HTA Protocol

Stakeholder feedback

Title	The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma
Technology	tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®)
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1. Preface

According to the predefined HTA process which can be consulted on www.bag.admin.ch/hta, the FOPH conducts a stakeholder consultation on the HTA protocol. A stakeholder consultation was held from 24. 01. 2023 to 21. 02.2023 for the HTA-protocol on "The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma". The protocol was submitted to stakeholders, such as health insurance associations, patient organisations, healthcare professional associations, professional societies, industry associations or other interested parties. Stakeholders were notified of the protocol 20 working days in advance and were given 20 working days to comment on the protocol.

This document details the authors' responses to stakeholder feedback on the HTA protocol for a Health Technology Assessment (HTA) on "The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma". The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by comment boxes and stakeholder, in alphabetical order. Responses provided in red are the original responses provided by stakeholders, and the black text underneath each red response is an English translation of the original (red) comment.

2. List of invited stakeholders for consultation

The following stakeholders have been invited on 24. 01. 2023 to submit feedback regarding the HTA protocol:

- ACSI - Associazione dei consumatrici e consumatori della Svizzera Italiana
- BSV - Bundesamt für Sozialversicherung, Invalidenversicherung
- curafutura - Die innovativen Krankenversicherer
- DVSP - Dachverband Schweizerischer Patientenstellen
- FMH - Verbindung der Schweizer Ärztinnen und Ärzte
- FRC - Fédération romande des consommateurs
- GDK - Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren
- Gilead Sciences Switzerland
- GSASA - Schweizerischer Verein der Amts- und Spitalapotheker
- H+ - Die Spitäler der Schweiz
- Intergenerika - Swiss Generics and Biosimilars

- Interpharma - Verband der forschenden pharmazeutischen Firmen der Schweiz
- Konsumentenforum
- Krebsliga Schweiz
- lymphome.ch - patientennetz schweiz
- Novartis Pharma Schweiz AG
- MTK - Medizinaltarif-Kommission
- Onkologiepflege Schweiz
- Pädiatrie Schweiz
- pharmaSuisse - Schweizerischer Apothekerverband
- PUE - Preisüberwachung
- SAKK - Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
- SAMW - Schweizerische Akademie der Medizinischen Wissenschaften
- santésuisse - Die Schweizer Krankenversicherer
- SAPhW - Schweizerische Akademie der Pharmazeutischen Wissenschaften
- SBK - ASI - Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner
- SGMO - Schweizerische Gesellschaft für Medizinische Onkologie
- SGPMR - Schweizerische Gesellschaft für Palliative Medizin, Pflege und Begleitung
- SGV - Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte
- SKS - Stiftung für Konsumentenschutz
- SPO - Patientenschutz
- SPOG - Schweizerische Pädiatrische Onkologie Gruppe
- sQmh - Schweizerische Gesellschaft für Qualitätsmanagement im Gesundheitswesen
- SVBG/FSAS - Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen
- VIPS - Vereinigung Pharmafirmen in der Schweiz

3. List of stakeholders who submitted feedback

The following stakeholders have submitted a feedback form within the stakeholder consultation round:

- Curafutura
- Gilead Sciences Switzerland Sàrl
- Interpharma
- Lymphome.ch Patientennetz Schweiz
- Novartis Pharma Schweiz AG
- Santésuisse
- Swiss Pediatric Oncology Group(SPOG) and Swiss Society of Pediatric Hematology and Oncology(SSPHO)

4. Stakeholder feedback

4.1 Comments regarding the research question

The following comments have been submitted by stakeholders regarding the research question of the HTA-protocol “The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma”.

Comment no.	Stakeholder	Stakeholder comment	Authors’ response
1.1	Curafutura	1. CAR-T - Therapie aufgrund des diesbezüglichen Eintrags in Anhang 1 KLV per se eine Pflichtleistung ist. Da das BAG die CAR-T - Therapie als ärztliche Leistung einstuft, muss jegliche CAR - T - Therapie, ob das Transfusionsprodukt in einem vergleichbaren Gesundheitssystem zugelassen ist oder nicht, unter dem Aspekt der Pflichtleistungsvermutung, welche dem KVG zugrunde liegt, beurteilt werden. Da es schwierig sein wird für den Vertrauensarzt, die Wirksamkeit und Zweckmässigkeit einer solchen Therapie, in einer Situation, wo eine zugelassene Alternative meist fehlt, als nicht gegeben einzustufen, ist die Betrachtung von spezifischen Indikationen für CAR-T - Produkte im Rahmen eines HTA ein theoretisches Unterfangen ohne praktische Auswirkungen auf die tägliche Anwendung dieser Methoden, da der generelle Eintrag in der KLV die spezifische Nennung dieser Indikationen in der KLV übersteuert. --------- 1. CAR-T therapy is per se a mandatory service due to the relevant entry in Appendix 1 KLV. Since the BAG classifies CAR-T therapy as a medical service, any CAR-T therapy, whether the transfusion product is approved	1. This comment raises questions about the principle of trust, respectively the entry in Annex 1 of the Health Insurance Benefits Ordinance (KLV) and the examination of the service by the medical officers and cannot be answered with this HTA.

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		in a comparable healthcare system or not, must be assessed from the point of view of the assumption of mandatory performance on which the KVG is based. Since it will be difficult for the medical examiner to classify the effectiveness and usefulness of such a therapy as not given in a situation where an approved alternative is usually missing, the consideration of specific indications for CAR-T products in the context of an HTA is a must theoretical undertaking without practical effects on the daily application of these methods, since the general entry in the KLV overrides the specific mention of these indications in the KLV.	
1.2	Gilead Sciences Switzerland Sàrl	Gilead macht neben generellen Bemerkungen (vgl. Ziff. 1 bis 11 unseres Schreibens vom 21.2.2023) auch einen eingehenden Kommentar zur Forschungsfrage (vgl. Ziff. 12 bis 22 unseres Schreibens vom 21.2.2023). Infolge der nicht nachvollziehbaren Zeichenbeschränkung verweisen wir auf unser Schreiben und wir verlangen vom BAG die Berücksichtigung der generellen Bemerkungen und unseres Kommentars. --- In addition to general comments (cf. Sections 1 to 11 of our letter of February 21, 2023), Gilead also makes a detailed comment on the research question (cf. Sections 12 to 22 of our letter of February 21, 2023). As a result of the incomprehensible character limit, we refer to our letter and we demand that the BAG consider the general remarks and our comment. 1. No multi-HTA with multiple CART therapies in one HTA - The HTA protocol assumes that all CAR Ts are the same, although clinical & real-world data proves the opposite: CAR T is a highly complex and individualized therapy. The implementation and analysis of multi-HTAs (several different active ingredients in one HTA) requires consistent and comparable study data on the individual interventions and comparative	1. No changes made. The analysis plan for the HTA will review the different active ingredients (Tisa-cel and Axi-cel) separately. None of the analyses will combine the two active ingredients. 2. As the research questions indicate, the analyses will separate the marketing authorisation (e.g. Axi-cel for treating DLBL or PMBCL). A sentence has been added to the executive summary, and footnote has been added to the PICO tables to make this clearer. 3. Presentation of results using the ICER/ICUR is the standard approach for cost-effectiveness analyses. Authors acknowledge the lack of a supported threshold in the Swiss context. ICUR results will be presented as a function of WTP. 4. Confidential tariffs for the CAR T products will not be used in the HTA (i.e. will remain confidential). The draft HTA report is submitted to all stakeholders including the marketing authorization holders for consultation. Subsequently, the HTA report is finalized and published on the FOPH website together with the comments of the stakeholders and the authors'

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		therapies. This requirement is not met in this HTA proposal. In countries with HTA institutions, each CAR T product was usually assessed separately (that is confirmed by most of the listed economic evidence in the appendix of the HTA protocol). The clinical heterogeneity of CAR T products and trials makes it difficult to compare these products and needs to be done with caution. The HTA process could result in inappropriate recommendations negatively impacting patient care and access. A multi-HTA requires consistent and comparable study data of the individual interventions, which is not the case for CAR T products. Therefore, a separation of axi-cel from tisa-cel research questions is requested/needed. 2. HTA protocol title is unclear and mixing indications of both products not according to marketing authorization (Axi-cel is indicated in DLBCL/PMBCL). A single HTA per product per indication is required. 3. There is no cost-effectiveness threshold value in Switzerland. As part of the planned economic evaluation (7.3 Economic evaluation methodology), Life Years (LY) and Quality- Adjusted Life Years (QALYs) and the Incremental Cost-Effectiveness Ratio (ICER) are aimed for as results. It is therefore not possible to conclude whether a medicinal product is cost- effective in Switzerland. 4. Confidential net price agreements have enabled reimbursement of CAR T cell therapies in Switzerland and other countries. In the case of HTA reports, the confidentiality of the prices must be maintained in order not to jeopardize the market access for patients in Switzerland. We suggest that the FOPH should consider providing the HTA results to the license holders before publication of the draft and final report to others so that the license holder company may assert any business secrets.	responses to the stakeholders' comments. 5. A healthcare payer perspective on costs will be taken as this is the perspective of relevance to the decision-maker. 6. The assessment of the effectiveness and safety of CAR T cell therapy will not be based on the one conducted by Swissmedic. To ensure the applicability of the HTA results to the Swiss reimbursement system, only *de novo* analyses will be conducted. The additional research questions have been removed; they are included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis). 7. The additional research questions have been removed; they are included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis). 8. The additional research questions have been removed; they are included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis). 9. "Dose" has been replaced with "dosage concentration", and is included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis). 10. It is understood that this may not be the same for every patient. The additional research question has been removed, and is included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-

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		5. Societal costs (direct non-medicinal and indirect costs) of DLBCL are potentially material vs direct medicinal costs. We would like to highlight the importance of widening the analysis beyond the health care payer perspective to capture the benefit of this highly innovative therapy sufficiently. 6. Clinical benefit already evaluated by regulatory entities: Axi-cel is approved by Swissmedic, EMA, FDA etc. & recommended in many guidelines (e.g., NCCN, DGHO/S3 etc.) for treatment of 2L+ DLBCL with clinical data based on Phase 3 RCT vs SOC; for 3L+ DLBCL with indirect comparison to a historical cohort (SCHOLAR-1), therefore clinical benefit and safety profile has already been reviewed by the relevant regulatory authorities. As part of the marketing authorization approval process, questions regarding efficacy and safety were assessed in detail by Swissmedic. In addition, only small patient numbers are to be expected for the additional medical questions under point 5.1, which do not allow any meaningful statements. Therefore, the additional questions under 5.1 should be deleted. 7. Additional questions should be carefully assessed, e.g., "affected by the type / number of prior stem cell transplantations (i.e., autologous, allogeneic) the patients received?" is not relevant due to 2L+ CAR T. Please comment how this will be addressed and why do you believe this is relevant for this HTA. 8. Pre-medication questions (incl. those only for axi-cel) are not relevant and should be evaluated if relevant in a clinical study and not in this HTA. 9. The dose of axi-cel for all patients in DLBCL/PMBCL is the same. The	analysis). 11. As above. Confidential tariffs for the CAR T products will not be used in the HTA (i.e. will remain confidential). If available, current market share data will be considered as part of the analysis.

