Health Technology Assessment (HTA) Protocol

Stakeholder Feedback on the Migraine HTA Protocol

Contents

Preface

This document details the authors' responses to stakeholder feedback on the protocol for an HTA on *calcitonin gene-related peptide antagonists for the prevention of migraine.*

The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by stakeholder, in alphabetical order.

Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; subsequent comments instruct the reader to cite the original response.

1. Curafutura

Domain	Comment	Author Response
1. Comments on research question	1. Die Forschungsfrage ist prägnant formuliert und korrekt, insbesondere der Gruppen - interne Vergleich ist wünschenswert. Die HTA key questions sind korrekt gewählt. Bei den Kostenberechnungen müssen die aktuell in der Schweiz geltenden Preismodelle der SL als Parameter verwendet werden (wichtig auch für die Berechnung des budget impacts). Man muss berücksichtigen (6.1 Additional Questions), dass in der Schweiz keine Rückerstattung vorgesehen ist bei einem Präparatewechsel. 2. Hinsichtlich Population wird ein wichtiger Aspekt ausgelassen: Wie will man mit multimorbiden Personen umgehen oder mit Personen, bei denen Kontraindikationen bei einem Comparator bestehen?	1. Thank you for the feedback. These comments have been noted and will be considered during the evaluation of the evidence during the HTA phase. Spezialitätenliste pricing will be used for economic and budget impact analyses. 2. Where evidence is available to assess multimorbid people or contraindications in the populations of interest, this issue will be addressed during the HTA phase.
2. Comments on PICO	Population: Hier wäre ein Stratifizierung der Population hinsichtlich Nebendiganosen, welche relevant sind für die Therapie der zu untersuchenden Krankheiten, prüfenswert (z.b. sind Betablocker contraindiziert bei Asthmatikern). Bei diesen Populationen könnte zum Teil die Standardtherapie gar nie angewendet werden.	Where evidence is available to assess contraindications in the populations of interest, this issue will be addressed during the HTA phase.
3. Comments on database and search strategy	Search - Umfang korrekt mit diesen drei Datenbanken abgedeckt Datenfilter korrekt Zeitrahmen korrekt Klar definierte Kriterien	Thank you for the feedback.
4. Comments on data extraction, analysis and synthesis	Datenextraktion korrekt, inklusive Datenselektion Analayse der Evidenz-Qualität ist korrekt, verwendet GRADE-Kriterien Oekonomische Evaluation ist korrekt Outcome-Messung ist korrekt, Discount - rate korrekt	Thank you for the feedback.

2. Eli Lilly (Suisse) SA

Domain	Comment	Author Response
1. Comments on research question	1. Lilly expresses concerns about the procedure. The FOPH is tackling an HTA on innovative medicinal products that are still researched. CGRPs have been developed specifically for migraine while this is not the case for the oral treatments, the R&D and innovation efforts should be factored in. There are no legal basis in Switz for a cost-effectiveness threshold value. It is therefore not possible to conclude whether a medicinal product is cost-effective. It should be noted that the BAG assessed the Emgality WZW criteria for inclusion in the SL in 2021. 2. Other HTA institutions already pointed out that the clinical heterogeneity of CGRPs and oral intervention trials makes it difficult to compare these agents and need to be done with caution. The HTA process could result in inappropriate recommendations negatively impacting patient care. There is evidence that even when treated with currently oral medications, patients with migraine continue to experience unacceptable levels of disability.	1. Thank you for the feedback. We understand that CGRP antagonists are relatively new technologies. This HTA will seek to identify all relevant literature that has been published that directly compares CGRP antagonists to the relevant SoC comparators to ensure an informed decision can be made by policymakers. Results will be compared against a range of cost-effectiveness values in acceptability curves and a hypothetical willingness-to-pay threshold of CHF100,000. 2. Noted, we will ensure appropriate methods are used and appropriate conclusions are drawn to ensure an informed decision can be made by policymakers.
2. Comments on PICO	1. The protocol assumes that all CGRPs are the same, although clinical data proves the opposite: the 4 CGRPs have different molecular properties, show different study data, efficacy and tolerability profiles. Due to the extremely heterogeneous data and patient populations, the planned analysis is medically and technically questionable. A multi-HTA requires consistent and comparable study data of the individual interventions, which is not the case for the CGRPs and the oral interventions. How the HTA plans to cope with heterogeneity? 2. The considered direct costs will have to be defined. Further indirect costs like the productivity loss should be included as well the impact of migraine on QoL, physical and mental health, and social and family life. It is not clear what prices will be used: CGRPs price has been determined for use in patients not eligible for at least two oral therapies. 3. On the basis of the 3rd line price no statement about use in 'all-comers' 1st line patients can be made.	1. The authors are aware that the 4 CGRP antagonists are all unique. To clarify, each CGRP antagonist will be assessed separately against the included comparators, rather than in combination. Further detail has been added to the HTA Protocol to ensure this is clear to all readers. The comparability of included trials will be assessed during the HTA phase. Appropriate methods will be implemented to ensure clinical diversity/variation is judged, with meta-analyses only conducted in groups of studies which are sufficiently homogenous in terms of population, comparator, intervention and outcomes to provide meaningful summaries. Where heterogeneity is uncovered during meta-analysis, steps will be taken to investigate the cause and conduct further analyses (e.g. sensitivity analyses) where appropriate. 2. Items for direct costing will be identified during the evaluation once key sources of evidence have been reviewed. They will be translated to Swiss costs using Spezialitätenliste, TARMED, Swiss diagnosis-related group (DRG) unit costs. Indirect costs will not be considered as this is outside the scope of this review. 3. The HTA is seeking to include a population as close to the current Swiss usage as possible. As such, "all comers" are not a key population. If evidence exists in patients using CGRP antagonists as a 3rd line

