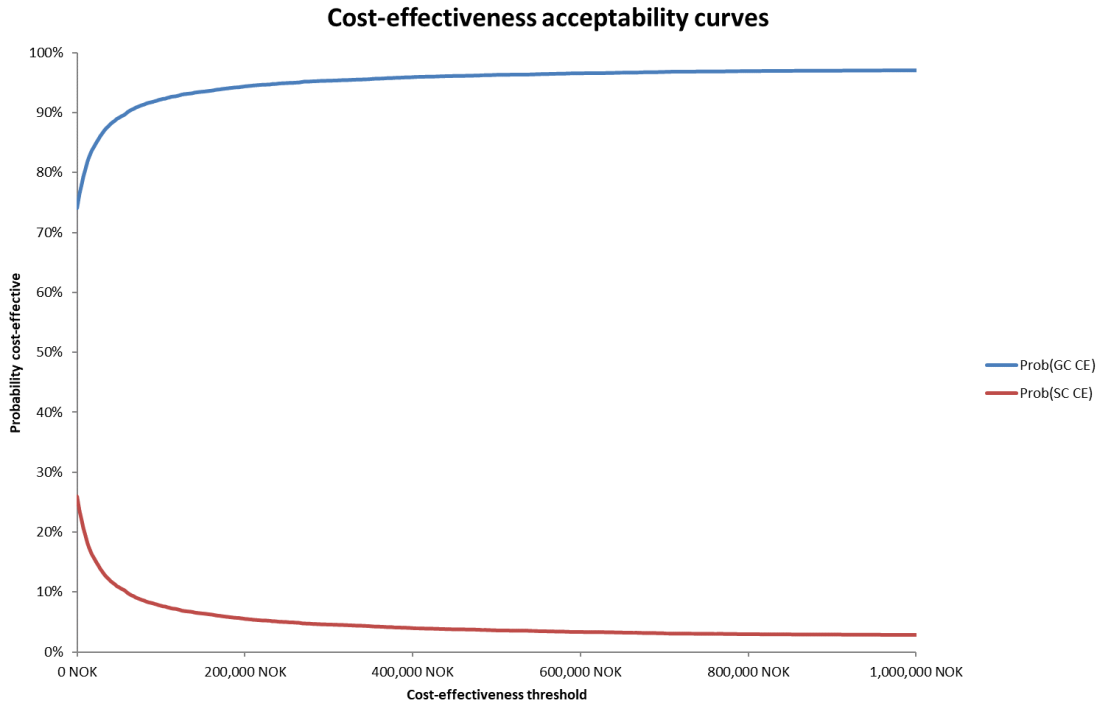


Figure 11: *Cost-effectiveness acceptability curves of PSA using 10,000 simulations*

NIPH comments:

The results of the probabilistic sensitivity analysis found that gammaCore plus SoC was dominant over SoC with a cost saving ICER of NOK -35,765 considering all uncertainty in the parameters of the model around their respective distribution for the base-case (*Table 20*).

The C-E plane for the 10,000 simulations in *Figure 10* found Figure that most of the point corresponding to incremental QALYs and costs for gammaCore plus SoC were spread across south-east quadrant of the C-E plane implying cost savings.

The results of the probabilistic sensitivity analysis presented as a cost effectiveness acceptability curve (*Figure 11*Figure) found that gammaCore was found to have a 95% probability of being cost-effective for a willingness to pay threshold of ≥ NOK 400,000 per QALY.

Scenario Analysis

The scenario analysis is presented in Appendix (*Table A 12*).

NIPH comments:

The results of the multi-way scenario analysis using a different response rate definition, a different base-case medication use in the SoC or gammaCore for the non-responder health states in both arms, and a varied response loss rate for gammaCore are presented in *Appendix Table A 12*. All scenarios resulted in cost-savings for gammaCore plus SoC. The results should be interpreted keeping in mind that the main assumption regarding response for treatment implies that both gammaCore plus SoC and SoC arms have no

response post 1 month. Conversely, initial response loss is assumed for gammaCore plus SoC, but all patients are non-responders for SoC post 1-month. Based on the electroCore's evaluation this was assumed to avoid lower costs for SoC responders as non-responders continue to use medications.

As most of the results of scenario analysis reduce costs as compared to SoC and have higher health gains it is important to analyse the cost savings under different assumptions for response loss in the intervention arm. As all scenarios produced a negative ICER implying cost savings, therefore, the submitter only presented the relative cost savings associated with each scenario's assumption.

Budget Impact Analysis

From the submission:

The budget impact model examines the annual budgetary impact of the introduction of gammaCore for refractory patients with episodic or chronic cluster headache (CH) from the perspective of the Norwegian healthcare system within the first 5 years after a positive reimbursement decision.

This analysis assumes that gammaCore is used twice daily as prophylactic therapy and that the use of gammaCore has no impact on the use of other prophylactic therapies. Therefore, the model does not consider changes in the costs of prophylactic therapies, only the additional costs for the (preventive) use of gammaCore are considered. The model focusses strictly on medication costs. It examines the impact of gammaCore on the frequency of CH attacks and the associated change in the use of acute medication and the associated costs based on data from the PREVA trial.

The key assumption of the model and structure are provided in Appendix 3.2.4.

Number of expected patients over 5 years

Based on a prevalence estimate of CH of 0.1% (6) combined with official population statistics from Norway, an estimate about the share of patients for whom standard treatment is ineffective or contraindicated, a responder rate obtained from the PREVA study and assumptions about the distribution of patient among subgroups (eCH, cCH), the number of CH patients eligible for long-term use of gammaCore in Norway was estimated to be n=342 per year. These patients are assumed to use three different formulations of the comparator:

- *Comparator 1: Oxygen + Sumatriptan s.c.*
- *Comparator 2: Oxygen + Zolmitriptan nasal spray*
- *Comparator 3: Oxygen + Sumatriptan nasal spray*

After a positive reimbursement decision, a technology adoption path with increasing annual rates is assumed to extrapolate anticipated patient numbers in the four treatment alternatives. These adoption rates are:

- *current adoption rate (year 0): 0%*
- *adoption rate year 1: 20%*
- *adoption rate year 2: 40%*
- *adoption rate year 3: 60%*
- *adoption rate year 4: 80%*
- *recommended adoption rate (year 5): 95%*

Table 23 and *Table 24 shows the distribution of patients among the treatment alternatives for the case, that regular reimbursement of gammaCore treatment will not be implemented in Norway. Table 25 shows the anticipated patient numbers for the case that regular reimbursement of gammaCore treatment will be implemented in Norway, based on the outlined adoption path.*

Table 21: *Prevalence of CH in Norway and sub-group used in the Budget impact model.*

	Patients (%)
Prevalent CH Norway	4280
Share of patients SoC ineffective	20%
Share of patient benefit from gammaCore (responder rate ≥50%).	40%
Eligible for long term use of gammaCore in Norway	(4280 x 20% x 40%) = 342
Chronic CH share from eligible (%)	68 (20%)
Episodic CH share from eligible (%)	274 (80%)
Cumulated total duration of CH episodes per year prevalence	
3 months	90 (33%)
6 months	90 (33%)
9 months	93 (34%)

Table 22: *Proportion of eCH in Norway and % share in comparators.*

Episodic CH	**Comparator 1**	**Comparator 2**	**Comparator 3**
Share (in%) per Comparator (eCH)	60%	30%	10%
Absolute share per Comparator (eCH)	164	82	27
Intervention 1	Oxygen	Oxygen	Oxygen
Intervention 2	Sumatriptan subcutaneous	Zolmitriptan nasal spray	Sumatriptan nasal spray

Table 23: *Proportion of cCH in Norway and % share in comparators.*

Chronic CH	**Comparator 1**	**Comparator 2**	**Comparator 3**
Share (in%) per Comparator (cCH)	60%	30%	10%
Absolute share per Comparator (cCH)	41	21	7
Intervention 1	Oxygen	Oxygen	Oxygen
Intervention 2	Sumatriptan subcutaneous	Zolmitriptan nasal spray	Sumatriptan nasal spray

Table 24: *Number of patients expected to be treated during the next five-year period – if the intervention is NOT implemented*

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Intervention	0	0	0	0	0	0
Comparator 1	205	205	205	205	205	205
Comparator 2	103	103	103	103	103	103
Comparator 3	34	34	34	34	34	34

Table 25: *Number of patients expected to be treated over the next five-year period – if the intervention is implemented*

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Intervention	0	68	137	205	274	325
Comparator 1	205	164	123	82	41	10
Comparator 2	103	82	62	41	21	5
Comparator 3	34	27	21	14	7	2

Table 26: *Expected budget impact (in NOK) of adopting the intervention for the relevant indication*

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Total over 5 years
The Intervention is adopted	20,121,862	19,304,459	18,979,219	18,653,979	18,328,739	18,207,850	113,596,108
Minus: The intervention is not adopted	20,121,862	20,121,862	20,121,862	20,121,862	20,121,862	20,121,862	120,731,172
Budget Impact	0	-817,403	-1,142,643	-1,467,883	-1,793,123	-1,914,012	-7,135,064

Estimated budget impact of adopting gammaCore as regular treatment for refractory CH patients

Combining estimated patient numbers with average annual per patient cost in the different treatment alternatives yields the estimated budget impact over 5 years. Table shows the estimated budgets for the scenario in which gammaCore is adopted, and for the scenario in which gammaCore is not adopted. The difference between both scenarios is defined as budget impact.

The annual budget impact increases over time from 0 to -1.9 million NOK in year 5, due to increasing adoption rates and a negative cost difference between both scenarios. The cumulated budget impact after 5 years is -7.1 million NOK, representing remarkable absolute savings to the national health care budget.

The total budget per year for the scenario of gammaCore adoption is depicted in figure 12. Given increasing adoption rates, increases in the share of costs of gammaCore therapies can be observed, while the total budget devoted to CH patients is continuously decreasing.