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		corresponding research question is therefore irrelevant. 10. The pre-medication of axi-cel for all patients in DLBCL/PMBCL is the same. The corresponding research question is therefore irrelevant. 11. Market share (MS) and price assumptions significantly influence Budget Impact Analysis. The confidentiality of the prices must be maintained in order not to jeopardize the market access for patients in Switzerland. The current share and trend in DLBCL in the Swiss CART registry in favor of axi-cel must be considered.	
1.3	Interpharma	1. Im Rahmen der geplanten wirtschaftlichen Beurteilung (7.3 Economic evaluation methodology) werden als Ergebnisse Life Years (LY), Quality- Adjusted Life Years (QALYs) und die Incremental Cost-Effectiveness Ratio (ICER) angestrebt. Für die damit verbundenen Schwellenwerte zur Beurteilung der Kosteneffektivität fehlen gesellschaftlich und politisch breit abgestützte Rahmenbedingungen als Grundlage. 2. Bei CAR T handelt es sich um eine hochkomplexe und individualisierte Therapie. Die Durchführung und Analyse von Multi-HTAs (mehrere verschiedene Wirkstoffe in einem HTA) erfordert konsistente und vergleichbare Studiendaten zu den individuellen Interventionen und Vergleichstherapien. Diese Voraussetzung ist im vorliegenden HTA nicht gegeben. In anderen Ländern wurde jedes CAR T Produkt jeweils konsequent separat beurteilt. 3. Vertrauliche Nettopreisvereinbarungen haben die Rückerstattung von CAR T Zelltherapien ermöglicht. Im Rahmen des vorliegenden HTA-Protokolls und dem nachfolgenden Bericht muss die Vertraulichkeit der Preise gewahrt bleiben, um den Marktzugang von Patienten in der Schweiz nicht zu gefährden.	1. Presentation of results using an incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR) is the standard approach in cost-effectiveness analysis. We acknowledge the lack of a supported threshold in the Swiss context. ICUR results will be presented as a function of willingness-to-pay (WTP). 2. The analysis plan for the HTA will review the different active ingredients (Tisa-cel and Axi-cel) separately. None of the analyses will combine the two active ingredients. 3. Confidential tariffs for the CAR T products in Switzerland will not be used in the HTA (i.e. will remain confidential). An external price will be used, and sensitivity analysis in relation to the CAR T product cost undertaken. This will include one-way deterministic sensitivity analysis (DSA) as well as an exploration of the required product price for the ICUR to meet various threshold values. 4. A healthcare payer perspective on costs will be taken as this is the perspective of relevance to the decision-maker. 5. The assessment of the effectiveness and safety of CAR T cell therapy will not be based on the one conducted by Swissmedic. To ensure the applicability of the HTA results to the Swiss

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		4. Eine Reduzierung auf die Payor-Perspektive erfasst den Nutzen dieser hochinnovativen Therapie nicht ausreichend. Hierzu sollten auch nicht- medizinische und indirekte Kosten berücksichtigt werden. 5. Die durch Swissmedic im Rahmen des Zulassungsverfahrens vorgenommene eingehende Beurteilung der Wirksamkeit und Sicherheit der CAR T Zelltherapie sollte als Basis für das vorliegende HTA herangezogen werden. Zudem sind bei den zusätzlichen medizinischen Fragen unte-r Punkt 5.1 nur kleine Patientenzahlen zu erwarten, die keine aussagekräftigen Aussagen ermöglichen. Die zusätzlichen Fragen unter 5.1 sind daher zu streichen, da diese besser im Rahmen von klinischen Studien evaluiert werden. -------- 1. As part of the planned economic evaluation (7.3 Economic evaluation methodology), Life Years (LY), Quality-Adjusted Life Years (QALYs) and the Incremental Cost-Effectiveness Ratio (ICER) are the intended results. There is a lack of socially and politically broadly supported framework conditions as a basis for the associated threshold values for assessing cost-effectiveness. 2. CAR T is a highly complex and individualized therapy. The implementation and analysis of multi-HTAs (several different active ingredients in one HTA) requires consistent and comparable study data on the individual interventions and comparative therapies. This requirement is not met in the present HTA. In other countries, each CAR T product was consistently assessed separately. 3. Confidential net price agreements have enabled reimbursement of CAR T cell therapies. In the context of the present HTA protocol and the following report, the confidentiality of the prices must be preserved in	reimbursement system, only *de novo* analyses will be conducted. The additional research questions have been removed; they are included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis).

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		order not to jeopardize the market access of patients in Switzerland. 4. A reduction to the payor perspective does not adequately capture the benefit of this highly innovative therapy. To this end, non-medical and indirect costs should also be taken into account. 5. The detailed assessment of the effectiveness and safety of the CAR T cell therapy carried out by Swissmedic as part of the approval process should be used as the basis for this HTA. In addition, only small patient numbers are to be expected for the additional medical questions under point 5.1, which do not allow any meaningful statements. The additional questions below 5.1 should therefore be deleted, as these are better evaluated in the context of clinical studies.	
1.4	Lymphome.ch Patientennetz Schweiz	1. Die Forschungsfrage ist ausführlich dargelegt. Das Ziel der HTA-Fragestellung klar. --------- 1. The research question is explained in detail. The aim of the HTA question is clear.	1. Thank you for your feedback. No action required.
1.5	Novartis Pharma Schweiz AG	*Wir verweisen auf unsere separate Stellungnahme vom 21. Februar 2023.* 1. Uns erschliesst sich nicht, wieso lediglich die zwei CAR-T Zelltherapien Kymriah® und Yescarta® in dem HTA Protokoll evaluiert werden sollen. Die Anwendung von CAR-T Zelltherapien fällt zum aktuellen Zeitpunkt unter die Pflichtleistungsvermutung und ist demnach unter dem Vertrauensprinzip für ärztliche Leistungen zu betrachten. Folglich müssten alle CAR- T Zelltherapien mit einer Zulassung durch Swissmedic durch ein HTA evaluiert werden, um eine Ungleichbehandlung zu vermeiden. 2. Im Abschnitt 1 (Policy Question) wird beschrieben, dass im	1. In this HTA, two CAR T cell therapies listed as "under evaluation" in Annex 1 of the Health Insurance Benefits Ordinance are investigated. This HTA is therefore part of the overall evaluation of these two CAR T cell therapies according to the evaluation concept. The evaluation concept was approved by all stakeholders involved. 2. As the policy question specifies; CAR T therapies are provisionally listed in Annex 1 of the Health Insurance Benefits Ordinance 1. The HTA is needed to inform future reimbursement decisions using contemporary, best available, evidence. 3. As above. A healthcare payer perspective on costs will be taken

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		Generellen HTAs bestehende Kontroversen einer Technologie adressieren. Die CAR-T Zelltherapien wurden durch Swissmedic im Rahmen des Zulassungsverfahren hinsichtlich Wirksamkeit und Sicherheit eingehend beurteilt und unbefristet zugelassen. In der Policy Question wird nicht adressiert in welchem Bereich Kontroversen bestehen. Der Einsatz erfolgt heute basierend auf der klinischen Evidenz der Wirksamkeit & Sicherheit entsprechend der Marktzulassung, d.h. hier sind die Kriterien der Wirksamkeit und Zweckmässigkeit erfüllt. Bei Nichterfüllung eines der WZW Kriterien erfolgt keine Kostenübernahme durch den Krankenversicherer. Advanced Therapy Medicinal Products (ATMPs) wie die CAR-T Zelltherapien werden von der EMA als "groundbreaking new opportunities for the treatment of disease" gesehen. 3. Aus unserer Sicht eignet sich die Perspektive des vorliegenden HTA Protokolls und damit auch der Policy Question nicht, um dem innovativen Charakter der CAR-T Zelltherapie gerecht zu werden. Durch die Reduzierung auf die «payer perspective» wird der Nutzen der Therapien nicht ausreichend erfasst. Darüber hinaus sollen «…ethical, legal, social and organisation issues» evaluiert werden. Hierzu benötigt es einen Wechsel der Perspektive und die Berücksichtigung weiterer Parameter wie nicht-medizinische und indirekte Kosten. Diese sind bei der Kosteneffektivitätsanalyse (CEA) als auch bei der Budget Impact (BI) zu berücksichtigen. 4. Die zusätzlichen Fragestellungen im Abschnitt 5.1 (Additional questions) sind rein klinischer Natur und aus unserer Sicht nicht durch ein HTA zu evaluieren. Ergebnisse aus den Zulassungsstudien und Real World Evidence (RWE) Daten können	as this is the perspective of relevance to the decision-maker. 4. The additional research questions have been removed; they are included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis).