		treatment, that will be used. Any findings from the review will be interpreted in light of the applicability to the Swiss context and we will appropriately consider evidence applicability when forming conclusions.
3. Comments on database and search strategy	1. RWE should be considered as it supplements the clinical value of treatments in a real life setting where there is diversity in physician practice and patient types. We would suggest including observational studies. 2. Studies on Patient preference and on the device should be included. 3. It must be ensured that the latest guidelines and publications are taken into account. As new data on CGRPs is constantly generated the exclusion of posters and abstracts from international congresses neglects possible relevant data. 4. It is not clear how the HTA will take into account that the evidence on the efficacy, HRQoL and safety/tolerability of oral treatments in patients for whom prior preventive treatments have failed is very limited. 5. Please consider to include interictal burden (MIBS), work productivity and activity impairment (WPAI), Total Pain Burden (TPB) scale results.	1. Thank you for the feedback. Based on the hierarchical selection process noted in section 7.4 (study design) of the HTA Protocol, RCTs will be considered for inclusion in the first instance. However, where comparative data is unavailable, real-world evidence including observational studies will be included to assess the HTA domains of efficacy/effectiveness/safety and costs/budget impact/cost-effectiveness. 2. Studies on patient preference will not be considered for inclusion, as the domains of ethical, legal, social and organizational aspects will not be assessed during the HTA phase. 3. Thank you for the feedback. The latest guidelines will be summarised as part of the HTA phase, addressed as 'additional issues'. However, posters and conference abstracts will not be considered for inclusion as these publications are not peer-reviewed and are often published as original articles shortly after each international congress/meeting. 4. Evidence on the efficacy, HRQoL and safety/tolerability of oral treatments in patients for whom prior preventive treatments have failed will be considered during the HTA phase. Where evidence is limited, a wider inclusion of evidence will be considered, and comments will be made on applicability issues. 5. Total pain burden (TPB) will be added to the HTA Protocol as a measure of health-related quality of life. This outcome will be extracted where reported across the included literature. However, migraine interictal burden (MIBS) and work productivity and activity impairment (WPAI) will not be included as an outcome, as they are outside the scope of this review.
4. Comments on data extraction, analysis and synthesis	1. A statement about "cost effectiveness" cannot be made as cost effectiveness criteria are not defined in Switzerland. The BAG assessed the WZW criteria of Emgality as well two other CGRPs for SL inclusion less than twelve months ago and the use of CGRPs has already been significantly reduced by restricting the reimbursement to those patients "not eligible for at least two SoC therapies". Consequently, an HTA seems not justifiable. 2. The protocol intend to determine the impact of a disinvestment of the CGRPs. By adding this detail, the scoping pre-concludes that the result of the HTA will be unfavorable for CGRPs. Please clarify what is meant with	1. As per response to comment *2.1.1.*, results will be compared against a range of cost-effectiveness values in acceptability curves and a hypothetical willingness-to-pay threshold of CHF100,000. 2. As stated in the policy question, "Of particular interest are the financial consequences of a positive reimbursement decision, provided the drugs are efficacious and safe." Unfortunately, an error in language was used to describe the methods of the budget impact analysis. This has since been changed to "Budget impact analysis will be conducted to examine the financial implications for different reimbursement scenarios".