After 5 years, cumulated savings stemming from the reduction in acute medication are as high as 33 million NOK, assuming an adoption of the gammaCore treatment strategy. Although the cost of gammaCore treatments need to be subtracted from this number to derive the budget impact, a negative net budget impact can be seen in figure 13.

The primary finding of the OWSA is, that all investigated scenarios produce a negative total budget impact, representing absolute savings to the Norwegian health care system. The highest degree of uncertainty is associated with the percentage reduction of acute medication associated with gammaCore therapy, followed by costs (net price) per 3 months of gammaCore therapy, and prevalence of CH in Norway (Figure 14).

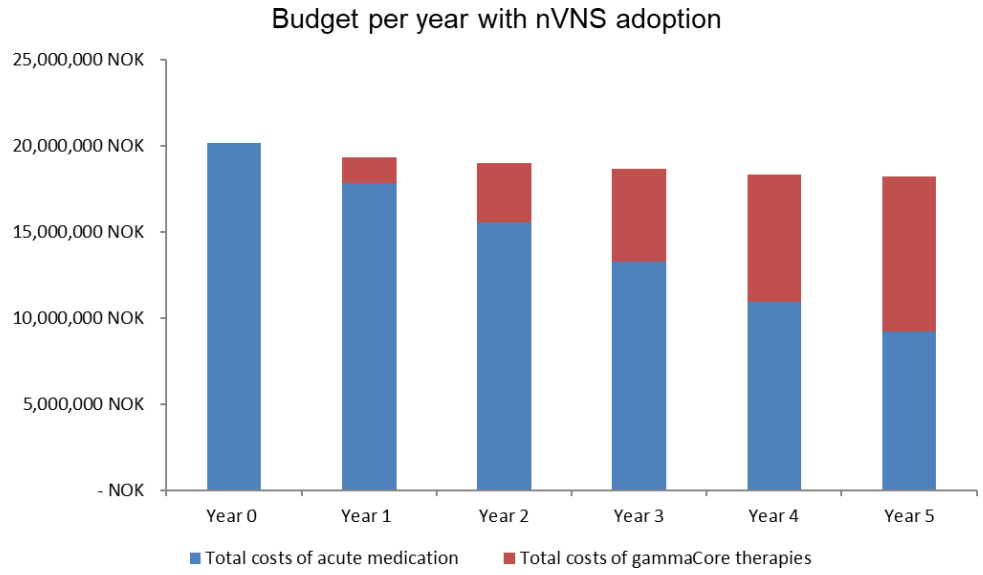


Figure 12: *Budget per year with nVNS adoption*

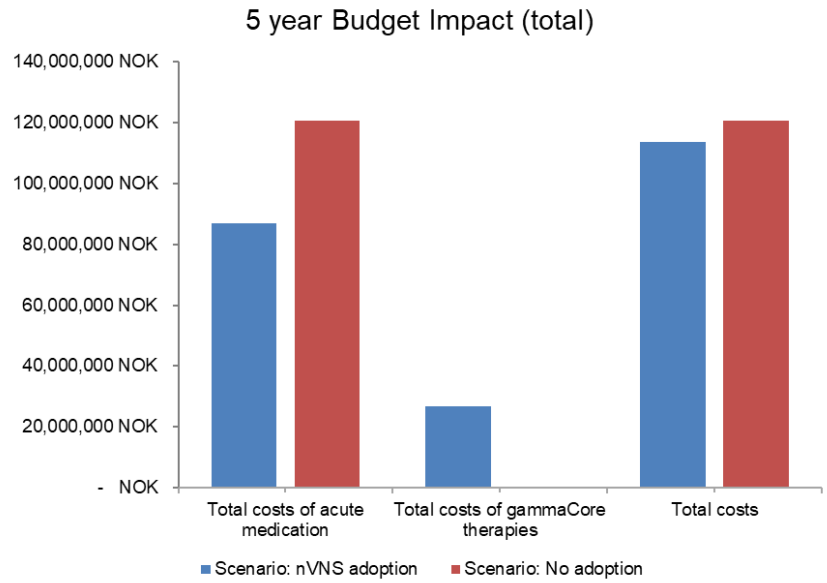
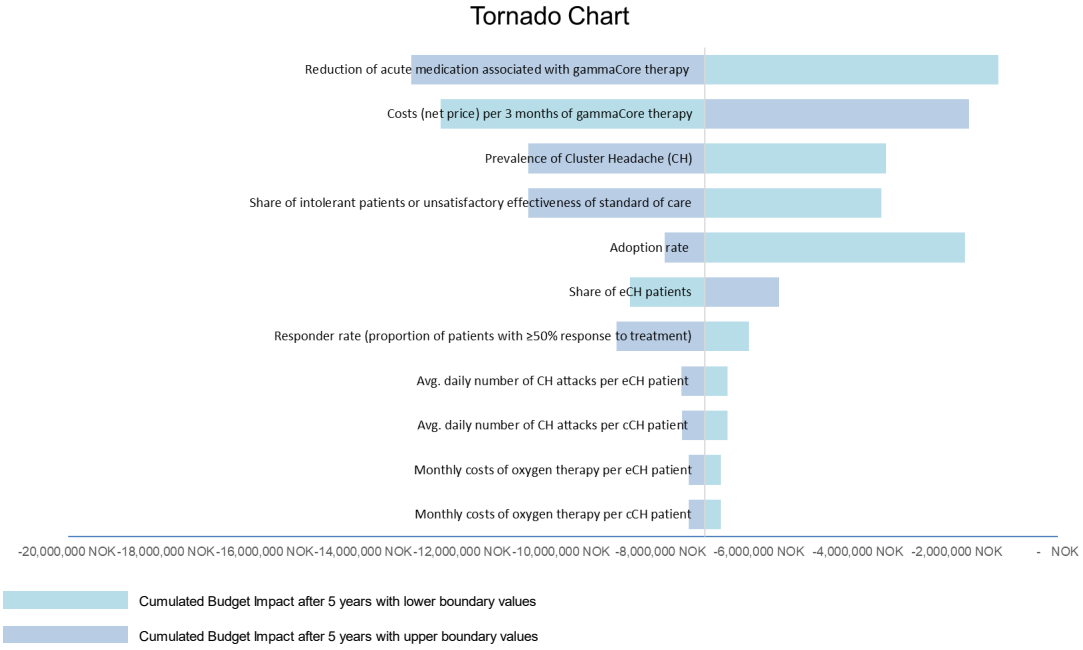


Figure 13: *Cumulated 5-year total budget impact*



Responder rate refers to the proportion of patients achieving ≥50% response to treatment (Appendix, Table A11)

Figure 14: *One-way sensitivity of Budget impact model*

NIPH Comments:

The budget impact of the intervention is based on the prevalence of CH in Norway. A set of different assumptions was used to reflect the possible scenarios for budget consequences in Norway, by taking into consideration both subgroups of episodic and chronic CH patients.

We believe that considering expert recommendations on the share of eCH and cCH seems appropriate as no direct evidence is available for the exact percentage of patients in both subgroups.

The calculation was performed based on the prevalent number of CH patients in Norway using the prevalence estimate "0.1%" (4280 patients) and finding eligible patients for the gammaCore plus SoC (342 patients). This was estimated by using published evidence on proportion of patients for whom SoC is ineffective (72) and the proportion of patients that would benefit from gammaCore based on a ≥50% response to treatment criteria (i.e., greater than or equal to 50% reduced attacks for 40% of the patients) (16). The share of type of subgroup of patients is presented in Table 22Table and Table 23.

Furthermore, for the proportion of patients in eCH (80%) and cCH (20%), the attack frequency for estimating CH total costs for each subgroup was assumed to be 3.5 daily mean attacks per patient (Gaul et al., 2011). The total costs for each subgroup can be found in the *Appendix Table A 9* and *Table A 10*. We found this assumption to be reasonable for the chronic cluster headache patients, considering the short duration of the PREVA study. In addition, the uncertainty was captured in the one-way sensitivity analysis for the budget impact analysis in *figure 14* and did not show that the budget was sensitive to daily average attacks.

The budget impact was performed by allocating patients among three different comparators based on their weights (*Table* and *Table*) to calculate the total costs of SoC. Both eCH and cCH patients were divided between these comparators, with the highest proportion of patients being allocated to comparator 1 (oxygen + sumatriptan subcutaneous). The assumptions seemed reasonable for the Norwegian settings.

As the total costs per cCH is higher than for eCH patients, we conducted a separate analysis to test the budget impact assuming just cCH patients. This shows that the budget impact, assuming 20% cCH patients alone, was NOK - 6.2 million, as compared to NOK - 7.1 million (*Table 27*). Therefore, based on this calculation the absolute savings attributed to the episodic patients in the model would be estimated at NOK -0.8 million. However, the estimated cost offsets for this patient group cannot be supported by the PREVA trial, and it is also unclear as to whether the initial trial period of 93 days free use has been included for this patient subgroup.

It seems evident that the cost saving to the national healthcare budget is significantly driven by the share of chronic patients and the uncertainty around the reduction in acute medication associated with gammaCore (Figure 14).

Table 27: *Expected budget impact (in NOK) of adopting the intervention for the relevant indication of cCH patients.*

Expected budget impact of adopting nVNS over 5 years							
	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Total over 5 years
nVNS is adopted	6,896,678	6,405,755	6,013,264	5,620,773	5,228,282	4,958,522	35,123,274
Minus: nVNS is not adopted	6,896,678	6,896,678	6,896,678	6,896,678	6,896,678	6,896,678	41,380,069
Budget Impact	-	-490,923	-883,414	-1,275,905	-1,668,396	-1,938,156	-6,256,795

Patient perspective

How the condition affects patients' quality of life

The representative from the patient organisation 'Hodepine Norge' has completed a questionnaire from NIPH in which she states that: "*Cluster headache affects all aspects of life. The pain is accompanied by a great deal of anxiety in anticipation of the next attack or period. The mental strain on this patient group is significant. The pain is so severe that when it occurs, it is impossible to focus on anything other than breathing."*

The patient representative believes that chronic cluster headache patients suffer the most. But all cluster headache patients live under difficult circumstances as long as they do not receive help in reducing the intensity of the attacks. The patient representative states that she personally would most appreciate a reduction in the intensity of the attacks. She does not expect a cure for the disease.