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		lediglich deskriptiv wiedergegeben werden. Um fundierte Kenntnisse zu den zusätzlichen Fragestellungen zu erlangen müssen diese im Rahmen von kontrollierten Studien evaluiert werden. Daher sind die zusätzlichen Fragen unter Abschnitt 5.1 zu streichen. ---------- *We refer to our separate statement of February 21, 2023.* 1. We do not understand why only the two CAR-T cell therapies Kymriah® and Yescarta® should be evaluated in the HTA protocol. The use of CAR-T cell therapies is currently subject to the presumption of compulsory performance and is therefore to be considered under the principle of trust for medical services. Consequently, all CAR-T cell therapies approved by Swissmedic would have to be evaluated by an HTA in order to avoid unequal treatment. 2. Section 1 (Policy Question) describes how, in general, HTAs address existing controversies about a technology. The CAR-T cell therapies were assessed in detail by Swissmedic as part of the approval process in terms of efficacy and safety and approved for an unlimited period. The Policy Question does not address the area in which there is controversy. It is used today based on the clinical evidence of effectiveness and safety in accordance with the market approval, i.e. the criteria of effectiveness and appropriateness are met here. If one of the WZW criteria is not met, the health insurer will not assume the costs. Advanced Therapy Medicinal Products (ATMPs) such as CAR-T cell therapies are seen by the EMA as "groundbreaking new opportunities for the treatment of disease". 3. From our point of view, the perspective of the present HTA protocol and	

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		thus also the policy question is not suitable to do justice to the innovative character of CAR-T cell therapy. Due to the reduction to the «payer perspective», the benefits of the therapies are not adequately recorded. In addition, «...ethical, legal, social and organization issues» are to be evaluated. This requires a change of perspective and the consideration of other parameters such as non-medical and indirect costs. These must be taken into account in the cost-effectiveness analysis (CEA) as well as in the budget impact (BI). 4. The additional questions in Section 5.1 (Additional questions) are of a purely clinical nature and, in our view, should not be evaluated by an HTA. Results from the approval studies and Real World Evidence (RWE) data can only be presented descriptively. In order to gain in-depth knowledge of the additional questions, these must be evaluated in controlled studies. Therefore, the additional questions under Section 5.1 should be deleted.	
1.6	Santésuisse	1. In addition to the research questions mentioned above, the two CAR-T therapies (axi-cel, tisa-cel) will also be compared with each other in DLBCL with regard to safety / side effects, efficacy and cost-effectiveness. Of crucial importance is also the question of whether the safety and efficacy of CAR-T treatments differ between patient groups (e.g. subgroups / patient characteristics, ECOG, predictive factors, etc.) or between treatment regimens (e.g. pre-therapies / SCT, bridging, lymphodepleting chemotherapy, etc.) and follow-up therapy (incl. ICU stays).	1. The analyses will not compare the two CAR-T therapies (axi-cel, tisa-cel) to each other in DLBCL. Potential effect modifiers (e.g. prior treatment, pre-medication, dose, etc.) that could impact a treatment effect and a patient's outcome will be explored using subgroup analyses. These effect modifiers and analyses have been specified *a priori* in order to prevent bias from impacting the results.
1.7	Swiss Pediatric Oncology Group(SPOG) and	1. Die Forschungsfrage dreht sich darum, was als Comparator herangezogen wird, d.h. was ist die Standard of care Behandlung, mit der sich CAR-T vergleichen muss. Heute würden wir als Standard of	1. No changes made. The challenge of clearly defining the comparator for this HTA is acknowledged and will continue to be of relevance throughout the HTA process. The choice of

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	Swiss Society of Pediatric Hematology and Oncology(SSPHO)	care beim 2. Rezidiv oder Rezidiv nach SZT (=Indikation CAR-T) eine Immuntherapie, plus Chemo plus SZT ansehen. 2. Eine randomis. Studie könnte hier Klärung bringen, ist aber ethisch nicht zu rechtfertigen. Hinzu kommt, dass sich in der jüngsten Zeit die CAR-T Therapie in etwa bei 50% der Patienten lediglich als "Bridge-to-SCT" herausstellte. 3. Für die Entscheidung SZT post CAR wird neben dem Response auch die Genetik der Leukämie herangezogen. Die Genetik wird in der Forschungsfrage nicht berücksichtigt. Alle erwähnten Zusatzfragen sind in der Indikation päd ALL überflüssig: Alle Patienten erhielten bisher die Standard-Konditionierung mit Fludarabin/Endoxan. Alle Patienten erhalten Antihistaminika iv und die Dosierung ist gemäss Fachinfo erfolgt. Einfluss Dosis auf Outcome nur prospektiv erheben. --- 1. The research question revolves around what is used as a comparator, i.e. what is the standard of care treatment that CAR-T has to compare itself to. Today we would consider immunotherapy plus chemo plus SCT as the standard of care for the second recurrence or recurrence after SCT (=indication CAR-T). 2. A random study could clarify this, but it cannot be ethically justified. In addition, the CAR-T therapy has recently turned out to be only a "bridge-to-SCT" in about 50% of the patients. 3. In addition to the response, the genetics of the leukemia are also used to decide SZT post CAR. Genetics are not considered in the research question. All the additional questions mentioned are superfluous in the indication of ped ALL: all patients have received the standard conditioning with fludarabine/endoxan. All patients receive	comparator listed in the HTA has been based on available clinical practice guidelines, noting that there may be divergence from these guidelines in practice. 2. No changes made. Thank you for offering this feedback, it is noted. 3. No changes made. Stem cell treatment post CAR T is beyond the scope of this HTA and protocol. The additional research questions have been removed; they are included in section 6.5.4 subgroup and sensitivity analysis only (i.e. to investigate possible causes of heterogeneity in the meta-analysis).

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		antihistamines iv and the dosage is according to the specialist information. Influence of dose on outcome should only be recorded prospectively.	

4.2 Comments regarding the PICO

The following comments have been submitted by stakeholders regarding the PICO of the HTA-protocol "The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma".

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2.1	Curafutura	1. Die Zeitspanne, welche hier bei der bALL betrachtet wird, hat medizinisch neben der CAR-T - Therapie andere potente Therapien (Blinotumumab, Inotuzumab) hervorgebracht, welche die Chemotherapie verdrängt haben bei der Behandlung des Rezidivs. Deshalb sollte man klar beschreiben im PICO, was als "Standardtherapie" betrachtet wird, respektive man sollte dies differenzieren. 2. Diese Bemerkung gilt auch für das DLBCL/PMBCL, da es auch hier im Falle eines Rezidivs keine wirkliche Standardtherapie gibt, sondern eine Vielzahl (mindestens 213 zugelassene Kombinationen) von Therapien mit einem unterschiedlichen Wirkungsprofil. 3. Da jedes Rezidiv, insbesondere in der neueren Zeit mittels genetischer Typisierung (NGS-Panels), individuell behandelt wird, ist sicherlich keine homogene Vergleichs - Kohorte	1. As above. No changes made. The issue of clearly defining the comparator for this HTA is acknowledged and will continue to be of relevance throughout the HTA process. The most representative examples of standard care for the Swiss context, as nominated by Swiss clinicians, were specified in the HTA protocol (***Section 7.3.1.4***). Inotuzumab and blinatumomab were identified as key comparators for paediatric ALL. These will all be considered as comparators for the paediatric ALL population. 2. As above. No changes made. The authors acknowledge the complexity around the comparator for the HTA. Salvage chemotherapy with any of the following regimens were identified by clinical experts engaged in the drafting of the protocol for DLBCL/PMBCL: (1) rituximab, gemcitabine, and oxaliplatin; (2) rituximab and bendamustine; (3) rituximab, polatuzumab and bendamustine; (4) tafasitamab and lenalidomide; (5) gemcitabine

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		vorhanden. 4. Bei "Outcome" hätte man neuere Erfolgsparameter wie MDR 10 hoch -5 einschliessen können, da dies die sCR besser abgrenzt gegenüber CR/PR 5. Es ist unklar, ob man die ITT - Population nimmt. --------- 1. In addition to CAR-T therapy, the period of time considered here for bALL has produced other potent medical therapies (blinotumumab, inotuzumab), which have replaced chemotherapy in the treatment of recurrence. Therefore, one should clearly describe in the PICO what is considered "standard therapy", or one should differentiate between them. 2. This comment also applies to the DLBCL/PMBCL, since here too there is no real standard therapy in the event of a recurrence, but rather a large number (at least 213 approved combinations) of therapies with different efficacy profiles. 3. Since every recurrence, especially in recent times, is treated individually by means of genetic typing (NGS panels), there is certainly no homogeneous comparison cohort available. 4. In "Outcome" one could have included newer success parameters such as MDR 10 to the power of -5, as this better distinguishes the sCR from CR/PR 5. It is unclear whether to take the ITT population.	and oxaliplatin. Alternatively, palliation was also identified as a relevant comparator (***Section 7.3.1.4***). 3. The issue around the comparator for this HTA is acknowledged as a challenge. We have attempted to identify the most representative examples of standard care through engagement with Swiss clinicians and clinical practice guidelines. Nevertheless, uncertainties remain and will be duly described in the HTA. 4. No changes made. MDR will not capture the health states and treatment effectiveness/safety relevant to the HTA report. 5. Accepted. An ITT approach will be used and this has been clarified in ***Section 6.3*** of the protocol.
2.2	Gilead Sciences Switzerland Sàrl	Gilead macht einen eingehenden Kommentar zum PICO (vgl. Ziff. 23 bis 29 unseres Schreibens vom 21.2.2023). Infolge der nicht nachvollziehbaren Zeichenbeschränkung verweisen wir auf unser	1. It is noted that there is likely to be limited evidence for the PMBCL group. The analysis may need to be combined if, for example, studies report mixed populations. If this is the case, it will be noted

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		Schreiben und wir verlangen vom BAG die Berücksichtigung unseres Kommentars. --- Gilead makes an in-depth comment on PICO (see paragraphs 23 to 29 of our letter dated 02/21/2023). As a result of the incomprehensible character limit, we refer to our letter and we ask the BAG to take our comment into account: 1. It is recommended combining DLBCL & PMBCL together due to rare data/publications regarding PMBCL (in line with the conclusions of the initial search results in the HTA protocol). 2. Comparators need to be reviewed and compared carefully due to potential impact on the HTA results. Outcome measurements & focus on clinically relevant parameters: 3. Event-free survival (EFS) has been excluded in the planned HTA with the reasoning of "different definitions", but how will be the heterogeneity of definitions of PFS & other outcomes be addressed? E.g., the PFS definition for both products (timing and start point for evaluation) differs in the studies. Please separate the protocol for both products. 4. Regarding complete response rate (CRR): What does "all signs of cancer" mean? It is not clear. Does it mean Complete Response (CR) per Lugano criteria? It needs to be clearly defined for CR and ORR. 5. Treatment free interval (TFI) as an endpoint is not captured in ZUMA-1 trial or generally in DLBCL. Please remove it. 6. Definition of grades in neurological events and how to manage	as a deviation from the protocol. However, where studies report on each population separately, the indications will be evaluated separately as originally planned. 2. As above. No changes made. The issue around the comparator for this HTA is acknowledged as a challenge. Authors have attempted to identify the most representative examples of standard care through engagement with Swiss clinicians. Nevertheless, uncertainties remain and will be duly described in the HTA. 3. No changes. Outcomes data will only be extracted and analysed if it meets the definition described in the HTA protocol. 4. Accepted. The outcome has been clarified. 5. Regardless of the anticipated outcomes, all clinically relevant outcomes need to be specified *a priori*. 6. The use of different grading systems and management of adverse events and their impact on the results will be discussed in the report. 7. Acknowledged with thanks.