	"different disinvestment scenarios". Please change to "What is the potential budget impact of xxxx". 3. Market Share (MS) and prices assumptions significantly influence BIA. Please comment on what basis MS and price will be determined for both use in all comers and 3rd line.	3. Prices will be sourced from the Spezialitätenliste, and sensitivity analyses included. MS data will be derived from the FOPH.

3. Interpharma

Domain	Comment	Author Response
1. Comments on research question	1. The protocol assumes equality between CGPRs, although they have different molecular properties, efficacy and tolerability profiles and heterogeneity in clinical trials. How will the differences be addressed? 2. How will assessment reports by other authorities be considered? 3. Section 6: will the analysis be conducted for the overall and reimbursed population in all HTA key questions? 4. Indirect costs (72-98% migraine related cost) need to be included in the evaluation. 5. Placebo was defined as scheme comparator, but is not included in economical questions, why? 6. Section 6.1: Which population will be assessed in questions 11/12: overall population and/or subgroups 1, 2? Define the term "different class of CGRP antagonist". 7. To consider: the current oral migraine preventive medicines were not developed for use in migraine prevention, many are used off-label and lack robust clinical evidence. They are associated with a range of AEs, DDIs and often require special monitoring.	1. See response to comment *2.2.1.* 2. Prior published HTA reports will be searched for and summarised in this HTA where evidence is identified. 3. Yes, the overall and reimbursed population will be assessed separately where evidence is available to inform these analyses (as noted in section 7.4.3 of the HTA Protocol, two or more RCTs are required to perform meta-analysis on each outcome). 4. Indirect costs will not be considered as this is outside the scope of this review. 5. A sensitivity analysis could possibly be presented for placebo, if included in key trials outlined in the clinical evidence section. 6. Thank you for the feedback. Both the overall population and reimbursed population will be considered separately for each additional question. This has been changed in the HTA Protocol to ensure clarity. Additionally, 'different classes of CGRP antagonists' has now been changed to 'erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®), and eptinezumab (Vyepti®)' for consistency with the other HTA key questions. 7. Adverse events for all comparator treatments will be considered and reported where comparative evidence is available. Data on special monitoring will likely be captured in the economics section.
2. Comments on PICO	1. Population: BAG limitations include 3 additional subgroups to consider: Patients who discontinued ≥2 prevention therapies due to AEs, cannot otherwise be treated due to contraindications, after combination of one failed treatment and one discontinuation. 2. The study populations of the CGRPs trials are very different to the oral intervention population. Indirect comparisons lead to impermissible mixing of study populations. 3. Also, there is limited QoL, safety, tolerability data for oral interventions after failure of prior preventive treatments. 4. Comparators: Placebo was defined as comparator and needs to be the comparator in all 10 HTA key questions and the 2 additional questions (overall population/subpopulations 1, 2).	1. As noted in Appendix 9.1 of the HTA Protocol and included in the subgroups for analysis, those who have been pre-treated with at least 2 prophylactic therapies or in those who have contraindications or responded insufficiently will be considered where evidence is available across the literature. 2. Indirect comparisons will not be conducted in this HTA report. Additional detail has been added to the HTA Protocol to ensure this is clear to all readers. Additionally, where RCT evidence is available which compares CGRP antagonists to SoC treatments, the populations will be comparable within these studies based on the studies selected inclusion/exclusion criteria.