In short, the patient representative believes that the disease involves a significant loss of vitality and quality of life. The current available treatment is inadequate as it entails patients being bound to their homes, for weeks at a time. The new intervention is important as it can potentially improve the quality of life of many patients.

How the condition affects patients' relatives

"This is a condition that you cannot hide when the attacks occur. In periods that are particularly bad, it is difficult to perform tasks outside the home, as one might not have oxygen available or be afraid to be seen while suffering an attack. Even social interaction with friends and family might constitute a challenge and going to the cinema or a concert is impossible for many."

How well do patients handle the condition with existing methods (standard care)

"It is not easy to carry a 5 L oxygen tank everywhere. Oxygen works for me, it reduces the duration of my attacks from two-three hours down to approximately 30 minutes. However, it is cumbersome to use, and the tank replacement location is over 20km away. This is the most important part of treatment for me, but with up to six attacks a day in the cluster periods, it takes all my time and energy."

Experiences and/or views on the method that is under consideration

The patient representative does not have personal experience with the intervention, but has heard that vagus nerve stimulation can interrupt, suppress or shorten seizures in those patients where it has an effect. Also heard that it does not work for everyone, and that there are no important side effects in connection with the device.

Discussion

Key findings

Cluster headache is a severe disease, as described in a qualitative study comprising seven patients with chronic cluster headache in Norway (73). The pain associated with a cluster headache attack is described as being of a high intensity and brutal in nature. Patients characterize the pain as being similar to having a knife with barbed wire, a crowbar or a screw moved back and forth or twisted around in your head or eye. It may also feel like being suspended from a fishhook or that one's head is exploding, according to the participants in the study.

Effectiveness and safety

The submitter identified 10 studies and 2 reviews that described the effect of nVNS to treat cluster headaches. Some of the studies compared nVNS to a sham, however many of these also included migraine patients. In order, to focus on the cluster headaches NIPH performed additional meta-analysis based on the RCT's (ACT 1 (11), ACT 2 (10), PREVA (16)) and the pooled analysis by de Coo et al. (8). The subgroups of cluster headaches, episodic and chronic have been shown through the included studies to react differently to the vagus nerve stimulation. One of the few studies to examine this was de Coo et al. (8) which pooled results from ACT 1 (11) and ACT 2 (10).

To determine the certainty of the evidence in the selected studies we used GRADE. In the studies evaluating the effect of nVNS for acute treatment of eCH, we found that nVNS probably improves response by more than three times for patients who responded at 15 min to the first attack, improves pain free status at 15 min for 17% of treated attacks, and may lead to a one - point reduction in pain intensity after 15 min. The nVNS treatment probably improves the sustained response rate by more than three times.

For studies that evaluated nVNS for acute treatment for cCH, we found that the effect was less clear, showing that it may lead to little or no difference in response rate and sustained response rate. The nVNS treatment may make little or no difference for patients who responded to the first attack within 15 min, achieved pain – free status, experienced a change in pain intensity within 15 min.

One study we evaluated focused on preventative treatment of cCH where nVNS was combined with standard of care (SoC), this may lead to a reduction in attacks by almost four

per week. nVNS combined with SoC may also result in fifteen times less use of abortive medication and 0.2 points higher quality of life, assessed with EQ-5D-3L.

The real - world data presented in the submission file suggests that nVNS can provide an improvement, reduce attacks frequency, and reduce medication or oxygen use. In this data the subgroup of cCH also does not show the same improvement as a mixed group of eCH and cCH. This evidence should be interpreted with care, as it is not randomized, controlled or blinded, and there is no synthesis of studies available.

The gammaCore device has been approved for the European market since 2011 and in the US since 2018 to treat cluster headaches. There have been no reported serious adverse events since being on the European market according to the adverse event database of the MHRA, and only 1 event reported in MAUDE. The studies identified by the submitter and the Redgrave et al. (44) review comprehensively report adverse events. The reported adverse events were temporary, infrequent, and moderate in nature. There is, however, very limited safety data related to patients with cardiological histories, as patients with these conditions were excluded from the studies. It is therefore important that physicians authorizing gammaCore devices are aware of the warnings provided in the Instructions for Use (13), related to cardiological conditions, as described in detail in the Safety – Adverse events Section. The most common reported adverse effects are also described in the Instructions for Use, see the Section on Regulatory status and market access, and are transient.

Health economic evaluation

The cost effectiveness analysis found that nVNS together with SoC have total cost of NOK 29,494 and total QALY 0.525 as compared to the total cost of standard of care NOK 32,355 and total QALYs 0.441 in the base-case. gammaCore together with SoC was dominant over SoC and generated cost saving with an ICER of NOK -33,803per QALY in the base-case with assumption of no response loss post 2 months and using a 50% response rate definition for reduction in attacks.

The incremental cost effectiveness ratio of an alternative scenario such as with constant rate of response loss at 10% was estimated to be NOK -80,922 for incremental costs of NOK -2,724 and incremental QALYs of 0.034. Whereas for the scenario for reducing probability of response with fixed percentage at 10% the ICER was NOK -75,852, with incremental cost of NOK -2,709 and incremental QALYs of 0.036. Both scenarios generated cost saving for additional QALYs.

The probability of response discontinuation, initial probability of response of gammaCore was found to be the most significant in driving the result of cost saving for the intervention.

Evidence quality and limitations

Effectiveness and safety

The patient category in the scope and selection criteria for this submission was cluster headache, with chronic (cCH) and episodic (eCH) subgroups. Other headache conditions were excluded based on exclusion criteria when evaluating the effect. In spite of this, there were several studies on migraine patients in both primary studies and meta-analyses, which made the basis for NIPH's assessment narrower than it might have appeared at first glance. We have omitted migraine studies, however there are a number of studies which include both cluster headache and migraine studies, and we have therefore performed our own meta-analysis, as described previously. The complexity of the cluster headaches which encompasses episodic and chronic patients who respond differently to nVNS treatment, and the gammaCore device which can be used both preventatively and acutely adds additional complexity to both interpreting the studies and understanding the effect of the nVNS treatment. None of the studies evaluated all these aspects, and there were only three primary studies which we could use in our meta-analysis. However, we evaluated the risk of bias and have used GRADE to evaluate the certainty of the evidence we have collected, the details of which can be found in the Clinical effectiveness and safety Section.

Health economic model

The current economic model was informed by the PREVA study, one of the studies that was evaluated by meta-analysis. It had a short duration of a few weeks and only included cCH patients from Europe, as it was preventative. Therefore, the data for the economic analysis was only based on a trial of 93 patients (ITT). Based on the evidence available, the predictive validity of the current model with regards to long-term outcomes for Norway is low as the prevalence of CH is low and the prevalence of the eCH and cCH subgroups is uncertain.

Transition between eCH to cCH is spontaneous but can occur and vice versa. Such transitions in trials including both episodic and cluster patients may distort treatment response and outcomes.

As the health economic model is driven by clinical studies relating to cCH patients, it avoids the issue of heterogeneity. This was in relevance to literature and our findings on effect that has suggested including episodic patients with chronic may lead to false conclusion (8).

The results of cost effectiveness of other company-sponsored studies using PREVA such as in Germany have also found that the ICER of gammaCore plus standard of care was dominant over standard of care alone resulting in cost saving from NOK 4104 – 6144 (converted from pound to NOK at £ = 12) (50). Nevertheless, the alternate scenarios for diminishing response loss and constant response loss did not yield loss in QALYs as they were cost saving with higher effect and lower costs.

Our results are inherently impacted through response rate definition and discontinuation in response in the economic model, implying that gammaCore may incur costs to the health care system if the 3-month trial period was removed from the analysis as supported by NICE (67).

A significant limitation of the submitted economic analysis is the assumption that the model results are also relevant for episodic patients. It is possible that there will be cost savings due to gammaCore providing relatively rapid pain relief once an attack has occurred, but both the model and the budget impact analysis assume a preventative effect for these patients. The submitter has not provided documentation to support this.

The use of standard of care as a comparator may seem to be somewhat confusing, as it encompasses both preventative and acute treatment. The latter, is a down-stream outcome/cost item rather than a comparator, strictly speaking.

However, the limitations and challenges to the current study were not considerably different from those reported in NICE' evaluation of gammaCore in the UK. The current studies comprise a small number of patients and UK based study are rather observational or responder studies (67). There is a need to undertake clinical trials in this field. Dodick et al. (74) note that current guidelines in preventive treatment for cluster headache tend to be based on off-label therapies supported by a small number of randomised, controlled clinical trials. They further point out that:

"*For example, the excruciating pain associated with CH demands a suitably limited baseline duration, rapid treatment efficacy onset, and poses a specific issue regarding duration of investigational treatment period and length of exposure to placebo. In episodic CH, spontaneous remission as part of natural history, and the unpredictability and irregularity of cluster periods across patients present additional key challenges."*

As reported by NICE, the current evidence is only indicative of short-term effect of gammaCore, but the degree of benefit is not clear (67), and there exists uncertainty regarding the long-term response of the intervention for preventative or acute use gammaCore for CH.

Neurologists need to determine the appropriate response in clinical practice as this significantly affects the cost effectiveness results for the Norwegian healthcare.

We believe as the submitter would pay for the first 93 days of use, it will therefore be up to the patient's consulting neurologist to decide whether or not the treatment has been worthwhile. NICE also noted in its assessment of gammaCore that it is not likely that a patient will continue with a treatment that is not effective (67).