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		adverse events (AEs) were different in the pivotal studies. 7. The management of cytokine release syndrome (CRS) and neurological events (NE) has improved in real-world vs pivotal trial.	
2.3	Interpharma	--	--
2.4	Lymphome.ch Patientennetz Schweiz	1. Bei den 4 Populationen gibt es keinerlei Hinweise über mögliche weitere Erkrankungen bzw. Nebendiagnosen. Die Intervention, ist klar und als Vergleich bei allen Gruppen wird die Standardbehandlung angegeben. Was ist, wenn die Standardbehandlung nicht toleriert wird in Bezug auf starke Nebenwirkungen? --- 1. In the 4 populations there are no indications of possible further diseases or secondary diagnoses. The intervention is clear and standard treatment is given as a comparison for all groups. What if standard treatment is not tolerated in terms of severe side effects?	1. No changes. Three populations are included, not four. If standard treatment is not well tolerated the risk ratio (RR) will favour CAR T.
2.5	Novartis Pharma Schweiz AG	*Wir verweisen auf unsere separate Stellungnahme vom 21. Februar 2023.* 1. Die Komplexität der hämatologischen Behandlungen des DLBCL und pALL wird in dem HTA Protokoll nicht adäquat abgebildet. 2. Die therapeutischen Optionen, welche zur Behandlung der DLBCL und pALL zur Verfügung stehen, einschliesslich der CAR-T Zelltherapie hängen von vielfältigen Faktoren ab:	1. No changes. It is beyond the scope of this HTA and protocol to comprehensively detail the complexity of DLBCL and ALL treatment. 2. As above. No changes. It is beyond the scope of this HTA and protocol to compressively detail the complexity of DLBCL and ALL treatment. 3. We acknowledge this is a limit inherent in the evidence base; however, such points as raised here will be highlighted and

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		○ Dem Stadium der Erkrankung ○ Den Eigenschaften der Therapieoptionen ○ Dem Gesundheitsstatus des Patienten ○ Eventuelle Vortherapien und deren Eigenschaften ○ Dem Zeitpunkt des Rückfalls ○ Der Zellqualität des Patientenzur Herstellung der CAR-T Zelltherapie In den vorgeschlagenen PICOs wird diese Komplexität vernachlässigt. 3. Bei der Patientenpopulation muss berücksichtigt werden, dass bei der Einführung der hochinnovativen CAR-T Zelltherapie Behandlungsunterbrechungen häufiger vorgekommen sind und daher die Daten der pivotalen Zulassungsstudien nicht den status quo des Schweizer Behandlungsalltags widerspiegeln. In der frühen Phase der klinischen Entwicklung wurden aufgrund fehlender Erfahrung bei der Durchführung globaler Studien für die komplexe und individualisierte CAR-T Zelltherapie, Herausforderungen bei der Herstellung (Kapazität und Verfahren) und der Logistik, unerwartet hoher Nachfrage aufgrund des ungedeckten medizinischen Bedarfs hohe Behandlungsabbruchraten beobachtet. Die neueren Daten aus der Praxis (Margarida Rodrigues, ASH 2021. Optimizing Commercial Manufacturing of Tisagenlecleucel for Patients in the US: A 4-Year Experiential Journey) zeigen, dass die Abbruchrate aufgrund von Verbesserungen bei den Herstellungskapazitäten und -verfahren, der Planung der Versorgungskette, der Erfahrung bei der Bereitstellung von	discussed in the additional issues section of the report. 4. The issue around the comparator for this HTA is acknowledged and will continue to be of relevance throughout the HTA process. 5. Thank you for the feedback. Sentence added into ***Section 7.3.2.1*** stating the following: *"Adverse events associated with SCT will be considered when determining costs and utility decrements associated with SCT."* No further adjustments made to the protocol. Applicability of the available evidence to the Swiss context (including of OS estimates for SOC) will be assessed during the HTA. 6. Amended, the list of comparators provided to the experts has been added in the appendices of the HTA protocol. 7. As above. No changes. Outcome data will only be extracted and analysed if it meets the definition described in the HTA protocol.

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		Zelltherapien usw. minimal ist. Daher ist die Verwendung der intent-to-treat-(ITT) Population aus der pivotalen Zulassungstudie als primäre Ressource für die Schätzung der klinischen Wirksamkeit und Sicherheit und der damit einhergehenden Kosteneffizienz von CAR-T Zelltherapien nur beschränkt geeignet. Es führt zu einer Verzerrung und Unterschätzung des Nutzens von CAR- T Zelltherapien. Die HTA-Bewertung muss diese Einzigartigkeit der CAR-T Zelltherapien berücksichtigen und ihre Auswirkungen in die HTA-Analysen einbeziehen. 4. In Bezug auf die Comparatoren (C) spielt die Transplantation als Konsolidierungstherapie nach der Salvagetherapie eine wichtige Rolle bei der Behandlung der Patienten. In der HTA-Analyse ist eine sorgfältige Anpassung erforderlich, um Verzerrungen zu verringern. Der Nutzen der Transplantation in Bezug auf die Wirksamkeit spiegelt sich in der Literatur, die zur Schätzung des overal survival (OS)-Nutzens der standard of care (SOC)-Arme verwendet wird im Gesamtüberleben wieder. 5. Der Prozentsatz der Patienten, die in der Literatur mit einer Transplantation behandelt wurden um den OS-Vorteil der SOC-Arme abzuschätzen, stimmt jedoch möglicherweise nicht mit dem Prozentsatz der Patienten im Schweizer Behandlungsalltag überein. Daher ist eine Anpassung erforderlich, um den OS-Nutzen aus der Literatur neu zu schätzen und an das Schweizer Gesundheitssystem anzupassen. Andernfalls wird der OS-Nutzen in der HTA-Analyse verzerrt. Darüber hinaus ist es von größter	

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		Bedeutung, die Auswirkungen der Transplantation auf die Kosten - sowohl kurz- als auch langfristig - in die HTA-Bewertung einzubeziehen. Dabei geht es nicht nur um die Kosten im Zusammenhang mit der Transplantation selbst, sondern auch um die Kosten im Zusammenhang mit der Behandlung von kurz- und langfristigen Nebenwirkungen. Hierzu gehört insbesondere die Graft-versus-host Erkrankung (GvHD), die in diesem Zusammenhang auftreten kann. Idealerweise sollten auch die Auswirkungen der Transplantation auf die Lebensqualität in die HTA-Bewertung einfließen. 6. Im Allgemeinen besteht hinsichtlich der Comparatoren nicht die erforderliche Transparenz. Bei der Auswahl der relevanten Comparatoren für das vorliegende HTA ist nicht klar welche Behandlungsalternativen den Experten vorgelegt wurden. 7. In Bezug zum Outcome muss sichergestellt werden, dass dieselben Definitionen hinsichtlich der Parameter verwendet werden. Bei der pALL wurde in der pivotalen Zulassungsstudie das event free survival (EFS) und overall remission rate (ORR) verwendet und nicht das progression free surival (PFS) und die complete response rate (CRR). Die Berücksichtigung ist ausschlaggebend für den Vergleich zum SOC in den Analysen. Ferner muss bei der pALL der Prozentsatz der Patienten die nach CAR-T Infusion eine Transplantation erhalten haben auf Basis der pivotalen Zulassungsstudie geschätzt werden, da die OS-Daten die Transplantation bereits berücksichtigen. Eine Verwendung	

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		anderer Prozentsätze führt zu einer Verzerrung des OS Outcomes. Ferner ist bei der Betrachtung der unerwünschten Ereignisse (UEs) zu berücksichtigen, dass Dank erheblicher Anstrengungen der medizinischen Fachkreise und der Zulassungsinhaberinnen sich das Management von unerwünschten Ereignissen von CAR-T Zelltherapien im Laufe der Zeit verbessert hat. Demnach haben sich die Häufigkeit und der Schweregrad von Nebenwirkungen im Laufe der Zeit verringert (Pasquini et al. 2020). Bei der HTA-Bewertung sollte dies bei der Beurteilung der Sicherheit und Kosteneffektivität berücksichtigt werden. Darüber hinaus ist zu beachten, dass die verwendeten Rating-Skalen zur Klassifizierung der UEs nicht immer identisch sind zu denjenigen, die in den pivotalen Studien verwendet wurden. Daher ist beim Vergleich des Schweregrads von UEs und damit der Auswirkungen auf Kosten und Lebensqualität zwischen CAR-T und SOCs Vorsicht geboten. --- *We refer to our separate statement of February 21, 2023.* 1. The complexity of the hematological treatment of DLBCL and pALL is not adequately reflected in the HTA protocol. 2. The therapeutic options available to treat DLBCL and pALL, including CAR-T cell therapy, depend on multiple factors: o The stage of the disease o The properties of the therapy options o The health status of the patient	

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		o Any previous therapies and their characteristics o The time of relapse o The patient's cell quality to produce the CAR-T cell therapy In the proposed PICOs, this complexity is neglected. 3. With regard to the patient population, it must be taken into account that treatment interruptions occurred more frequently when the highly innovative CAR-T cell therapy was introduced and therefore the data from the pivotal approval studies do not reflect the status quo of everyday Swiss treatment. In the early phase of clinical development, high treatment discontinuation rates were observed due to a lack of experience in conducting global trials for complex and individualized CAR-T cell therapy, manufacturing (capacity and process) and logistics challenges, unexpectedly high demand due to unmet medical needs . Recent real-world data (Margarida Rodrigues, ASH 2021. Optimizing Commercial Manufacturing of Tisagenlecleucel for Patients in the US: A 4-Year Experiential Journey) shows that dropout rates are increasing due to improvements in manufacturing capabilities and processes, supply chain planning , which has minimal experience in delivering cell therapies, etc. Therefore, the use of the intent-to-treat (ITT) population from the pivotal registration study as the primary resource for estimating the clinical efficacy and safety and the associated cost-effectiveness of CAR-T cell therapies is only of limited use. It leads to a bias and underestimation of the benefits of CAR-T cell therapies. HTA evaluation must take into account this uniqueness of CAR-T cell therapies and include its implications in HTA analyses.	