	5. Outcome: The protocol does not include indirect cost of migraine. Migraine affects mostly working people and leads to substantial indirect cost, which needs to be included in the cost-utility analysis to do justice to the burden of migraine for patients and society.	3. Where QoL and safety data is presented in the literature comparing CGRP antagonists to SoC treatments, this will be assessed during the HTA phase. 4. As discussed with the FOPH, placebo has been included for all clinical HTA key questions which assess the efficacy, effectiveness and safety of these technologies. However, will not be included as a comparator for the economic HTA key questions (Question 5-10). Additionally, placebo has not been added as a comparator to the 'Additional questions' (Question 11-12) as this question directly seeks to understand whether 'switching' could be of value to those who have not responded to initial treatment with either of the 4 CGRP antagonists. 5. Indirect costs will not be considered as this is outside the scope of this review.
3. Comments on database and search strategy	1. The HTA-protocol tackles innovative medicines that are not yet fully researched. How will the constantly generated new data be handled, seeing that any literature research is outdated with a few months? 2. Also the exclusion of conference proceedings from the search neglects possibly relevant data in this fast evolving field. 3. The large body of available Real-world Evidence, which substantiates the effectiveness and tolerability of CGRPs needs to be included in the analysis. Consider inclusion of observational and patient preference studies. 4. Apply transparent search algorithms, some might only have been "established" by Cochrane. 5. It is planned to include only studies based in WHO-Mortality-Stratum A countries. As this is a Swiss HTA please ensure that at least all trials will be included that have been accepted by Swissmedic (regulatory approval) and BAG (WZW for SL listing) previously. 6. Secure comparability of the trials to ensure reliable results without methodically unfair comparisons	1. Thank you for the feedback. This is a common issue when conducting any HTA, unfortunately a living review is outside the scope for this project. If required, the report can be updated if substantial new evidence is published after the search dates. 2. See response to comment *2.3.3.* 3. See response to comment 2*.3.1.* and *2.3.2.* 4. The authors believe that transparent search techniques have been described in this HTA Protocol, with appropriate references/evidence provided to justify the decisions that have been described for implementation during the HTA phase. 5. All relevant clinical trials accepted by Swissmedic and BAG will be included if they meet the appropriate selection criteria. The study selection criteria of WHO-Mortality-Stratum A countries has been removed from the HTA Protocol. 6. Noted. The comparability of included trials will be assessed during the HTA phase. Appropriate methods will be implemented to ensure clinical diversity/variation is judged, with meta-analyses only conducted in groups of studies which are sufficiently homogenous in terms of population, comparator, intervention and outcomes to provide meaningful summaries. Where heterogeneity is uncovered during meta-analysis, steps will be taken to investigate the cause and conduct further analyses (e.g. sensitivity analyses) where appropriate.

4. Comments on data extraction, analysis and synthesis	1. Please define the specific criteria to assess the clinical important difference for dichotomous and continuous outcomes 2. Please provide a list of all direct costs that will be considered. There is concern that indirect costs like the productivity loss are not included in the model. 3. The core problem of the HTA appears to be the "cross-class" HTA, the complexity of the assessment increases to such an extent that ultimately no valid statements and results can be generated. 4. This HTA does not intended to determine the individual budget impact of the four CGRPs in an unbiased manner, the protocol intends to determine the impact of a disinvestment of the CGRPs («Budget impact analysis will be conducted to examine the financial implications for different disinvestment scenarios»). The HTA protocol not only pre-concludes, that the result of the HTA will be unfavorable for CGRPs, but also translates the pre-concluded outcome into a consequence and decision: Disinvestment.	1. MCID will be further detailed during the HTA phase. For each outcome, published thresholds will be sought via systematic/targeted searches to inform the interpretation of results. 2. See response to comment *2.2.2.* 3. See response to comment *2.2.1.* 4. See response to comment *2.4.2.*

4. Interpharma: Opinion

Domain	Comment	Author Response
General comment	Mit dem vorliegenden HTA-Protokoll analysiert das BAG innovative Medikamente zur Migräneprophylaxe. Literatur Recherchen sind durch die rasch voranschreitende Forschung in diesem Gebiet innerhalb kurzer Zeit veraltet. Im HTA-Protokoll ist nicht ersichtlich, wie die laufend neu erscheinenden Daten integriert werden.	See response to comment *3.3.1.*
Comment 1	Gemäss dem vorliegenden HTA-Protokoll sind 72-98% der durch Migräne verursachten Kosten auf indirekte Kosten zurückzuführen (z.B. Arbeits- und Produktivitätsausfall). Dennoch werden die mit Migräne verbundenen indirekten Kosten im HTA nicht berücksichtigt. Um dem Anspruch der gesamtgesellschaftlichen Betrachtung gerecht zu werden, müssen die indirekten Kosten zwingend in die Analyse eingeschlossen werden.	Indirect costs will not be considered as this is outside the scope of this review.
Comment 2	Fokus auf Desinvestment bei einer neuen, hoch-innovativen Produktklasse, zumal einer der im HTA-Protokoll eingeschlossenen Wirkstoffe noch nicht in die SL-Liste aufgenommen wurde.	See response to comment *2.4.2.*
Comment 3	Die Durchführung und Analyse von Multi-HTAs (verschiedene Wirkstoffe in einem HTA) erfordert konsistente und vergleichbare Studiendaten zu den individuellen Interventionen. Diese Voraussetzung ist im Fall der cGRPs und vor allem der gebräuchlichen Standardtherapien nicht erfüllt.	See response to comment *2.2.1.*
Comment 4	Mit Blick auf die sehr heterogene Datenlage bezüglich Patientenpopulationen, erscheint die im Rahmen des HTA geplante Analyse medizinisch und technisch fragwürdig. Die zahlreichen Annahmen, welche zwangsläufig getroffen werden müssen, lassen Zweifel an der Relevanz der resultierenden Aussagen aufkommen.	See response to comment *2.2.1.*
Comment 5	Der finanzielle Einfluss der cGRPs auf das Schweizer Gesundheitswesen wurde durch die Einschränkung der Vergütung auf Patienten «die auf mindestens zwei Standardtherapien nicht angesprochen haben» (SL Limitatio) bereits stark reduziert. Ein Desinvestment oder weitere Einschränkungen im Bereich der dringend benötigten, innovativen Therapien zur Migräneprophylaxe, würden zu einer Verlagerung auf Art. 71 KVV Gesuche führen, was mit dem Prinzip des für alle Patienten gleichberechtigten Zuganges zu innovativen Therapien nicht kompatibel ist.	See response to comment *2.4.2.*