"*gammaCore's response" rate is higher and its therapeutic benefits more sustained than would be expected for a placebo treatment*." (6)

One of our clinical experts suggests that, on average, the chronic patients would be expected to see a consultant neurologist four times a year. The introduction of

gammaCore will therefore not have any bearing on attendance in this group. As regards seeing a neurologist every third month, it is likely that episodic patients will consult a specialist in periods when they experience attacks.

Consistency with other studies and reviews

NIPH performed checks to verify that the relevant clinical trials had been identified, and did not identify any additional RCTs, though additional literature was identified. Additional literature has been reviewed for the discussion, but overall is consistent with the literature provided by the submitter(44;75-77).

Redgrave et al. performed a systematic review on Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans (44), and found that the most common side effects were local skin irritation from electrode placement, headache and nasopharyngitis. Overall Redgrave et al found 30 SAE occurred, but only 3 were assessed to be possibly caused by tVNS. The tVNS was applied on different sites and for different conditions. Most studies reported the neck as the stimulation site.

The safety data from registries and published articles all show only a few severe adverse events. The studies are informed by the same clinical trials and have evaluated the treatment effect of nVNS for both migraine and cluster headaches with comparison to other SoC and implantable VNS, identifying the non-invasive nature of the gammaCore device to be a clear advantage (75;78), and has been discussed in detail in the Clinical effectiveness and safety Section.

The health economic model was consistent with the cost-effectiveness study in Germany and NICE evaluation of the CH patients in the UK. We have discussed this earlier in our discussion for evidence quality and strengths.

Need for further research

As noted, it is challenging to undertake clinical trials on cluster headache. However, the follow-up at three-month intervals of CH patients by neurologists, a premise of the submitter's model, might allow for the collection of real-world data on effectiveness, for preventative and acute treatment of both eCH and cCH. A registry study could be carried out, subject to caveats such as the small CH population in Norway and that eCH patients experience attacks at given times of the year and sometimes with long intervals. There is also a need for more RCTs, and if possible, the trials should be designed for subgroup analysis of episodic and chronic cluster headaches. The trials should also, if possible, clearly show whether the treatment is preventative or acute, and for a longer time than those already performed.

Conclusion

For patients with eCH, nVNS seems to be effective in the treatment of ongoing attacks. nVNS compared to sham for acute treatment probably improves response rates and may lead to reduced pain intensity after 15 min. Patients with cCH may have little or no benefit of nVNS in the treatment of ongoing attacks.

One study suggests that nVNS may play a preventative role in the treatment of cCH. As compared with standard of care alone, nVNS combined with standard of care may reduce the frequency of attacks by almost four per week. nVNS combined with SoC may also reduce the need for abortive medication and improve the quality of life. Preventative effects of nVNS among patients with eCH were not documented.

The RCTs clearly show that there is a difference in response from eCH and cCH, indicating that eCH patients are more responsive to nVNS in the acute phase (8). However, for the cCH patients a preventative benefit has been shown (16). The safety of the device is also well documented, with no serious adverse events reported. In contrast to SoC and implantable versions, the simplicity of use and non-invasive nature of nVNS allow for patients with cluster headaches to try the device and easily discontinue if no effect is achieved.

The base-case health economic analysis is based on effectiveness data from patients with cCH. The results of this analysis suggest a potential cost-saving for the Norwegian healthcare, as nVNS plus SoC dominates SoC alone, but there are uncertainties. First, it is uncertain whether preventative effect seen in cCH can be generalised to eCH. Second, the short duration of the PREVA study implies uncertainty around the response rate of the intervention, and hence, a careful evaluation, discontinuing patients who don't respond, should be considered at the end of a 3-month evaluation period.

If gammaCore is offered alongside standard of care subject to 93 days free use, it may generate cost savings to the Norwegian health care system. NIPH considers the economic analysis to be reasonable for patients with cCH, but there are important uncertainties with respect to its relevance for those with eCH.

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Appendix

1.0 Machine Learning Tools

To verify the searches performed and identify new relevant references, we used OpenAlex to search for references based on the studies in the submission file and identified through “SearchRefinery” tool (25) as described in the Results from the Search Section.

To assess titles and abstracts, we used the ranking algorithm "priority screening" (28). The algorithm is taught by the researchers' decisions about the inclusion and exclusion of references at title and abstract level. References that the algorithm considers more relevant are pushed forward in the "queue". When a clear flattening of the inclusion curve in the software or after screening 100 studies without finding a relevant reference, one project worker assesses the next 50 references alone. After the project worker still does not find a relevant reference, we stopped the screening manually, based on the assumption that the remaining references are most likely irrelevant.

The included articles were then full text screened using the «Cochrane RCT classifier»(29) as described in Results from the Search Section. During this the articles that were more than 10% likely to be an RCT were evaluated by two project workers and either included as ‘RCTs’ or background articles.

1.2 Results of literature search using EPPI reviewer

Articles sourced through OpenAlex, additional to those presented as part of effect data by electroCore through the classifier ‘likely to be an RCT’:

1. Gaul Charly, Diener H C and Solbach K ; Silver Nicholas ; Straube Andreas ; Magis Delphine ; Reuter Uwe ; Andersson A ; Liebler Eric ;. (2014). EHMTI-0364. Non-invasive vagus nerve stimulation using gammacore® for prevention and acute treatment of chronic cluster headache: report from the randomized phase of the preva study. *Journal Of Headache And Pain*.
2. Gaul C, Magis D and Liebler E ; Straube A ;. (2017). Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the random-ised, controlled PREVA study. *J Headache Pain*, 18(1), pp.22.

3. Goadsby Peter J, de Coo I and Silver Nicholas ; Tyagi Alok ; Ahmed Fayyaz ; Gaul Charly ; Jensen Rigmor ; Diener Hans-Christoph ; Straube Andreas ; Liebler Eric ; Marin Juana ; Ferrari M D;. (2017). Non-invasive Vagus Nerve Stimulation for the Acute Treatment of Episodic and Chronic Cluster Headache: Findings from the Randomized, Double-blind, Sham-Controlled ACT2 Study. *Headache*.
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6. Morris J, Straube A and Diener H C; Ahmed F ; Silver N ; Walker S ; Liebler E ; Gaul C ;. (2016). Cost-effectiveness analysis of non-invasive vagus nerve stimulation for the treatment of chronic cluster headache. *J Headache Pain*, 17, pp.43.
7. Mwamburi M, Liebler E J and Tenaglia A T;. (2017). Cost-effectiveness of gammaCore (non-invasive vagus nerve stimulation) for acute treatment of episodic cluster headache. *Am J Manag Care*, 23(16 Suppl), pp.S300-s306.
8. Mwamburi M, Tenaglia A T and Leibler E J; Staats P S;. (2018). Review of evidence on noninvasive vagus nerve stimulation for treatment of migraine: efficacy, safety, and implications. *Am J Manag Care*, 24(24 Suppl), pp.S507-s516.
9. Nesbitt AD, Marin J and Goadsby P J;. (2013). Treatment of hemicrania continua by non-invasive vagus nerve stimulation in 2 patients previously treated with occipital nerve stimulation. *Journal Of Headache And Pain*.
10. Schroeder Celina F, Möller Maike and May Arne ;. (2019). nVNS sham significantly affects the trigeminal-autonomic reflex. *Neurology*, 93(5), pp.e518-e521.
11. Silberstein Stephen D, Mechtler Laszlo L; Kudrow David and Tepper Stewart J; Calhoun Anne H; Liebler Eric ; Spitzer Lia ; Saper Joel ;. (2015). Efficacy and Safety Outcomes of Non-invasive Vagus Nerve Stimulation for the Acute Treatment (ACT1) of Cluster Headache Study.
12. Strickland I, Mwamburi M and Davis S ; Ward J C. R; Day J ; Tenaglia A T; Leibler E J; Staats P S;. (2018). Noninvasive vagus nerve stimulation in a primary care setting: effects on quality of life and utilization measures in multimorbidity patients with or without primary headache. *Am J Manag Care*, 24(24 Suppl), pp.S517-s526.

Articles sourced through OpenAlex, and determined as background and/or safety related articles:

1. Chaudhry S R, Lendvai I S; Muhammad S and Westhofen P ; Kruppenbacher J ; Scheef L ; Boecker H ; Scheele D ; Hurlemann R ; Kinfe T M;. (2019). Inter-ictal

assay of peripheral circulating inflammatory mediators in migraine patients under adjunctive cervical non-invasive vagus nerve stimulation (nVNS): A proof-of-concept study. *Brain Stimul*, 12(3), pp.643-651.
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7. Hilz Max J and Bolz Armin. (2022). Transcutaneous vagus nerve stimulation and the realm of its therapeutic hopes and physiologic enigmas. *Autonomic Neuroscience: Basic And Clinical*, 243, pp.103039-103039.
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11. Lambru G and Matharu M S. (2014). Peripheral neurostimulation in primary headaches. *Neurol Sci*, 35 Suppl 1, pp.77-81.
12. Lantéri-Minet Michel, Fontaine Denys and Magis Delphine ;. (2020). Neurostimulation: Why, When, and Which One?. *Headache*, , pp..
13. Lipton Richard B and Goadsby Peter J;. (2018). Comment: Noninvasive neurostimulation for migraine should be part of the general neurologist's therapeutic armamentarium. *Neurology*, , pp..
14. Lloyd J, Biloshytska M and Andreou A P; Lambru G ;. (2021). Noninvasive Neuromodulation in Headache: An Update. *Neurol India*, 69(12 Suppl 1), pp.S183-s193.
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16. May A and Jürgens T P. (2011). [Therapeutic neuromodulation in primary headaches]. *Nervenarzt*, 82(6), pp.743-52.