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		4. Regarding the comparators (C), transplantation as a consolidation therapy after salvage therapy plays an important role in the treatment of patients. Careful adjustment is required in HTA analysis to reduce bias. The usefulness of transplantation in terms of efficacy is reflected in the literature available for estimation of the overal survival (OS) benefit of the standard of care (SOC) arms used is reflected in overall survival. 5. However, the percentage of patients treated with transplantation in the literature to estimate the OS benefit of the SOC arms may not match the percentage of patients in everyday Swiss treatment. Therefore, an adjustment is required to re-estimate the OS benefit from the literature and adapt it to the Swiss healthcare system. Otherwise, the OS utility will be biased in the HTA analysis. In addition, it is of paramount importance to include the cost implications of transplantation—both in the short and long term—in the HTA assessment. It's not just about the costs associated with the transplant itself, but also the costs associated with treating short- and long-term side effects. This includes in particular the Graft-versus-host disease (GvHD), which can occur in this context. Ideally, the impact of transplantation on quality of life should also be included in the HTA assessment. 6. In general, there is not the required transparency with regard to the comparators. When selecting the relevant comparators for the present HTA, it is not clear which treatment alternatives were presented to the experts. 7. With regard to the outcome, it must be ensured that the same definitions are used with regard to the parameters. For pALL, the event free survival (EFS) and overall remission rate (ORR) were	

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		used in the pivotal approval study and not the progression free surival (PFS) and the complete response rate (CRR). The consideration is decisive for the comparison to the SOC in the analyses. Furthermore, for pALL, the percentage of patients who received a transplant after CAR-T infusion must be estimated based on the pivotal registration study, since the OS data already take the transplant into account. Using other percentages leads to a distortion of the OS outcome. Furthermore, when considering adverse events (AEs), it must be taken into account. Thanks to significant efforts by the medical community and marketing authorization holders, the management of adverse events from CAR-T cell therapies is improving.	
2.6	Santésuisse	1. Population 1: The exclusion of patients over 26 years of age from B cell ALL is not explained. It is known from various sources that patients over 26 years of age are also treated with CAR-T therapies. Therefore, the exclusion criterion should be reviewed. 2. Population 1, 2 and 3: In addition to the outcomes mentioned, EFS, relapse, relapse-free survival (RFS), non-relapse mortality (NRM) and follow-up therapy (incl. 2nd treatment CAR-T) should also be included in the analysis.	1. The population definition for ALL in this HTA is from the CAR T provisional listing in Annex 1 of the Health Insurance Benefits Ordinance. 2. No changes. RFS and NRM were not included as they were not regularly included in published literature. In addition, this HTA is reviewing CAR T for a curative intent and not as a bridging therapy and therefore RFS and NRM are less important than the included outcomes (e.g. CRR, ORR, etc.). With regards to EFS, it is currently excluded due to definition heterogeneity.
2.7	Swiss Pediatric Oncology Group(SPOG) and Swiss Society of Pediatric Hematology and Oncology(SSPHO)	1. Population und Intervention bei päd ALL klar definiert, aber nicht der Comparator. Kritischer Punkt der Studie. 2. Outcome Daten werden systematisch erfasst, bis auf bisher QoL und TFI. QoL Erhebung müsste definiert werden, wird aber im Moment nicht systematisch erhoben. TFI wird ebenfalls aktuell nicht systematisch erfasst.	1. The issue around the comparator for this HTA is acknowledged and will continue to be of relevance throughout the HTA process. 2. Regardless of the anticipated outcomes, all clinically relevant outcomes need to be specified *a priori.*

Comment no.	Stakeholder	Stakeholder comment	Authors' response
		------ 1. Population and intervention in paediatric ALL clearly defined, but not the comparator. Critical point of the study. 2. Outcome data is systematically recorded, except for QoL and TFI so far. QoL survey would have to be defined, but is not systematically surveyed at the moment. TFI is also currently not systematically recorded.	

4.3 Comments regarding databases and search strategy

The following comments have been submitted by stakeholders regarding the databases and search strategy of the HTA-protocol ""The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma".

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3.1	Curafutura	1. Die meisten Studien über CAR- T laufen in China. Durch die Sprachbeschränkung auf englisch, deutsch, französisch und italienisch sind diese ausgeschlossen. 2. Die berücksichtigten Datenbanken sind ausreichend. ----- 1. Most studies on CAR-T are in China. Due to the language restriction to English, German, French and Italian, these are excluded. 2. The databases considered are sufficient.	1. Accepted. Language restrictions have been removed. 2. Thank you for your feedback.

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3.2	Gilead Sciences Switzerland Sàrl	Gilead macht einen eingehenden Kommentar zu Datenbanken und Suchstrategie (vgl. Ziff. 30 bis 37 unseres Schreibens vom 21.2.2023). Infolge der nicht nachvollziehbaren Zeichenbeschränkung verweisen wir auf unser Schreiben und wir verlangen vom BAG die Berücksichtigung unseres Kommentars. --- Gilead provides an in-depth comment on databases and search strategy (see paragraphs 30 to 37 of our letter dated 02/21/2023). As a result of the incomprehensible character limit, we refer to our letter and we ask the BAG to take our comment into account. 1. Please consider guidelines with most recent updates. 2. Please ensure the results are checked according to patient population, settings, age of study and other possible variables, which may affect the results. 3. Please ensure comparability of selected studies. 4. The Swiss CAR T registry is used as one of the data sources in this HTA (7.3.2.1 The role of SCT, 7.3.4.1 CAR T cell therapy costs, 7.4.2.1 Patient numbers). As recorded in the protocol, this data is not yet fully developed and must be interpreted with the utmost caution. Comprehensive RWD from the USA and Europe are available, which are more meaningful than the Swiss registry data due to larger population and longer follow-up. It should also be noted that the Swiss registry data is not direct or indirect comparative data and that there was no matching-adjusted indirect comparison (MAIC) due to the small patient population. A recent independent indirect comparison of axi-cel vs tisa-cel not yet considered in this HTA is from the French CAR T registry	1. All evidence-based guidelines identified will be reviewed for inclusion. 2. It is standard HTA protocol to conduct detailed extractions for all included studies including characteristics such as patient population, settings, study date etc. All extractions are checked by a second reviewer. 3. All studies that meet the PICO criteria will be eligible for inclusion. Any differences in the studies that could possibly affect the results will be discussed, and investigated using subgroup and sensitivity analyses where appropriate. 4. Thank you for the feedback. The reference provided presents a propensity score matched comparison between axi-cel and tisa-cel. Such a comparison is beyond the scope of this HTA. Published real-world evidence (RWE) from international registries will be picked up in the systematic literature search for consideration as RWE in the clinical evidence evaluation (if they meet all eligibility requirements). The Swiss CAR T registry is referenced in the protocol as a possible source of information on patient demographics and utilisation patterns of CAR T (incl. prior/subsequent therapies) among Swiss patients (necessary to consider applicability of the clinical evidence to the Swiss context); whether it is included will be determined during the study selection phase, and we do note this data set has limitations (as does everything). 5. All data captured using the search strategy outlined will be eligible for inclusion depending on whether it meets the PICO criteria. HTAs typically do not include data from conference abstracts as they do

Comment no.	Stakeholder	Stakeholder comment	Authors' response
		highlighting stronger efficacy of axi-cel vs tisa-cel (Bachy et al. 2022: A MATCHED COMPARISON OF TISAGENLECLEUCEL AND AXICABTAGENE CILOLEUCEL CAR T CELLS IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A REAL-LIFE LYSA STUDY FROM THE FRENCH DESCAR-T REGISTRY) https://library.ehaweb.org/eha/2022/eha2022-congress/357124/emmanuel.bachy.a.matched.comparison.of.tisagenlecleucel.and.axicabtagene.html?f=listing%3D4%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Aspeaker%3D8 80507 5. Consideration of most current data: CAR T cell therapy is a new, highly innovative drug for which new data is constantly being generated. Therefore, the current data (e.g., clinical data, guidelines, health economic data, current label) should be used for each product. In addition, current data is presented regularly, e.g., at the American Society of Hematology Congress (ASH) in December and at other congresses. These should be considered in the HTA. Please consider capturing latest data e.g., single long-term follow-up data points with a) conference abstracts and b) the current SMPC (aktuelle Fachinformation) approved by Swissmedic. 6. Appendix: 11.3.2 HTA with an economic evaluation component & 11.4.5 Table 19: Summary of existing HTAs with an economic evaluation component: NICE approval from Jan'23 for axi- cel in routine use to include https://www.nice.org.uk/News/Article/more-than-400-people- set-to-benefit-after-nice-approves-ground-breaking-car-t-therapy-to-treat-aggressive-form-of- blood-cancer	not contain adequate data and the information may not be dependable as most abstracts are not peer reviewed and are often based on limited or preliminary analyses. 6. Thank you for your reference, it will be assessed for its inclusion eligibility based on the study selection criteria in the HTA, noting that conference abstracts will not be included. Among other reasons, their data is often incomplete, and can not be appraised effectively for risk of bias, and have not been through a peer-review process. 7. The list of HTA agencies provided in Table 11 is based on the INAHTA member list. The additional agencies suggested have not been included as they do not appear on this list. 8. Reviewed; no studies missed due to omission of these 3 terms. The additional terms were each individually searched in Econlit on 16/03/23. (TX)CAR T: 11 hits, 1 potentially relevant captured in original search; (TX)CAR T-cell: 1 hit, potentially relevant but already captured in original search; (TX)CAR-T: 2 hits, 1 potentially relevant captured in original search.

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		7. Appendix: Table 11: HTA agency websites: missing agencies to add: MSAC & PBAC for Australia, DMC for Denmark, AIFA for Italy, NOMA for Norway, TLV for Sweden, ICER for United States 8. Appendix: Table 13: Economic search results: Econlit missing queries to add: "CAR T", "CAR T-cell" & "CAR-T"	
3.3	Interpharma	--	--
3.4	Lymphome.ch Patientennetz Schweiz	1. Die Literatursuche mittels 4 Datenbanken ist abgedeckt. 2. Studien ab 1.1.2010 aufgrund der neuen Technologie sinnvoll. 3. Die Suchstrategie-Filter ist richtig platziert. 4. Geplante Suchstrategien jeder Datenbank wird beschrieben. --- 1. The literature search using 4 databases is covered. 2. Studies from January 1st, 2010 make sense due to the new technology. 3. The search strategy filter is placed correctly. 4. Planned search strategies of each database are described.	1. Thank you for your feedback. No action required. 2. Thank you for your feedback. No action required. 3. Thank you for your feedback. No action required. 4. Thank you for your feedback. No action required.
3.5	Novartis Pharma Schweiz AG	*Wir verweisen auf unsere separate Stellungnahme vom 21. Februar 2023.* 1. Grundsätzlich erscheint uns die Methodik der Literatursuche den üblichen Standards entsprechend. Deshalb sollten für jedes Produkt jeweils die aktuellen Daten (z.B. klinsche Daten, Guidelines, gesundheitsökonomische Daten) herangezogen werden. Für CAR-T Zelltherapien werden zunehmend langfristige Nachbeobachtungsdaten verfügbar. Zum Beispiel sind die 5-Jahres-Follow-up-Daten der	1. Thank you for your feedback. Only published data that has been peer reviewed will be eligible for use in modelling. 2. Thank you for the feedback. The Swiss CAR T registry is referenced in the protocol as a possible source of information on patient demographics and utilisation patterns of CAR T (incl. prior/subsequent therapies) among Swiss patients (necessary to consider applicability of the clinical evidence to the Swiss context). Published real-world evidence (RWE) from international registries will be picked up in the systematic literature search for