5. Migraine Action

Domain	Comment	Author Response
1. Comments on research question	1. Study methodology, definition of study population and evaluating instruments have changed considerably, the lack of common denominator might hamper the proposed comparative evaluation of SOC versus CGRP mAb. 2. It remains unclear how to overcome the lack of long-term studies due to SOC adherence problems, major differences inclusion/exclusion criteria, only partially covering cost-efficacy evaluating instruments, non-differentiation between migraine with and without aura or CM with or without medication over use, unequal distribution and or non-evaluation of concomitant use of other preventive treatments or influencing coping strategies (e.g. aerobic exercise) 3. Suggestion: Direct SOC vs CGRP mAb RCT using a validated questionnaire (covering major areas e.g., Eurolight questionnaire) over different time periods (up to 3 years). In order to save MD consulting time, the tool should be validated for patient self-reporting. 4. Efficacy of a re-uptake of initial treatment in case of relapse.	1. Noted. The literature that is available will be used to compare CGRP antagonists to SoC treatments. 2. All available evidence that is identified will be analysed where appropriate. Additionally, where RCT evidence is available which compares CGRP antagonists to SoC treatments, the populations will be comparable within these studies based on the studies selected inclusion/exclusion criteria. Furthermore, where feasible, additional subgroup analyses will be conducted to investigate possible treatment-effect modifiers, secondary disorders or other noteworthy features (as outlined in section 7.4.3.3 of the HTA Protocol). 3. Unfortunately, conducting an RCT comparing CGRP antagonists to SoC treatments is not feasible. 4. Efficacy of re-uptake of initial treatment in case of relapse is outside the scope of this review.
2. Comments on PICO	1. Although it remains unclear how to obtain the answers the following prerequisites are important: 2. P: - Similar exclusion/inclusion criteria (e.g. limitation of CGPR mAb or contraindications of SOC) - Subanalysis of patients with CM with and without MOH - Consideration of: existing comorbidities in the population (Caponnetto,JHP 2021), concomitant coping strategies, trigger factors (hormonal trigger) - Comparative diagnostic and screening test, validated burden/impact questionnaires 3. C: head-to -head comparison of different prophylactic treatments also versus atogepant /rimagepant 4. O: - Long-term costs (comorbidities, Chronification) after nonadherence to SOC	1. Thank you for the feedback. 2. - As mentioned above, where RCT evidence is available which compares CGRP antagonists to SoC treatments, the population will be comparable within these studies based on the studies selected inclusion/exclusion criteria. - Where appropriate, select subgroup analyses will be conducted as defined in section 7.4.3.3 of the HTA Protocol. - See response to comment *1.1.2.* - As described in section 5 (PICO) of the HTA Protocol, appropriate diagnostic and screening tests/questionnaires will be extracted. 3. Unfortunately, the inclusion of gepants as a comparator is outside the scope of this review as these drugs are not reimbursed in Switzerland. 4. - The costs of comorbidities and chronification could be included if these outcomes are identified in the clinical evidence and can be translated to QALYs (The outcome in the summary table). Issues such as length of follow-up of key trials may prevent their inclusion.