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18. Miller Sarah, Sinclair Alex J and Davies Brendan ; Matharu Manjit ;. (2016). Neurostimulation in the treatment of primary headaches. *Practical Neurology*, 16(5), pp.362-375.
19. Miller Sarah and Matharu Manjit . (2017). The Use of Electroceuticals and Neuromodulation in the Treatment of Migraine and Other Headaches. *Springer International Publishing Ebooks*, , pp.1-33.
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2.0 SAFETY – ADVERSE EVENTS

Detailed tables of the safety data collected by the Submitter, though NIPH has supplemented and revised the tables to provide a more adequate overview of the adverse events reported in clinical trials, registry data and other RWD.

Table A 1: Table of previously identified and appraised cluster headache studies from the submission file with safety data added to provide an overview of reported adverse events.

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
Silberstein SD, Mechtler LL, Kudrow DB, et al. *Headache*. 2016;56(8):1317-1332. (11)	ACT1 (Double-blinded phase)	Episodic and chronic cluster headache (US)	nVNS (acute)	Sham	None	nVNS – 2.7% Sham – 20.3% nVNS – 11% Sham - 0% nVNS – 0% Sham – 9.1%	Application Site reactions Lip or facial droop pulling/twitching Dysgeusia/ metallic taste
Goadsby PJ, de Coo IF, Silver N, et al. *Cephalalgia*. 2018;38(5):959-969. (10)	ACT2 (Double-blinded phase)	Episodic and chronic cluster headache (EU)	nVNS (acute)	Sham	None	nVNS – 10% Sham – 4% nVNS – 0% Sham - 2% nVNS – 4% Sham – 2%	Application Site reactions Myalgia Application site paraesthesia
de Coo IF, Marin JCA, Silberstein SD, et al. 30 January 2019. (8)	de Coo et al (2019)	Episodic and chronic cluster headache (pooled analysis of ACT1 and ACT2)	nVNS (acute)	Sham	Based on ACT 1 and ACT 2 reported above		
Gaul C, Diener H-C, Silver N, et al. *Cephalalgia*. 2016;36(6):534-546.	PREVA	Chronic cluster headache (EU)	SoC+nVNS (preventive)	SoC alone	None	nVNS – 16% Sham – 18%	Nervous system disorders

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
(16)						nVNS – 2% Sham - 8% nVNS – 6% Sham – 2% nVNS – 6% Sham – 0%	Infections and infestations Oropharyngeal pain Neck pain
Lai, Y. H., Huang, Y. C., Huang, L. T., Chen, R. M., & Chen, C. *Neuromodulation: Technology at the Neural Interface*. 2020. 23(6), 721-731. (32)	Lai et al. 2020	Episodic and chronic cluster headache and migraine (meta analysis of ACT 1, ACT 2, and PREVA)*	nVNS (acute and preventive)	Sham + SoC (ACT1, ACT2, EVENT, PREMIUM, PRESTO) & SoC (PREVA)	Based on ACT 1, ACT 2 and PREVA reported above		
List of relevant published safety studies							
Tassorelli C, Grazzi L, de Tommaso M, et al. *Neurology*. 2018;91(4):e364-e373. (79)	PRESTO	Episodic migraine (EU)	nVNS (acute)	Sham	None	nVNS – 2.5% Sham – 0.8% nVNS – 0% Sham - 2.4% nVNS – 0% Sham – 2.4%	Application site discomfort Application site erythema Application site pain

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
						nVNS – 1.6% Sham – 4.8% nVNS – 0% Sham – 2.4%	Infections and infestations Nervous system disorders
Silberstein SD, Calhoun AH, Lipton RB, et al. *Neurology*. 2016;87(5):529-538. (80)	EVENT (Randomised phase only)	Chronic migraine (US)	nVNS (preventive)	Sham	None	nVNS – 6% Sham – 3% nVNS – 9% Sham - 10% nVNS – 3% Sham – 3% nVNS – 0% Sham – 7% nVNS – 17% Sham – 6%	Application site discomfort Infections and infestations Oropharyngeal pain Neck pain Facial twitch/pain/ numbness
Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. *Cephalalgia*. 2014;34(12):986-993. (81)	Goadsby et al (2014)	Migraine (US)	nVNS (acute)	N/A	None	nVNS – 3.3% nVNS – 3.3% nVNS – 3.3%	Neck twitch Raspy voice Redness at the device site

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
Diener, H. C., Goadsby, P. J., Ashina, M., Al-Karagholi, M. A. M., Sinclair, A., Mitsikostas, D., ... & Ferrari, M. D. Cephalalgia. 2019. 39(12), 1475-1487 (9)	PREMIUM (Double-blinded period only)	Episodic migraine (EU)	nVNS (preventive)	Sham	nVNS – 1.2% Sham – 0.6% Reported as not adverse device related events	nVNS – 9.5% Sham – 20.4% nVNS – 7.7% Sham - 7% nVNS – 5.3% Sham – 4.1% nVNS – 26.7% Sham – 16.9%	Application site discomfort Dizziness Oropharyngeal pain Nasopharyngitis / influenza
Najib, U., Smith, T., Hindiyeh, N., Saper, J., Nye, B., Ashina, S., ... & Lipton, R. B. *Cephalalgia*. 2022. 0(0) 1–10. (82)	PREMIUM II	Migraine (episodic and chronic)	nVNS	sham	Adverse events not described in detail.		
Natelson, B. H., Stegner, A. J., Lange, G., Khan, S., Blate, M., Sotolongo, A., ... & Helmer, D. A. *Life Sciences*, 2021, 282, 119805. (83)	Natelson et al (2021)	Gulf War Illness (widespread pain incl. headache)	nVNS	sham	1 serious adverse event – chest pain in nVNS group, reported as not device related	nVNS – 38% Sham – 42% nVNS – 38% Sham - 35% nVNS – 15% Sham – 14%	Application site discomfort Muscle spasm / tightness

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
						nVNS – 0% Sham – 21% nVNS – 15% Sham – 0%	Lip or facial droop / quiver Dysgeusia/ metallic taste Tenderness

Abbreviations: nVNS, non-invasive vagus nerve stimulation; SoC, standard of care

*****_The analyses are also based on the studies EVENT, PRESTO and PREMIUM, so this is an error in the submitter's table._

Table A 2: Table of unpublished vagus nerve stimulations studies from the submission file with safety data added to provide an overview of reported adverse events.

Data source	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
Rubenstein Engel E, Blake J, Liebler E. Presented at: 67th AAN Meeting; April 18-25, 2015; Washington, DC. (45)	Rubenstein Engel et al (2015)	Asthma (assessment of cardiovascular AEs) (US)	nVNS	N/A	See description	nVNS – 13.8% nVNS – 3.4% nVNS – 0% nVNS – 0% nVNS – 44.8%	Premature atrial contractions Premature ventricular contractions Atrial arrhythmias Ventricular arrhythmias Benign sinus arrhythmia
NIH. ClinicalTrials.gov. NCT03410628.	NCT03410628	Migraine (pain and allodynia symptoms) (South Africa)	nVNS (acute)	N/A	None reported	nVNS – 4.76%	Diarrhoea

Abbreviations: nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table A 3: Table of included vagus nerve stimulations studies for non-CH treatment from the submission file with safety data added to provide an overview of reported adverse events.

Data source	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
Chaudhry, S. R., Lendvai, I. S., Muhammad, S., Westhofen, P., Kruppenbacher, J., Scheef, L., ... & Kinfe, T. M. *Brain Stimulation.* 2019. 12(3), 643-651. (84)	Chaudry et al (2019)	Refractory migraine (defined as having failed at least four classes of preventive medications)	nVNS	none	None	n= 30 in the study so there are few events reported.	*One device-related adverse event (DAE) was noted for both groups (dysfunction), while in the sham group two non-device-related adverse events occurred (1 cold, 1 worsening of headache requiring changed medication).*
Kamourieh, S., Lagrata, S., & Matharu, M. S. *Journal of Neurology, Neurosurgery & Psychiatry*. 2019. 90(9), 1072-1074. (85)	Kamourieh et al (2019)	Chronic paroxysmal hemicrania	nVNS	none	None	No adverse events reported.	
Chapman, S. J., Helliwell, J. A., Naylor, M., Tassinari, C., Corrigan, N., & Jayne, D. G. Colorectal Disease. 2021. 23(5), 1225-1232. (86)	Chapman et al (2021)	patients undergoing colorectal surgery for malignancy	nVNS	Sham	None	.nVNS – 5.3% Sham – 5.0%	Stimulation pain

Abbreviations: nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table A 4: Table of 'other'vagus nerve stimulation studies from the submission file with safety data added to provide an overview of reported adverse events.

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Serious Adverse Device Events	Adverse events (generally)	Details of Adverse Events
Gottfried-Blackmore, A., Adler, E. P., Fernandez-Becker, N., Clarke, J., Habtezion, A., & Nguyen, L. *Neurogastroenterology & Motility*. 2020. 32(4), e13769. (87)	Gottfried-Blackmore et al. 2019	Idiopathic and diabetic gastroparesis, functional dyspepsia	nVNS	none	None	No adverse events reported.	
Schroeder, C. F., Möller, M., & May, A. *Neurology*. 2019. 93(5), e518-e521. (46)	Schroeder et al. 2019	Healthy subjects	nVNS	No stimulation, Sham I, Sham II	None		No serious adverse events occurred during either nVNS or KOS treatment. The regular gammaCore nVNS device caused tingling sensations, whereas the gammaCore sham device (sham II) caused prickling sensations and transient redness of the skin at the stimulation site.

Abbreviations: nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table A 5: QALY and probability of response comparison between chronic and episodic model.