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		ELIANA-Studie für Kymriah® bei pALL verfügbar. Wir fordern das BAG auf, mit den Zulassungsinahberinnen zusammenzuarbeiten, um die neuesten Daten für die Modellierung zu nutzen. 2. Als eine der Datenquellen wird in dem HTA Protokoll auf das Schweizer CAR-T Register verwiesen. Diese Daten sind, wie auch im Protokoll festgehalten, nicht ausgereift und müssen mit höchster Vorsicht interpretiert werden. In diesem Zusammenhang gilt es festzuhalten, dass es sich bei den Register Daten um RWE handelt, die von den Behörden bei anderen Fragestellungen nicht akzeptiert werden. Zudem liegen umfassende RWE-Daten aus den USA und aus Europa vor, die aussagekräftiger als die Schweizer Registerdaten sind. *We refer to our separate statement of February 21, 2023.* 1. Basically, the methodology of the literature search seems to us to correspond to the usual standards. Therefore, the current data (e.g. clinical data, guidelines, health economic data) should be used for each product. Long-term follow-up data are increasingly available for CAR-T cell therapies. For example, the 5-year follow-up data from the ELIANA study are available for Kymriah® in pALL. We call on the FOPH to work with the authorization holders to use the latest data for modelling. 2. The HTA protocol refers to the Swiss CAR-T register as one of the data sources. As recorded in the protocol, this data is not mature and must be interpreted with the utmost caution. In this context, it should be noted that the register data relates to RWE,	consideration as RWE in the clinical evidence evaluation (if they meet all eligibility requirements).

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		which the authorities do not accept for other issues. In addition, comprehensive RWE data from the USA and Europe are available, which are more meaningful than the Swiss register data.	
3.6	Santésuisse	1. Santésuisse agrees with the search strategy.	1. Thank you for your feedback. No action required.
3.7	Swiss Pediatric Oncology Group(SPOG) and Swiss Society of Pediatric Hematology and Oncology(SSPHO)	1. Müsste hier nicht auch das EBMT registry herangezogen werden, zumindest zum Abgleich der Daten? Besser Datenbanken nutzen, da sonst Gefahr Publikationsbias. 2. Review für randomisierte Studien ist erwähnt, diese sind aber nicht existent bisher. Daher streichen und nur nicht-randomisierte Studien plus Register als Quelle heranziehen. --- 1. Shouldn't the EBMT registry also be used here, at least to compare the data? It is better to use databases, otherwise there is a risk of publication bias. 2. A review for randomized studies is m entioned, but these do not yet exist. Therefore delete and only use non-randomized studies plus registers as a source.	1. No changes made. As above. Published real-world evidence (RWE) from international registries will be picked up in the systematic literature search for consideration as RWE in the clinical evidence evaluation (if they meet all eligibility requirements). 2. Regardless of the anticipated study types, the types of studies that would be included if available need to be specified *a priori.*

4.4 Comments regarding data extraction, analysis and synthesis

The following comments have been submitted by stakeholders regarding the data extraction, analysis and synthesis of the HTA-protocol ““The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma”.

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4.1	Curafutura	1. Die Annahme, dass alle Therapieoptionen für "Standard care" gleichwertig sind, muss man als möglichen Bias betrachten, siehe Bemerkung oben. 2. das übrige Vorgehen ist unserer Meinung nach korrekt. 3. Die Berechnung des ICER's im schweizerischen Setting ist nicht möglich, da vertrauliche Preise gelten. Somit ist das HTA in diesem Bereich nur unvollständig bis gar nicht möglich, das eben auch für die alternativen Medikamente überwiegend Rabattmodelle bestehen (siehe SL). --- 1. The assumption that all therapy options for "standard care" are equivalent, must be considered as a possible bias, see comment above. 2. The rest of the procedure is correct in our opinion. 3. The calculation of the ICER's in the Swiss setting is not possible because confidential prices apply. Thus, the HTA in this area is only incomplete or not possible at all, which is why there are mostly discount models for alternative medicines (see SL).	1. Acknowledged. The assumption that standard care is equivalent will be highlight as a limitation in the HTA report. 2. Thank you for your feedback. No action required. 3. As above. Confidential tariffs for the CAR T products will not be used in the HTA. An external price will be used (e.g. use of an international reference price), and extensive sensitivity analysis in relation to the CAR T product cost undertaken.
4.2	Gilead Sciences Switzerland Sàrl	Gilead macht einen eingehenden Kommentar zu Datenextraktion, Analyse und Synthese (vgl. Ziff. 38 bis 48 unseres Schreibens vom	1. As above. Presentation of results using the ICUR is the standard approach. We acknowledge the lack of a supported

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		21.2.2023). Infolge der nicht nachvollziehbaren Zeichenbeschränkung verweisen wir auf unser Schreiben und wir verlangen vom BAG die Berücksichtigung unseres Kommentars. --- Gilead provides detailed commentary on data extraction, analysis and synthesis (see paragraphs 38 to 48 of our letter dated 02/21/2023). As a result of the incomprehensible character limit, we refer to our letter and we ask the BAG to take our comment into account. 1. There is no cost-effectiveness threshold value in Switzerland. As part of the planned economic evaluation (7.3 Economic evaluation methodology), Life Years (LY) and Quality- Adjusted Life Years (QALYs) and the Incremental Cost-Effectiveness Ratio (ICER) are aimed for as results. It is therefore not possible to conclude whether a medicinal product is cost- effective in Switzerland. 2. Market Share (MS) and price assumptions significantly influence Budget Impact Analysis. The confidentiality of the prices must be maintained in order not to jeopardize the market access for patients in Switzerland. The current share and trend in DLBCL in the Swiss CART registry in favor of axi-cel must be considered. 3. Long term efficacy (Overall Survival – OS) focus is key in 3L+ DLBCL/PMBCL with comparison outside RCT due to palliative setting. For ethical reasons all study patients should receive CART and not salvage chemotherapy in the trial, therefore indirect comparison only according MAIC (comparable patient population) with historical cohort (SCHOLAR-1). 4. The license holder company should be involved in the development of the model (or provide the model for criticism), and	threshold in the Swiss context. ICUR results will be presented as a function of WTP. 2. As above. Confidential tariffs for the CAR T products will not be used in the HTA (i.e. will remain confidential). If available, current market share data will be considered as part of the analysis. 3. Acknowledged, no changes required. 4. The draft HTA report is submitted to the marketing authorization holder and all other stakeholders involved. During this consultation, the marketing authorization holder is given the opportunity to review the economic model and the entire draft HTA report. Subsequently, the HTA report is finalized and published on the FOPH homepage. The economic model will make use of the best available (published) evidence. There are approaches to overcome a lack of individual patient data (IPD). For example, previous models have digitised published Kaplan-Meier curves (e.g. Wittington et al. 2018 and Wittington et al. 2019). The approach(es) to be used in this HTA have not yet been decided. Evidence used in the economic evaluation will align with evidence used in the clinical evaluation. 5. Thank you for the feedback. A search of HTA databases for existing HTAs will be conducted. The HTA mentioned should be identified via this mechanism and will be considered along with other HTAs in the final report. 6. No changes will be made to the PICO populations. The eligible populations were defined per Appendix 1 of the Health Insurance Benefits Ordinance in Switzerland.

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		where possible, data be made available commercial in confidence which is a standard practice in HTA like the NICE assessment. The de-novo model in this HTA is being developed and populated by a third-party, thus access to data is limited to what is publicly available. However, basic inputs, such as survival analysis using a cure model require individual patient level data to accurately estimate cost- effectiveness. Furthermore, resource use data collected in trials cannot be utilized. As a result, the cost-effectiveness model does not make use of the best available evidence and therefore may be unfit for decision making. 5. Recent HTA for axi-cel in 3L+ DLBCL/PMBCL in the United Kingdom to consider that was so far not captured in the HTA protocol: The National Institute for Health and Care Excellence (NICE) has issued final draft guidance in Jan'23 "recommending the treatment be made routinely available on the NHS for suitable patients. (…) NICE's independent appraisal committee considered new evidence, including data from a clinical trial and from people having axicabtagene ciloleucel through the Cancer Drugs Fund (CDF) before making the recommendation. It suggests that people having axicabtagene ciloleucel live longer than people having chemotherapy and have longer before their condition gets worse." https://www.nice.org.uk/News/Article/more-than-400-people-set-to-benefit-after-nice- approves-ground-breaking-car-t-therapy-to-treat-aggressive-form-of-blood-cancer 6. Section 7.1.2.3 says that most studies assessing the cost-effectiveness of axi-cel considered a combined population of adults with LBCL. We recommend adjusting the PICO of this HTA	7. Acknowledged. IPD would be beneficial, but is seldom available. The subgroup analyses are intended to investigate heterogeneity in any meta-analyses; they are not separate research questions per se. 8. Thank you for the feedback. The cited NMA reports a comparison between axi-cel, tisa-cel and another CAR-T product, using historical SoC as a common comparator. While the intra CAR T comparisons are beyond the scope of this HTA, the individual studies used in the meta-analysis, which compared a CAR T product with SoC, may be of relevance. If so, they would be included in the clinical evidence review. It appears the NMA used evidence from a publication in which "tisa-cel IPD was compared to CORAL IPD, a historical SoC cohort (and a sub-cohort of SCHOLAR-1)". If this study meets our inclusion criteria, it will be considered in the clinical evidence evaluation. 9. Page 10 provides a broad overview of the comparator 'standard care', whilst a more targeted definition of the most relevant comparators in the Swiss context is provided in Section 7.3.1.4 for the purposes of economic modelling, based on expert advice. Experts identified tafasitamab and polatuzumab as relevant comparators for patients with DLBCL. It will be assessed during the HTA if (1) single-arm data on these comparators needs to be retrieved; and (2) if so, whether available evidence is applicable to the decision problem. 10. Acknowledged, no changes. Expert advice received whilst drafting the protocol was that two thirds to 80% of patients may receiving bridging chemotherapy. If clinical evidence is

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		and combine DLBCL & PMBCL accordingly. 7. Subgroup analysis: SCHOLAR-1 IPD (individual patient level data) would be needed for a proper and balanced comparison. 8. Comparison: Will tisa-cel be evaluated against SCHOLAR-1 too? Please comment how imbalances will be corrected? The comparator needs to be the same and all confounders accounted for – this is difficult to do without individual patient level data (IPD). A network meta-analysis assumes randomization accounts for trial imbalances when there is a common comparator. A full protocol and statistical analysis plan (SAP) must be provided and for the license holder company to comment on it. Please find below a recent network meta-analysis from Locke et al. 2022 that was so far not considered in the protocol: (3346 Network Meta-Analysis (NMA) of Chimeric Antigen Receptor (CAR) T-Cell Therapy for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) after 2 Prior Treatments Using Published Comparative Studies) https://ash.confex.com/ash/2022/webprogram/Paper169812.html This NMA leverages "(…) available evidence to conduct an adjusted indirect comparison of axi- cel, liso-cel, and tisa-cel using published comparative studies of CAR-T products to historical SoC cohorts. (…) The search identified 467 publications, of which 3 were included in the evidence base. (…) In the first study, axi-cel individual patient data (IPD) was compared to SCHOLAR-1 (a historical SoC cohort) IPD using propensity score methods. For the second, a matching adjusted indirect comparison (MAIC) was used to compare liso-cel IPD to SCHOLAR-1 summary data. For	available on this model input, it will be used preferentially to expert opinion in the cost analysis. 11. There is no specified discount rate or reference model for HTA in Switzerland; however, use of a discount rate of 3% p.a. for both cost and effects has been standard practice in the HTAs we have done for the Swiss context. Sensitivity analyses using alternate rates (0% and 6%) will be undertaken (as mentioned in the protocol document).