	- MIDAS and accompanying symptoms e.g. nausea, vomiting, photophobia, and phonophobia) - PI-MBS (patient-centered approach for identifying and measuring burden of migraine that matter most to each patient)	- MIDAS is currently included as an outcome measure of interest and will be extracted and analyses where reported (if appropriate to do so). - PI-MBS is not included as an outcome of interest as this outcome will not provide relevant evidence to answer the policy question.
3. Comments on database and search strategy	1. The defined timeline, although enhancing equal comparison of diagnostic / screening criteria, might miss important data from standard of care investigations. 2. The modern (more patient burden and impact centered) evaluation parameters of the cost effectiveness of therapeutical interventions differ in many aspects to those a decade apart (see sections above).	1. As this HTA is only focused on direct comparisons made between CGRP antagonists and SoC treatments, the authors are certain that relevant direct evidence will be captured through the literature search, as the 4 CGRP antagonists received global approval between 2018-2021 with pre-marketing data/trials published in the few years before. 2. As per comment above.
4. Comments on data extraction, analysis and synthesis	No further comments (see sections above)	N/A

6. Santésuisse

Domain	Comment	Author Response
1. Comments on research question	1. With the selected "Policy Question", the main focus is on the financial consequences in the context of a continued positive reimbursement, which is understandable in principle, but leads to a too narrow focus. Equally to be considered and brought into focus is a possible delisting or a further restriction of the limit if WZW is not fulfilled. 2. The important examination of legal, social, ethical and organisational issues is missing. 3. The reflections on the research questions can be understood. The distinction between patients with chronic and episodic migraine is supported. 4. The scoping is not very detailed and only rudimentarily describes the procedure in the planned HTA. It is therefore not possible to assess at the present time whether it makes sense to carry out a full HTA.	1. Thank you for the feedback. These points have been noted. 2. The domains of ethical, legal, social and organizational aspects will not be assessed during the HTA phase. 3. Thank you for the feedback. 4. The 'scoping report' phase previously conducted as part of FOPH led HTAs is no longer preformed. The authors believe that the HTA methods have been sufficiently described.
2. Comments on PICO	1. The relevant comparative therapies are taken into account. Combinations of comparator therapies should also be considered in the study selection. It is not understandable why such combinations are even excluded as comparators. 2. Under the sub-aspect of safety, the comparators listed under efficacy must also be compared in any case (e.g. possible side effects when discontinuing the comparators). 3. Non-pharmacological therapeutic alternatives are not mentioned, although they are often used prior to a pharmacological therapy. These should be included since they have an important impact on a successful therapy that should not be underestimated.	1. Noted. Combination therapies with more than one comparator has since been removed as an exclusion criteria for study selection. 2. As this study focuses solely on the direct comparison of CGRP antagonists against SoC treatments, where safety data is presented for a relevant SoC treatments within this comparison, it will be analysed. 3. Unfortunately, non-pharmacological therapeutic alternatives are outside the scope of this review to be included as a comparator intervention. However, during data extraction concomitant and prior treatments/intervention will be of interest (section 7.4.1 of the HTA Protocol).
3. Comments on database and search strategy	1. Even if overlaps can be expected from searching several databases, more than three databases should be used for a literature search in the context of a full-HTA. Normally, the databases Cochrane Library, Embase, GoogleScholar, PubMed as well as ClinicalTrials.gov are considered. The latter, in particular, should be taken into account in order to include ongoing studies and information on expected data. 2. It should also be examined whether consulting guidelines can provide further information on relevant literature and framework conditions (duration of short-term use etc.).	1. As noted in section 7.1 and 7.2 of the HTA Protocol – PubMed, Embase, Cochrane Library, EconLit, the National Health Service Economic Evaluation Database (NHS EED) and the cost-effectiveness analysis (CEA) Registry hosted by Tufts Medical Centre, ClinicalTrials.gov, EU Clinical Trials Registry and the International Network of Agencies for Health Technology Assessment (INAHTA) will be searched. 2. The latest guidelines will be summarised as part of the HTA phase, addressed as 'additional issues'.