Parameter	lower boundary	base case value	uppper boundary
Chronic Model			
Utilities responder (SoC Alone)	0.65	**0.72**	0.79
Utility non responder (SoC Alone)	0.39	**0.44**	0.48
Utility responder (GC plus SoC Alone)	0.65	**0.73**	0.80
Utility non responder (GC plus SoC)	0.40	**0.44**	0.49
Probability response (SoC Alone)	2%	**8%**	18%
Probability response (GC plus SoC)	26%	**40%**	55%
Episodic Model			
Utility (GC plus SoC arm)	-	**0.82**	-
Utility (SoC Alone arm)	-	**0.72**	-
Utility Responders (Averaged by response)	-	**0.90**	-
Utility Non-responders (Averaged by noresponse)	-	**0.71**	-
Probability response (SoC Alone)	7%	**15%**	15%
Probability response (GC plus SoC)	24%	**42%**	64%
Probability of immediate failure from GC	0%	**20%**	30%
Probability of response after retraining non responders	30%	**40%**	50%

The utilities values between the responder and non-responder for both gammaCore (GC) and Standard of care (SoC) were interpretated differently **(Table A 5)**. The model approach and structure for episodic cluster headache model was based on different model structure using a decision tree for treatment of acute attacks with time period of 1-year to yield outcomes such as (1) failure to response, (2) non responders and (3) responders (details of which can be found elsewhere, (88)). The non-responders were patients who could experience partial effect of the treatments (1% - 50% responses to the treated attacks) or reduction in the intensity of attacks. However, the non-responders did not necessarily avoid the use of rescue medications. Likewise, the non-responder in the model could be retrained to achieve additional responder, partial responders, or failures. The decision tree model data was extracted from ACT pooled analysis data from meta-analysis (51) for the parameters applied in the base-case. Whereas the chronic model only differentiated between responders and non-responders

and allowed for alternative scenarios using reduced response loss at fixed percentage, constant rate of response loss and no response loss post 2 months. The non-responders in the chronic model (50) study continued to incur costs for abortive treatments and patients who did not respond to gammaCore discontinued the preventative treatment of gammaCore on a 3-month evaluation period.

The utilities for non-responders in the episodic and cluster headache model were not comparable due to the different methodology applied in current model as compared with the episodic model. However, the utility for non-responder in the current model for chronic cluster headaches was lower than the average utility for non-responders in the episodic model. The difference may be due to severity of headaches in the two different groups of patients. The probability of response had different definition in both models, as episodic patients' response to treatment would be decrease in the intensity of pain or attack, whereas the chronic patient's treatment response would be fewer attacks. However, the decision tree model does not assume recurrent events and are applicable for short and fixed time periods. Considering the differences, the probability of response (≥50% response to attacks) around 40% in both models for initial response of gamma Core. Nevertheless, the recurrent events of decrease in response is better captured by the Markov models. Further details about the episodic model are found elsewhere (51).

Table A 6: Variables used in one-way scenario-based deterministic sensitivity analyses

Variable	**Base-case value**	**Range of values**	
Probability of response (≥50% reduction) – SoC	8%	2%	18%
Probability of response – gammaCore	40%	26%	55%
Probability of discontinued response per month for initial responders	31%	16%	54%
zolmitriptan doses per 14 days – SoC responder	0.60	0.10	1.52
sumatriptan doses per 14 days – SoC responder	2.50	1.04	4.59
oxygen doses per 14 days – SoC responder	2.20	0.56	4.94
zolmitriptan doses per 14 days – SoC non responder	1.30	0.45	2.59
sumatriptan doses per 14 days – SoC non responder	7.50	4.88	10.67
oxygen doses per 14 days – SoC non responder	10.80	6.68	15.90
zolmitriptan doses per 14 days – gammaCore responder	0.60	0.10	1.52
sumatriptan doses per 14 days - gammaCore responder	2.50	1.04	4.59
oxygen doses per 14 days – gammaCore responder	2.20	0.56	4.94

Variable	Base-case value	Range of values	
zolmitriptan doses per 14 days – gammaCore non responder (on Tx)	2.50	0.32	6.89
sumatriptan doses per 14 days – gammaCore non responder (on Tx)	4.10	1.00	9.33
oxygen doses per 14 days – gammaCore non responder (on Tx)	11.20	5.45	18.98
zolmitriptan doses per 14 days – gammaCore non responder (baseline)	3.80	0.55	10.13
sumatriptan doses per 14 days – gammaCore non responder (baseline)	4.50	2.07	7.85
oxygen doses per 14 days – gammaCore non responder (baseline)	18.60	9.35	30.98
% using triptans at baseline	73%	56%	87%
% using oxygen at baseline	97%	66%	98%
% of oxygen treatments that are portable	50%	0%	60%
% of sumatriptan treatments that are s.c.	87%	66%	98%
oxygen per unit cost – static	6.28	5.58	6.98
oxygen per unit cost – portable	8.79	7.81	9.77

Table A 7: Variables used in multi-way scenario-based sensitivity analysis

Responder definition	Response loss assumption	Non-responder use assumption
25%	No response loss post month 2	SoC non-responder use from PREVA
25%	No response loss post month 2	gammaCore non-responder use from PREVA
25%	Constant rate of response loss	SoC non-responder use from PREVA
25%	Constant rate of response loss	gammaCore non-responder use from PREVA
25%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
25%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
40%	No response loss post month 2	SoC non-responder use from PREVA
40%	No response loss post month 2	gammaCore non-responder use from PREVA
40%	Constant rate of response loss	SoC non-responder use from PREVA
40%	Constant rate of response loss	gammaCore non-responder use from PREVA
40%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA

Responder definition	Response loss assumption	Non-responder use assumption
40%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
50% using means	No response loss post month 2	SoC non-responder use from PREVA
50% using means	No response loss post month 2	gammaCore non-responder use from PREVA
50% using means	Constant rate of response loss	SoC non-responder use from PREVA
50% using means	Constant rate of response loss	gammaCore non-responder use from PREVA
50% using means	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
50% using means	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
50%	No response loss post month 2	SoC non-responder use from PREVA
50%	No response loss post month 2	gammaCore non-responder use from PREVA
50%	Constant rate of response loss	SoC non-responder use from PREVA
50%	Constant rate of response loss	gammaCore non-responder use from PREVA
50%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
50%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
65%	No response loss post month 2	SoC non-responder use from PREVA
65%	No response loss post month 2	gammaCore non-responder use from PREVA
65%	Constant rate of response loss	SoC non-responder use from PREVA
65%	Constant rate of response loss	gammaCore non-responder use from PREVA
65%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
65%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA

Table A 8: Variable values used in probabilistic sensitivity analysis

Variable	Value	Distribution
Probability of response (≥50% reduction) – SoC	8.3%	Beta
Probability of response – gammaCore (≥50% reduction, using means from each arm)	40%	Beta
Probability of discontinued response per month for initial responders	31%	Normal (coefficient from exponential distribution)
zolmitriptan doses per 14 days – SoC responder	0.60	Gamma
sumatriptan doses per 14 days – SoC responder	2.50	Gamma
oxygen doses per 14 days – SoC responder	2.20	Gamma
zolmitriptan doses per 14 days – SoC non responder	1.30	Gamma
sumatriptan doses per 14 days – SoC non responder	7.50	Gamma
oxygen doses per 14 days – SoC non responder	10.80	Gamma
zolmitriptan doses per 14 days – gammaCore responder	0.6	Gamma
sumatriptan doses per 14 days - gammaCore responder	2.5	Gamma
oxygen doses per 14 days – gammaCore responder	2.2	Gamma
zolmitriptan doses per 14 days – gammaCore non responder (on Tx)	2.5	Gamma
sumatriptan doses per 14 days – gammaCore non responder (on Tx)	4.1	Gamma
oxygen doses per 14 days – gammaCore non responder (on Tx)	11.2	Gamma
zolmitriptan doses per 14 days - gammaCore non responder (baseline)	3.8	Gamma
sumatriptan doses per 14 days - gammaCore non responder (baseline)	4.5	Gamma
oxygen doses per 14 days - gammaCore non responder (baseline)	18.6	Gamma
% using triptans at baseline	73%	Beta
% using oxygen at baseline	97%	Beta
% of oxygen treatments that are portable	50%	Beta
% of sumatriptan treatments that are s.c.	87%	Beta
oxygen per unit cost - static	6.28	Gamma
oxygen per unit cost - portable	8.79	Gamma

Variable	Value	Distribution
Utility score - SoC responder	0.72	Multivariate Normal
Utility score - SoC non responder	0.44	Multivariate Normal
Utility score - gammaCore responder	0.73	Multivariate Normal
Utility score - gammaCore non responder	0.44	Multivariate Normal

From the submission file:

The model is divided into 5 steps, within which the user of the model can make changes to individual input parameters, e.g., to carry out further sensitivity analyses. The modifiable cells / input parameters are highlighted in light blue.

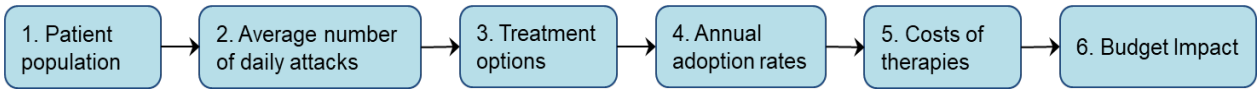

Figure 2: Structure of the budget impact model

Key Assumptions

1*. The present model distinguishes between cCH and eCH, whereby the group of eCH patients is further subdivided. In the model, cCH patients are assumed to treat daily CH attacks with correspondingly modeled acute medications. eCH patients are further divided into 3 groups with an annual cumulative CH episode duration of 3 months, 6 months or 9 months, within which they treat daily CH attacks with correspondingly modeled acute medications. No adjustments are made in the model for non-compliance or potential treatment delays.*

2*. The patient collectives considered only include adult patients above the age of 18. Relevant patient numbers are calculated on the basis of the adult population in Norway.*

3*. The triptan therapies defined in the model can be used up to a maximum of twice a day, in accordance with the safety instructions of the modeled drugs.*

4*. Some data (e.g. responder rate, daily number of attacks) were taken from the results of the PREVA study investigating the impact of gammaCore in chronic CH patients. In the absence of clinical trial data for episodic CH patients, it is assumed that the observed outcomes for cCH also apply to eCH patients (e.g. reduction of medication intake of gammaCore users).*