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		the third, tisa-cel IPD was compared to CORAL IPD, a historical SoC cohort (and a sub-cohort of SCHOLAR-1). The results from the ITT population of JULIET were used in this analysis. Available outcomes across all three studies included overall survival (OS) and overall response rate (ORR). Complete response (CR) was analyzed where possible. All three treatments were superior to SoC across all outcomes. (…) For OS, axi-cel had a significantly lower hazard ratio for death relative to liso-cel and tisa-cel. (…) Results of the analyses suggest that axi-cel leads to improved OS in r/r DLBCL relative to liso- cel and tisa-cel. Axi-cel and liso-cel were comparable with respect to response outcomes, showing favorable ORR relative to tisa-cel. These results are in line with MAIC results, where efficacy between CAR-T treatments have been directly compared but offer the advantage of being able to include a common comparator in the absence of placebo controlled RCTs." 9. Comparison: An inclusion of tafasitamab and polatuzumab as DLBCL comparators would lead to inconclusive results. Section 7.3.1.4 mentions tafasitamab and polatuzumab as DLBCL comparators, but those were not listed under "comparator" section in page 10. Please comment if these two are included as comparator or not. One important caveat about these products is that their studies include earlier treatment line patients. How would it be possible to make a comparison since their studies include a small number of patients when we try to match the population to ZUMA-1 trial, we will end up with very small number	

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		of patients. 10. Section 7.3.4.1 says 80% of patients receive bridging. The evaluation should be done as per trial and a scenario analysis with bridging. Including bridging might affect the probability of infusion. 11. Discount rate is set at 3.0% in the HTA protocol. Please provide the rationale for it and the sensitivity.	
4.3	Interpharma	Einschluss von Daten 1. Zur CAR T Zelltherapie werden fortlaufend neue Daten generiert. Für jedes Produkt sollten jeweils die aktuellsten Daten (klinische Daten, Guidelines, gesundheitsökonomische Daten) herangezogen werden und es gilt zu regeln, wie diese Daten laufenden in den HTA-Prozess integriert werden. 2. Als eine der Datenquellen wird in diesem HTA-Protokoll verschiedentlich das Schweizer CAR T Register herangezogen (7.3.2.1 The role of SCT, 7.3.4.1 CAR T cell therapy costs, 7.4.2.1 Patient numbers). Diese Daten sind, wie auch im Protokoll festgehalten, noch nicht ausgereift und müssen mit höchster Vorsicht interpretiert werden. In diesem Zusammenhang gilt es festzuhalten, dass es sich bei den Register Daten um «Real-World Data» handelt, die in anderem Kontext von den Behörden nicht akzeptiert werden. Zudem liegen umfassende RWD aus den USA und aus Europa vor, die aussagekräftiger als die Schweizer Registerdaten sind. --- 1. New data is constantly being generated for CAR T cell therapy. The most up-to-date data (clinical data, guidelines, health-economic data) should be used for each product, and it is	1. No changes. Data from any published studies identified through the specified search strategy that meets the PICO criteria is eligible for inclusion. 2. Thank you for the feedback. The Swiss CAR T registry is referenced in the protocol as a possible source of information on patient demographics and utilisation patterns of CAR T (incl. prior/subsequent therapies) among Swiss patients (necessary to consider applicability of the clinical evidence to the Swiss context). Published real-world evidence (RWE) from international registries will be picked up in the systematic literature search for consideration as RWE in the clinical evidence evaluation (if they meet all eligibility requirements).

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		necessary to regulate how this data is integrated into the HTA process on an ongoing basis. 2. The Swiss CAR T register is used as one of the data sources in this HTA protocol (7.3.2.1 The role of SCT, 7.3.4.1 CAR T cell therapy costs, 7.4.2.1 Patient numbers). As recorded in the protocol, this data is not yet fully developed and must be interpreted with the utmost caution. In this context, it should be noted that the register data is "real-world data" that is not accepted by the authorities in other contexts. In addition, comprehensive RWD from the USA and Europe are available, which are more meaningful than the Swiss registry data.	
4.4	Lymphome.ch Patientennetz Schweiz	1. Die Datenextraktion ist klar definiert, ebenso die Daten von Interesse. 2. Datensynthese: Habe Erklärungsbedarf beim Abschnitt: Angesichts der begrenzten Behandlungsmöglichkeiten für Patienten mit refraktärer oder rezidivierter ALL, DLBCL oder PMBCL nach mindestens zwei Therapielinien und der Tatsache, dass es nicht möglich ist, den personalisierten Charakter von Therapien der letzten Therapielinie in den geplanten Meta-Analyseverfahren zu berücksichtigen, wird davon ausgegangen, dass alle "Standardbehandlungen" in allen Studien gleichwertig sind. --- 1. Data extraction is clearly defined, as is the data of interest. 2. Data Synthesis: I need explanation for the section: Given the limited treatment options for patients with refractory or relapsed ALL, DLBCL, or PMBCL after at least two lines of therapy and the	1. Thank you for your feedback. No action required. 2. No changes. For the reasons previously stated, equivalency was assumed for standard care. This is due to the complex and personalised nature of treatment across the 3 populations. It is not possible to reflect this complexity within the meta-analysis methodology. This will be noted as a limitation in the HTA.

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		impossibility of considering the personalized nature of last-line therapies in the planned meta-analysis procedures, it is anticipated that that all "standard treatments" are equivalent in all studies.	
4.5	Novartis Pharma Schweiz AG	*Wir verweisen auf unsere separate Stellungnahme vom 21. Februar 2023.* 1. Aufgrund der oben geteilten Ausführungen ist aus unserer Sicht eine Revision des HTA Protokolls dringend notwendig. Andernfalls besteht ein erhebliches Risiko, dass für Patienten folgenschwere Entscheide basierend auf verzerrten Ergebnissen getroffen werden. 2. Generell stellt sich die Frage, ob aufgrund der fehlenden Klarheit hinsichtlich Zielvorgabe die Durchführung eines HTA der bereits etablierten CAR-T Zelltherapien Sinn ergibt. Eine gänzliche Streichung / Desinvestment einer dringend gebrauchten, innovativen Therapie aus dem Schweizer Versorgungskontext wäre mit dem Grundgedanken des KVG, den Schweizer Patienten einen einheitlichen Zugang zu den neusten Medikamenten zu gewähren, nicht vereinbar und auch rein ethisch äusserst fragwürdig. --- *We refer to our separate statement of February 21, 2023.* 1. Due to the statements shared above, we believe that a revision of the HTA protocol is urgently needed. Otherwise, there is a significant risk that decisions with serious consequences for patients will be made based on biased results. 2. In general, the question arises as to whether the implementation	1. Each statement shared above has been individually addressed. Small changes to the protocol have been made but no major revisions have been implemented. 2. CAR T therapies are provisionally listed in Appendix 1 of the Health Insurance Benefits Ordinance. This HTA will assess the safety, effectiveness and cost-effectiveness of the provisionally listed therapies to inform future reimbursement decisions. Authors do not enter the HTA with such motives (e.g. aim of disinvestment) and refrain from using such terminology in the HTA report.

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		of an HTA of the already established CAR-T cell therapies makes sense due to the lack of clarity with regard to the target. A total deletion / disinvestment of a much needed, innovative therapy from the Swiss care context would be incompatible with the basic idea of the KVG, to grant Swiss patients uniform access to the latest medicines, and would also be extremely questionable from a purely ethical point of view.	
4.6	Santésuisse	1. The analyses must take into account the ITT perspective, considering the different phases of treatment (apheresis to CAR-T infusion) as well as the causes of drop-out. 2. Santésuisse supports the development of a new cost-effectiveness analysis with relevant and up-to-date data from Switzerland. In addition, when assessing the intervention, the costs should also be taken into account if a patient is treated several times with tisa-cel. 3. An analysis of the budget impact of the therapy is supported. The potential budget impact of CAR T cell therapies should be estimated for a period of at least 10 years in addition to a period of 5 years.	1. As above. This has been amended in the HTA protocol. 2. The relevance of including multiple lines of CAR T in the economic modelling will be explored further during the HTA (e.g. is this standard practice, does it occur often in Switzerland, is there any clinical evidence available on repeat utilisation…?) 3. The budget impact analysis will be performed over a period of 5 years. Extension beyond this comes with uncertainty and will therefore not be included.
4.7	Swiss Pediatric Oncology Group(SPOG) and Swiss Society of Pediatric Hematology and Oncology(SSPHO)	1. Genetik der Leukämien berücksichtigen, diese beeinflussen die Behandlung post CAR. --- 1. Consider genetics of leukemias, these affect post-CAR treatment.	1. Questions around the genetics of leukemias are beyond the scope of the present HTA. Study populations will be assumed representative of Swiss patients receiving CAR T, including with respect to underlying genetics. Post CAR T treatments (to be considered in the economics) will be based upon evidence in available study populations and/or the Swiss registry; they will not be modelled based on genetics.

4.5 Additional stakeholder feedback

The following additional feedback has been submitted by stakeholders regarding the HTA-protocol ""The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma".