	3. Furthermore, the three languages of Switzerland (D, I, F) should at least be taken into account in the research in order to reflect regionality, especially in the question of ethical, social and legal aspects (which, as mentioned at the beginning, still need to be supplemented). 4. It is incomprehensible why the search period is limited to 10 years (for non-RCT even 5 years; comparators longer on the market).	5. Studies published in English, French, German and Italian will be considered for inclusion. This has since been added to section 7.3 (study selection) of the HTA Protocol. However, the domains of ethical, legal, social and organizational aspects will not be assessed during the HTA phase. 3. See response to comment *5.3.1.*
4. Comments on data extraction, analysis and synthesis	1. It can be assumed that CGRP antagonists are reimbursed to different extents in other countries. The analysis and synthesis should therefore be supplemented with information on the possible limitations in other countries (number of migraine days, discontinuation attempts, etc.) of the CGRP antagonists and included in the comparison. 2. It is stated that supplementary subgroup analyses will be carried out where possible and meaningful. We consider it very important that possible subgroups according to the current limitation are also included. 3. The economic assessment within the framework of a cost-utility analysis is supported.	1. Unfortunately, the focus of this report is the reimbursement criteria in Switzerland and analyses will not be supplemented with information from other countries. However, this issue will be partially addressed when looking at the latest guidelines on the use of CGRP antagonists. 2. Noted. As stated in the methods, analyses will be conducted to address the current limitation (i.e. reimbursement criteria) in Switzerland where evidence is identified. 3. Thank you for the feedback.

7. Swiss Headache Society (SKG) and Swiss Neurological Society (SNG)

Domain	Comment	Author Response
1. Comments on research question	1. How antagonising CGRP compares to other standard of care methods in migraine prophylaxis is an interesting and unstudied question. Conducting head-to-head trials is the only direct unquestionable way of obtaining conclusive answers to this question. Indirect analyses as proposed here rely on the tacit assumption that different study populations can be compared (Kim et al., Overview of methods for comparing the efficacies of drugs in the absence of head-to-head clinical trial data. Br J Pharmacol, 2014). Lack of significant differences in variables characterising study populations is not proof of absence of differences between these populations. Beyond the issue of study populations but relevant to the comparison is a significant difference in age of the studies that will be compared. Indeed, study methodology has changed and improved considerably over the past decades, with standard of care studies being much more dated than the very recent ones studying CGRP antagonisation.	1. See response to comments *3.2.2.*, *3.3.6.* and *5.3.1.*
2. Comments on PICO	1. The definition of subgroups partially reflects the current limitation in Switzerland but is contrary to inclusion criteria in pivotal studies leading to authorisation of CGRP antagonisation. If meant to reflect the limitation, it should also include SOC intolerance or contra-indication. 2. Placebo is not a suitable comparator as it is not applicable in clinical practice. If meant to reflect the current limitation, the suitable comparator of CGRP antagonisation with >50% response is SOC in a subgroup with intolerance or absent or insufficient response to SOC, in essence absence of effective treatment in high disease-burden migraine. If conducted this way, cost-effectiveness will be of interest and relevant but it is unclear how the data will be obtained for answering this question. 3. Comparison between different anti-CGRP medications is currently without relevance. Indication for switching between different anti-CGRP options lies in individual, not group efficacy.	1. Noted. The authors are aware that subgroup 1 and 2 (refer to section 5 - PICO of the HTA Protocol) may be substantially different to the populations included in pivotal clinical trials. This is the reason for inclusion of a broad episodic and chronic migraine population (population 1 and 2 [refer to section 5 – PICO of the HTA Protocol) in order to capture all relevant information. 2. Agree. Placebo is not a suitable comparator if not applicable in clinical practice. We will discuss the clinical relevance of these studies (if identified) and put the findings in context. For the economics, this will be included in a sensitivity analysis, if possible. 3. Noted. However, if evidence is identified which directly compares different CGRP antagonists, this data will be analysed to assess efficacy/effectiveness and safety.
3. Comments on database and search strategy	A time limit of 10 years for RCTs will miss the majority of data on standard of care approaches. It is also unlikely that data used for analyzing cost-effectiveness will be comparable for studies several decades apart.	See response to comment *5.3.1.*
4. Comments on data extraction,	No comments beyond the above.	N/A