5*. In the present model, gammaCore is used as a prophylactic therapy and the potentially conservative assumption is made that the use of gammaCore has no impact on the use of other prophylactic therapies. The model therefore does not analyse any differences in the costs of prophylactic treatments.*

***6**. The model is strictly focused on acute medication costs and does not examine potential cost differences caused by potentially reduced outpatient contacts and inpatient stays of gammaCore users.*

***7**. The model does not take into account potential clinical effects arising from adjunctive use as acute therapy for CH attacks. Due to the flat rate costs for a 3-month use of gammaCore considered in the model, however, the acute use is not associated with any additional costs and is therefore implemented in the model on the cost side.*

*Moreover, the main model assumption included that the share of patients that would benefit of gammaCore is assumed to be equal to the responder rate of nVNS patients in the PREVA trial (proportion of pa-tients with ≥50% response to treatment). These are the patients are eligble for long-term use of gammaCore (details can be found elsewhere, appendix, **Section 1.2 Input parameters**)*

1. Patient populations

In the first model step, relevant patient numbers are calculated for the eCH and cCH subgroups, as well as for the whole group of CH patients. Deterministic base case input values (non-modifiable) are provided in orange cells. Alternative values can be entered for the following variables (light-blue cells):

- *Prevalence of cluster headache*
- *Share of patients for whom standard treatment is ineffective or contraindicated*
- *Share of patients who benefit from the use of gammaCore in the long term (responder rate)*
- *Proportion of episodic (and chronic) CH patients*
- *Division of episodic CH patients into three further subgroups with different cumulative annual CH episode durations*

The annual prevalence of diagnosed CH in Norway was recently reported to be 48.6 per 100,000 [22]. However, the authors acknowledge that prior studies in Sweden, Norway and other countries report higher prevalence rates [23, 24]. One reason might be, that studies reporting 1-year prevalence rates of CH systematically underestimate the real prevalence as some patients might not have bouts during the observation period. In addition, diagnosed CH underestimates the true total of affected patients. In a Swedish study, only

four out of nine patients with CH had sought professional help even though they had experienced CH for 6 years on average [24]. For these reasons, it was agreed to use the globally verified and accepted prevalence value of 0.1% in the budget impact model."

For a reliable estimation of the number of patients eligible for gammaCore use, the share of patients for whom standard treatment is ineffective or contraindicated is required. Currently available literature reporting estimates of this share is extremely sparse. In fact, only one reference was found reporting 10% to 15% of all CH patients experiencing unsatisfactory effectiveness or contraindications of SoC therapies [25]. Discussions with international clinical experts and leading headache specialists (incl. those at NICE) revealed that this share is estimated to be around 20%, as used in the budget impact model. The effect of varying this uncertain input between 10% and 30% parameter was evaluated in a corresponding OWSA.

2. Average number of CH attacks

As a second step, the numbers of CH attacks are calculated for eCH and cCH subgroups as well as for the whole patient collective. Alternative values for the average daily attack frequency in the eCH and cCH subgroups can be entered (light-blue cells). The default average daily number of attacks used in the model is 3.5 for both subgroups.

3. SoC treatment Options

The budget impact model considers 3 different comparators for eCH and cCH, each divided into intervention 1 and intervention 2. The definition of each comparator as well as the applicable share of patients treated with each comparator can be varied in the model.

The Norwegian Electronic Medical Handbook's clinical guidelines on headache states that oxygen or triptans should be used for acute treatment of CH [26]. Of the available treatment options for CH, oxygen therapy is always the first choice because of its safety profile. Intervention 1 is therefore oxygen in all cases per default. As intervention 2, various triptan therapies can be selected.

4. gammaCore Annual Adoption Rates

The model assumes almost evenly distributed annual adoption rates of gammaCore over 5 years, which can be manipulated. Alternative adoption rates are investigated in sensitivity analyses.

5. Cost of Treatments

Medication costs were extracted from the website of the Norwegian Medicines Agency (https://www.legemiddelsok.no/) and the lowest cost option was chosen per default. The costs of oxygen therapy had to be calculated separately. The costs of using gammaCore are also given here and all values can be manipulated (e.g. for sensitivity analyses). Calculating cost of oxygen therapy for CH patients depends on a number of inputs with a broad cost range, given the multitude of providers and various sizes of O2 bottles and rental and purchasing schemes. However, as a conservative approach the applied calculation is based solely on the volume of oxygen used and does not include associated costs for:

- ☐ *Renting or purchasing gas bottles*
- ☐ *Necessary demand valves, and*
- ☐ *Non-rebreather masks*

Further assumptions include:

- ☐ *20 minutes per treatment*
- ☐ *12-15L/min flow rate, which results in 240 to 300L of oxygen per treatment*
- ☐ *Oxygen therapy is applied at home in 60%, and outside of the home in 40% of cases*

5.0 Input Parameters for Budget Impact Model

Patient numbers (Input 1)

Patient numbers are estimated using the total number of adult populations obtained from https://www.ssb.no/en/statbank/list/folkemengde/ *and a prevalence estimate of 0.1% of the population. Of these CH patients, another 20% are estimated to represent the share of patients for whom standard treatment is ineffective or contraindicated (23;71).*

Given the fact that nVNS is not effective for all CH patients in whom SoC is ineffective or contraindicated, the share of patients that would benefit of gammaCore was assumed to be equal to the responder rate of nVNS patients in the PREVA trial (proportion of patients with ≥50% response to treatment). These are the patients are eligble for long-term use of gammaCore and will subsequently enter the model calculations.

CH may be episodic (eCH) or chronic (cCH) and can often change between the two types. eCH is defined by attack periods that can last from 7 days to 1 year and are separated by a month-long pain-free period. Episodic headaches often recur predictably during certain times of the year. cCH attack periods are recurrent for more than 1 year, and headaches can be separated by headache-free periods of less than 3 months or may not be separated at all (23). There is currently no reliable evidence on the exact ratio of eCH to cCH patients, but expert poinions indicate an approximate share of 80% of eCH (and 20% of cCH) among all CH patients.

In the budget impact model, eCH patients are further divided into patients with a cumulated total duration of CH episiodes per year of 3, 6, and 9 months in order to accurately calculate the number of CH attacks. In absence of any data on the shares of these patients, 33% was assumed for the 3- and 6-months collective and 34% for the 9-months collective.

Number of CH attacks (Input 2)

The calculation of total amount of CH attacks (that will be treated) assumes 3.5 attacks per day for all CH patients (19). Combining this number with the total number of days with CH attacks per year in each subgroup yields the total number of CH attacks per year that will be treated either with SoC or with SoC + nVNS. Although a figure of 3.5 attacks per day has been used here, the model only calculates with a daily maximum dose of two triptan intakes per day, which is in line with maximum tolerated dose guidelines."

SoC Comparators (Input 3)

There is currently no prospect of a curative treatment for cluster headache. The attainable goal of treatment is total attack cessation or suppression of the headache until the next episode. A more conservative and realistic goal is to shorten the cluster period in eCH and to reduce the severity/frequency in both eCH and cCH. The Norwegian Electronic Medical Handbook's clinical guidelines on headache states that oxygen or triptans should be used for acute treatment of CH (15). Given the advantageous safety-profile of oxygen inhalation, this is usually the first-line acute treatment, followed by second-line subcutaneous sumatriptan, zolmitriptan nasal spray and sumatriptan nasal spray.

The model calculates costs of 3 different comparators consisting of the aforementioned pharmaceuticals. Patient shares allocated to the 3 comparators are based on expert opinion and can modified to analyse their effect in sensitivity analyses."

Treatment Costs (Input 4)

Treatment costs of pharamceuticals are assumed to equal the refund price per dose obtained from https://www.legemiddelsok.no.

The cost of oxygen therapy is uncertain due to the many suppliers and the quantity used per dose. There is a paucity of costing studies available for oxygen. The cost of oxygen treatment was estimated using information from a Norwegian expert in cluster headache. Treatments are assumed to last 20 minutes and consume 240 to 300L of oxygen per treatment assuming a 12-15L/min flow rate. Cost of a refill of 50L of compressed oxygen (1L compressed O2 = 860L O2 gas) are assumed to be 1,000 NOK. Portable oxygen refills, which are smaller and more frequent, are assumed to cost 40% more. The cost/L of oxygen was calculated using this information, ranging from 0.02 NOK to 0.03 NOK per litre.

In the base case scenario (3.5 attacks per day for all CH patients), a patient with episodic cluster headache is assumed to treat 642 attacks annually and to consume 173,325 litres of oxygen. A patient with chronic cluster headache is assumed to treat 1,278 attacks per year, and to consume 344,925 litres of oxygen. Mean cost per home oxygen treatment are 6.28 NOK and 8.79 NOK per portable oxygen treatment.

Mean annual costs of oxygen therapy per eCH patient are therefore 4,676 NOK and 9,305 NOK per cCH patient.

Cost Sharing (Input 5)

Assuming a general co-payment rate of 39% and a maximum total co-payment per patient 2,460 NOK, patient specific out-of-pocket costs and total per patient costs are calulated for eCH patients with a cumulated total duration of CH-episodes of 3, 6, and 9 months, as well as for cCH patients.

The modelled cost sharing between patients and payers assumes that patients do not trigger any other healthcare costs than those of managing CH (SoC medications incl. oxygen and gammaCore). Patients in Norway are reported to have a higher risk of potentially severe medical and psychiatric comorbidities and higher use of opioid analgesics (3). In real world practice, the annual maximum total co-payment of patients (2,460 NOK) will probably already be reached before gammaCore treatment might become relevant. However, in all analysed patient groups (eCH with cumulated total duration of CH-episodes of 3 months, 6 months, 9 months, and in cCH patients with daily attacks) and treatment alternatives (SoC and SoC + gammaCore), the maximum total co-payment will be reached.