analysis and synthesis		

8. Teva Pharma AG: Opinion

Domain	Comment	Author Response
General comment/ Allgemeiner Kommentar	Wir möchten darauf hinweisen, dass die CGRP-Antikörper noch nicht lange auf dem Schweizer Markt erhältlich sind. Aus diesem Grund ist die Datenlage bzgl. gewisser Themen noch unvollständig. Unter anderem sind Langzeit-Wirksamkeits- sowie Sicherheitsdaten für die CGRP-Antikörper noch ausstehend und Vyepti (Eptinezumab) ist noch nicht in der Spezialitätenliste aufgeführt. Es werden fortlaufend neue Daten generiert, welche zu einem späteren Zeitpunkt für die HTA-Analyse relevant sein können.	Thank you for the feedback. These points have been noted. Note: Since 1 May 2022 Eptinezumab (Vyepti®) is provisionally listed on the Spezialitätenliste until 30 April 2024.
Comment 1	1. Kapitel 5 – PICO outcomes: • Clinical outcomes Wir schlagen vor, einen weiteren, wichtigen clinical outcome hinzuzufügen: AE's leading to discontinuation. Begründung: Unerwünschte Arzneimittelwirkungen (UAW's) sowie fehlende Wirksamkeit sind Hauptgründe für einen Therapieabbruch. Vor allem auf herkömmliche orale Migräneprophylaktika eingestellte Migränepatienten nehmen je nach Situation UAW's im beträchtlichem Mass in Kauf – oft führen diese zu Therapieabbrüchen. (Sacco et al. 2019) Dieser Aspekt sollte unseres Erachtens im HTA berücksichtigt werden. 2. Kapitel 5 – PICO outcomes: • Health-economic outcomes Im Rahmen des HTA werden nur direkte Kosten evaluiert. Wir möchten darauf hinweisen, dass Migräne vor allem die berufstätige Bevölkerung betrifft. Die indirekten Kosten, welche für die Gesellschaft durch Beeinträchtigung u.a. aufgrund Absenzen am Arbeitsplatz entstehen, sind beachtlich und müssen evaluiert werden.	1. Thank you for the feedback. Adverse events leading to discontinuation has been added to the PICO (section 5 of the HTA Protocol). 2. Indirect costs will not be considered as this is outside the scope of this review. Note: Since 1 May 2022 Eptinezumab (Vyepti®) is provisionally listed on the Spezialitätenliste until 30 April 2024.
Comment 2	1. Kapitel 6 – HTA key questions: • What is the budget impact of CGRP antagonists Das Budget impact ist limitiert durch strenge Erstattungskriterien. Aktuell sind CGRP-Antikörper nur für sehr kranke Migränepatienten zugänglich. Wir stellen den Zeitpunkt der Analyse in Frage, um Fragen zu Budget impact ausschliessend beantworten zu können. Unseres Erachtens sind noch nicht genügend Daten erhältlich, um das Budget Impact zu evaluieren. Zum aktuellen Zeitpunkt sind die CGRP-Antikörper erst 2-3 Jahre in der Schweiz erhältlich und zudem wurde die Markteinführung durch die globale Pandemie beeinträchtigt.	1. Agree, the global pandemic is an issue. Sensitivity analyses will be presented. 2. These additional questions will not be added to the HTA Protocol as they are outside the scope of this review. However, it is important to note that AEs upon discontinuation of CGRP antagonists will be captured if reported.

	2. Kapitel 6 – HTA key questions: • 6.1. Additional questions Wir schlagen folgende zusätzliche Fragen vor: - Wann ist der ideale Zeitpunkt für die Beurteilung des Ansprechens auf die anti-CGRP-Behandlung? - Was ist die ideale Dauer einer anti-CGRP-Therapie? - Welches sind die Folgen für die Patienten durch die erzwungenen Therapieunterbrüche zur Beurteilung der Wirksamkeit zum Beispiel nach einem Jahr Behandlung?	
Comment 3	1. Kapitel 7 – Methodologie: • 7.5.1.4. Outcome Wir schlagen vor, folgende Methoden zur Beurteilung von Quality of Life (QoL) zu berücksichtigen: MIDAS (Migraine Disability Assessment) sowie WPAI (Work Productivity and Activity Impairment). 2. Kapitel 7 – Methodologie: • Proposed methodology - Perspective - Table 3 Summary of the proposed economic evaluation methodology Migräne ist eine chronische Krankheit und deshalb schlagen wir einen längeren Zeithorizont als 10 Jahre vor. Es könnte sogar ein lebenslanger Zeithorizont untersucht werden. Zudem sind Adhärenz und Therapieabbrüche unseres Erachtens wichtige Themen und sollten im angewendeten Modell berücksichtigt werden. Es gibt keine Angaben zu der Zykluslänge, welche eine wichtige Information darstellt.	1. As noted in the PICO (section 5 of the HTA Protocol), MIDAS is currently included to assess QoL. However, WPAI will not be included as an outcome as it is outside the scope of this review (relates to indirect costs which will not be assessed in this HTA). 2. The model will present a range of time frames in sensitivity analyses, which possibly could extend to lifetime. Adherence and treatment discontinuations will be included in the model and cycle length will be determined following review of the clinical evidence.