Total annual cost per patient

Total annual cost per CH patient (weighted mean) of standard care are 58,772 NOK, 100,718 NOK per cCH patient and 48,284 NOK per eCH patient. The highest share of these costs is attributable to the use of subcutaneous sumatriptan injections as abortive medication for CH attacks (see Feil! Fant ikke referansekilden.).

Table A 9*: Cost of SoC per patient*

Acute therapies	**Avg. total annual costs per CH patient**	**Avg. total annual costs per cCH patient**	**Avg. total annual costs per eCH patient**
Oxygen	3,740.64 NOK	9,304.95 NOK	2,349.56 NOK
Sumatriptan s.c. (Comparator 1)	38,944.95 NOK	64,692.60 NOK	32,508.03 NOK
Zolmitriptan nasal (Comparator 2)	12,197.21 NOK	20,261.15 NOK	10,181.23 NOK
Sumatriptan nasal (Comparator 3)	*3,888.73 NOK*	*6,459.69 NOK*	*3,245.99 NOK*
sum	*58,771.53 NOK*	*100,718.39 NOK*	*48,284.81 NOK*

Total annual cost per CH patient (weighted mean) of standard care + gammaCore therapy are 54,022 NOK, 72,059 NOK per cCH patient and 49,512 NOK per eCH patient. The highest share of these costs are attributable to the use of gammaCore *(see **Table A 9**).*

Table A 10: Cost of SoC + gammaCore per patient

Acute therapies	**Avg. total annual costs per CH patient**	**Avg. total annual costs per cCH patient**	**Avg. total annual costs per eCH patient**
Oxygen	1,608.47 NOK	4,001.13 NOK	1,010.31 NOK
Sumatriptan s.c. (Comparator 1)	16,746.33 NOK	27,817.82 NOK	13,978.45 NOK
Zolmitriptan nasal (Comparator 2)	5,244.80 NOK	8,712.29 NOK	4,377.93 NOK
Sumatriptan nasal (Comparator 3)	1,672.16 NOK	2,777.67 NOK	1,395.78 NOK
gammaCore	28,750.00 NOK	28,750.00 NOK	28,750.00 NOK

sum	54,021.76 NOK	72,058.91 NOK	49,512.47 NOK

Uncertainty in the budget impact model

"Uncertainty is assessed in the budget impact model by a one-way sensitivity analysis (OWSA). The following uncertain input parameters were varied and their effect on the total budget impact was evaluated:"

- *Prevalence of Cluster Headache (CH)*
- *Share of eCH patients*
- *Avg. daily number of CH attacks per eCH patient*
- *Avg. daily number of CH attacks per cCH patient*
- *Share of intolerant patients or unsatisfactory effectiveness of standard of care*
- *Responder rate (proportion of patients with ≥50% response to treatment)*
- *Costs (net price) per 3 months of gammaCore therapy*
- *Reduction of acute medication associated with gammaCore therapy*
- *Annual costs of oxygen therapy per eCH patient*
- *Annual costs of oxygen therapy per cCH patient*
- *Adoption rate*

Table A 11: Parameters used in OWSA provides an overview on the parameters and the applied values used in the

Parameter	**lower boundary**	**base case value**	**uppper boundary**
Prevalence of Cluster Headache (CH)	0.0486%	0.1000%	0.1500%
Share of eCH patients	75%	80%	85%
Avg. daily number of CH attacks per eCH patient	2	3.5	5
Avg. daily number of CH attacks per cCH patient	2	3.5	5
Share of intolerant patients or unsatisfactory effectiveness of standard of care	10%	20%	30%
Responder rate (proportion of patients with ≥50% response to treatment)	35%	40%	50%
Costs (net price) per 3 months of gammaCore therapy	4,600.00 NOK	5,750.00 NOK	6,900.00 NOK
Reduction of acute medication associated with gammaCore therapy	47%	57%	67%
Annual costs of oxygen therapy per eCH patient	5,739.04 NOK	8,198.64 NOK	10,658.23 NOK

Annual costs of oxygen therapy per cCH patient	11,420.98 NOK	16,315.69 NOK	21,210.40 NOK
Adoption rate			
Year 0	0%	0%	0%
Year 1	7%	20%	30%
Year 2	11%	40%	50%
Year 3	15%	60%	70%
Year 4	19%	80%	90%
Year 5	25%	95%	99%

Table A 12: Cost results of the scenario analyses

Responder definition	Response loss assumption	Non-responder use assumption	gammaCore plus SoC	SoC	Difference
25%	No response loss post month 2	SoC non-responder use from PREVA	30,827 NOK	32,355 NOK	-1,528 NOK
25%	No response loss post month 2	gammaCore non-responder use from PREVA	29,089 NOK	32,355 NOK	-3,266 NOK
25%	Constant rate of response loss	SoC non-responder use from PREVA	30,942 NOK	32,355 NOK	-1,413 NOK
25%	Constant rate of response loss	gammaCore non-responder use from PREVA	28,179 NOK	32,355 NOK	-4,176 NOK
25%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	30,963 NOK	32,355 NOK	-1,393 NOK
25%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	28,238 NOK	32,355 NOK	-4,117 NOK

40%	No response loss post month 2	SoC non-responder use from PREVA	30,153 NOK	32,355 NOK	-2,202 NOK
40%	No response loss post month 2	gammaCore non-responder use from PREVA	24,942 NOK	32,355 NOK	-7,413 NOK
40%	Constant rate of response loss	SoC non-responder use from PREVA	29,693 NOK	32,355 NOK	-2,662 NOK
40%	Constant rate of response loss	gammaCore non-responder use from PREVA	22,415 NOK	32,355 NOK	-9,940 NOK
40%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	29,736 NOK	32,355 NOK	-2,619 NOK
40%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	22,537 NOK	32,355 NOK	-9,818 NOK
50% using means	No response loss post month 2	SoC non-responder use from PREVA	32,339 NOK	32,355 NOK	-16 NOK
50% using means	No response loss post month 2	gammaCore non-responder use from PREVA	32,339 NOK	32,355 NOK	-16 NOK
50% using means	Constant rate of response loss	SoC non-responder use from PREVA	31,761 NOK	32,355 NOK	-594 NOK
50% using means	Constant rate of response loss	gammaCore non-responder use from PREVA	31,761 NOK	32,355 NOK	-594 NOK
50% using means	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	31,802 NOK	32,355 NOK	-554 NOK

50% using means	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	31,802 NOK	32,355 NOK	-554 NOK
50%	No response loss post month 2	SoC non-responder use from PREVA	29,494 NOK	32,355 NOK	-2,861 NOK
50%	No response loss post month 2	gammaCore non-responder use from PREVA	27,668 NOK	32,355 NOK	-4,688 NOK
50%	Constant rate of response loss	SoC non-responder use from PREVA	29,630 NOK	32,355 NOK	-2,725 NOK
50%	Constant rate of response loss	gammaCore non-responder use from PREVA	27,222 NOK	32,355 NOK	-5,133 NOK
50%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	29,646 NOK	32,355 NOK	-2,709 NOK
50%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	27,260 NOK	32,355 NOK	-5,096 NOK
65%	No response loss post month 2	SoC non-responder use from PREVA	28,686 NOK	32,355 NOK	-3,669 NOK
65%	No response loss post month 2	gammaCore non-responder use from PREVA	29,237 NOK	32,355 NOK	-3,118 NOK
65%	Constant rate of response loss	SoC non-responder use from PREVA	29,151 NOK	32,355 NOK	-3,205 NOK
65%	Constant rate of response loss	gammaCore non-responder use from PREVA	29,795 NOK	32,355 NOK	-2,560 NOK

65%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	29,145 NOK	32,355 NOK	-3,210 NOK
65%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	29,786 NOK	32,355 NOK	-2,569 NOK
25%	No response loss post month 2	SoC non-responder use from PREVA	30,827 NOK	32,355 NOK	-1,528 NOK
40%	No response loss post month 2	SoC non-responder use from PREVA	30,153 NOK	32,355 NOK	-2,202 NOK
50%	No response loss post month 2	SoC non-responder use from PREVA	29,494 NOK	32,355 NOK	-2,861 NOK
65%	No response loss post month 2	SoC non-responder use from PREVA	28,686 NOK	32,355 NOK	-3,669 NOK

Date	Correspondence
21. jun 2021	Commissioning date
29. jun. 2021	Contact with submitter established
13. sep. 2021	Pre-submission meeting held and intent to submit is confirmed
15. sep. 2021	Contacted the Secretariat for experts
30. sep. 2021	One expert from Helse Sør-Øst (south-eastern Norway) Regional Health Authority recruited
01. okt. 2021	One expert from Helse Midt (central Norway) Regional Health Authority recruited
5. okt. 2021	Both experts contacted for conflict of interest (CoI) form
15. okt. 2021	Received one form
19. okt. 2021	Reminder sent to the other expert (midt)
26. okt. 2021	Reminder two sent to expert (midt)
10. nov. 2011	Reminder three sent expert (midt)
18. nov. 2021	Expert (midt) declared a conflict of interest (excluded from the project) and named new possible expert
18. nov. 2021	Informed Secretariate and requested a replacement
24. nov. 2021	Replacement recruited, and CoI form sent and received
27. jan. 2022	Query to submitter about timeline/status for submission
8. feb. 2022	Informed experts of the delay
18. feb. 2022	Submitter contacted NIPH for verification of approach for the analysis
17. jun.2022	NIPH received submission
21. jun. 2022	NIPH contacted patient organisation
1. jul. 2022	**Project start date (valid submission confirmed)**
19. sep. 2022	NIPH received completed form from patient representative
27. sep. 2022	Digital meeting, clinical experts and NIPH
9. nov 2022	Digital meeting, submitter and NIPH for additional information and clarifications
16. may 2023	NIPH shares draft report with clinical experts for comments
23. jun 2023	NIPH shares drat report with submitter
6. jul 2023	Final report approved at NIPH
6. jul 2023	Report submitted to Commissioning Forum
6. jul 2023	**Project end date**

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