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5.2	Gilead Sciences Switzerland Sàrl	1. Gilead expresses concerns about the proposed HTA procedure. The focus of the FOPH's HTA program is on divestment while CAR T cell therapies are new highly innovative products not compatible to divestment-efforts. ATMPs such as CAR T cell therapies are seen e.g., by the European Medicines Agency (EMA) as "groundbreaking new opportunities for the treatment of disease". https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview Current OKP reimbursement via KLV Appendix 1 focuses on patients who meet the study inclusion criteria, which is checked using detailed checklists by the medical examiners. Axi-cel is used currently based on the clinical evidence of efficacy and safety in accordance with the marketing authorization. Divestment may be discriminatory for patients who benefit from treatment with axi-cel. This HTA discriminates CAR T cell therapies like axi-cel that are listed in Appendix 1 KLV compared to others that are not listed but remunerated according to the trust principle & mandatory service.	1. The focus of the assessment process (HTA phase) is to evaluate the safety, efficacy and cost-effectiveness of the two CAR T cell therapies to inform future reimbursement decisions. The HTA does not have the aim of disinvestment. 2. Presentation of results using the ICUR is the standard/preferred approach for HTAs. We acknowledge the lack of a supported threshold in the Swiss context. ICUR results will be presented as a function of WTP. 3. The two CAR T products will not be combined as a single intervention in any analysis in the report. They will be treated individually. 4. As above. Confidential tariffs for the CAR T products will not be used in the HTA (i.e. will remain confidential). The draft HTA report is submitted to all stakeholders (including the marketing authorization holders) for consultation. Subsequently, the HTA report is finalized and published on the FOPH website together with the comments of the stakeholders and the authors' responses to the stakeholders' comments.

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		(Vertrauensprinzip & Pflichtleistung). 2. There is no cost-effectiveness threshold value in Switzerland. As part of the planned economic evaluation (7.3 Economic evaluation methodology), Life Years (LY) and Quality-Adjusted Life Years (QALYs) and the Incremental Cost-Effectiveness Ratio (ICER) are aimed for as results. It is therefore not possible to conclude whether a medicinal product is cost- effective in Switzerland. 3. No multi-HTA with multiple CART therapies in one HTA. A single HTA per product per indication is required. The HTA protocol assumes that all CAR Ts are the same, although clinical & real-world data proves the opposite. CAR T is a highly complex and individualized therapy. The implementation and analysis of multi-HTAs (several different active ingredients in one HTA) requires consistent and comparable study data on the individual interventions and comparative therapies. This requirement is not met in this HTA proposal. In countries with HTA institutions, each CAR T product was usually assessed separately (that is confirmed by most of the listed economic evidence in the appendix of the HTA protocol). The clinical heterogeneity of CAR T products and trials makes it difficult to compare these products and needs to be done with caution. The HTA process could result in inappropriate recommendations negatively impacting patient care and access. A recent single HTA for axi-cel in 3L+ DLBCL/PMBCL in the United Kingdom that was so far not captured in the HTA protocol to consider: The National Institute for Health and Care	5. The highest quality and most up-to-date evidence available at the search data will be considered. Upcoming evidence will be discussed in the additional issues section of the HTA (informed by a search of clinical trial registries). Conference abstracts and SMPCs are not publication types eligible for inclusion. 6. Noted. However, the focus of this HTA is on CAR T use in the third-line setting, in line with the current provisional listings in Appendix 1 of the Health Insurance Benefits Ordinance. Safety, effectiveness and cost-effectiveness of CAR T as a second line therapy is beyond the scope of the policy question being asked. 7. As above. The economic model will make use of the best available (published) evidence. Evidence used in the economic evaluation will align with evidence used in the clinical evaluation. The draft HTA report is submitted to the marketing authorization holder and all other stakeholders involved. During this consultation, the marketing authorization holder is given the opportunity to review the economic model and the entire draft HTA report. Subsequently, the HTA report is finalized and published on the FOPH homepage. 8. The draft HTA report is also submitted to the stakeholders for consultation. All stakeholders will be pre-informed 4 weeks prior to the consultation. For more information about the HTA process, visit the FOPH

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		Excellence (NICE) has issued final draft guidance in Jan'23 "recommending the treatment be made routinely available on the NHS for suitable patients. (…) NICE's independent appraisal committee considered new evidence, including data from a clinical trial and from people having axicabtagene ciloleucel through the Cancer Drugs Fund (CDF) before making the recommendation. It suggests that people having axicabtagene ciloleucel live longer than people having chemotherapy and have longer before their condition gets worse." https://www.nice.org.uk/News/Article/more-than-400-people-set-to-benefit-after-nice- approves-ground-breaking-car-t-therapy-to-treat-aggressive-form-of-blood-cancer 4. Confidential net price agreements have enabled reimbursement of CAR T cell therapies in Switzerland and other countries. In the case of this HTA protocol and HTA report, the confidentiality of the prices must be maintained in order not to jeopardize the market access for patients in Switzerland. We suggest that the FOPH should consider providing the HTA results to the license holder before publication of the draft and final report to others so that the license holder company may assert any business secrets. 5. Consideration of most current data: CAR T cell therapy is a new, highly innovative drug for which new data is constantly being generated. Therefore, the current data (e.g., clinical data, guidelines, health economic data, current label) should be used for each product. In addition, current data is presented regularly, e.g., at the American Society of Hematology Congress (ASH) in December and at other	website. 9. It is standard protocol of the FOPH to disclose authors' names upon publishing the HTA protocol (or HTA report). 10. Experts were included on the premise of anonymity. Names will not be disclosed (nor sub-specialty due to the risk of identification); however, their general field of expertise was relevant (e.g. oncology). 11. Work on other HTA projects does not introduce a COI given each FOPH project addresses a different policy question. COI is better considered on a project-by-project basis.

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		congresses. These should be considered in the HTA. Please consider capturing latest data e.g., single long-term follow-up data points with a) conference abstracts and b) the current SMPC (aktuelle Fachinformation) approved by Swissmedic. 6. The HTA protocol does not consider the further development of these therapies. The use of axi-cel is already shifting to an earlier therapy line vs the line focused on in the HTA protocol due to statistically significant favorable primary endpoint vs standard-of-care which was analyzed in a randomized control trial (RCT). 7. The license holder company should be involved in the development of the model (or provide the model for criticism), and where possible, data be made available commercial in confidence which is a standard practice in HTA like the NICE assessment. The de-novo model in this HTA is being developed and populated by a third-party, thus access to data is limited to what is publicly available. However, basic inputs, such as survival analysis using a cure model require individual patient level data to accurately estimate cost-effectiveness. Furthermore, resource use data collected in trials cannot be utilized. As a result, the cost-effectiveness model does not make use of the best available evidence and therefore may be unfit for decision making. 8. The protocol does not detail the areas in which the license holder company will be consulted, how the companies' comments are addressed and timelines for doing so. It is important that all	

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		comments made by the company regarding the evaluation are addressed by the HTA entity in a timely manner. 9. Please disclose the authors, experts and vendors engaged in the HTA protocol and the HTA report to increase transparency. 10. Involving experts: at various points in the protocol, reference is made to a survey of experts (7.3.1.4 Relevant comparators to the Swiss context; 7.3.4 Cost inputs; 7.3.4.1 CAR T cell therapy costs). In principle, the involvement of experts is welcomed. However, if experts are involved, the selection criteria, the list of experts interviewed (name, discipline) and the questions/questionnaires asked must also be reported as part of the protocol. Otherwise, potential conflict of interest may not be discovered. 11. Potential conflict of Interest of the authors, experts and/or vendors: The authors may have potential conflict of interest in relation to this project & other HTA assessments if regularly selected as HTA third-party vendor. Please comment if selected third-party vendor is also used for other FOPH projects.	
5.3	Interpharma	1. Der Hauptfokus des HTA-Programms des BAG liegt auf Desinvestment. Bei der CAR T Zelltherapie handelt es sich jedoch um eine neue, hoch- innovative Produktklasse, was nicht mit Desinvestment-Bestrebungen vereinbar ist. Die OKP-Rückerstattung über KLV Anhang 1 erfolgt heute nur für Patienten, die den Studieneinschlusskriterien entsprechen, was anhand detaillierte Checklisten überprüft wird. Der Einsatz der Therapie basiert auf 2. der klinischen Evidenz, der Wirksamkeit und Sicherheit	1. The focus of the assessment process (HTA phase) is to evaluate the safety, efficacy and cost-effectiveness of the two CAR T cell therapies to inform future reimbursement decisions. The HTA does not have the aim of disinvestment. 2. These CAR T therapies are provisionally listed on Appendix 1 of the Health Insurance Benefits Ordinance. The HTA will assess the safety, effectiveness and cost-effectiveness of the provisionally listed therapies to inform

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		entsprechend der Marktzulassung, d.h. hier sind die Kriterien der Wirksamkeit und Zweckmässigkeit erfüllt. Bei Nichterfüllung einer der WZW-Kriterien erfolgt bereits heute keine Kostenübernahme durch die Krankenkasse. 3. An verschiedenen Stellen im Protokoll wird auf eine Befragung von Experten verwiesen (7.3.1.4 Relevant comparators to the Swiss context; 7.3.4 Cost inputs; 7.3.4.1 CAR T cell therapy costs). Grundsätzlich wird der Einbezug von Experten begrüsst. Wenn jedoch Experten einbezogen werden, müssen auch die Auswahlkriterien, die Liste der befragten Experten (Name, Fachrichtung) und die gestellten Fragen/Fragebogen als Teil des Protokolls ausgewiesen werden. --- 1. The main focus of the BAG's HTA program is on divestment. However, the CAR T cell therapy is a new, highly innovative product class, which is not compatible with divestment efforts. The OKP reimbursement via KLV Appendix 1 is currently only for patients who meet the study inclusion criteria, which is checked using detailed checklists. 2. The use of the therapy is based on the clinical evidence, the effectiveness and safety in accordance with the market approval, i.e. the criteria of effectiveness and appropriateness are met here. If one of the WZW criteria is not met, the health insurance company will not assume the costs. 3. At various points in the protocol, reference is made to a survey of experts (7.3.1.4 Relevant comparators to the Swiss context; 7.3.4 Cost inputs; 7.3.4.1 CAR T cell therapy costs). In principle, the	future reimbursement decisions. 3. Experts were included on the premise of anonymity. Names will not be disclosed (nor sub-expertise due to the risk of identification); however, their general field of expertise (e.g. oncology) and the questions they were asked will be stated in the report.

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		involvement of experts is welcomed. However, if experts are involved, the selection criteria, the list of experts interviewed (name, discipline) and the questions/questionnaires asked must also be identified as part of the protocol.	
5.5	Novartis Pharma Schweiz AG	Wir haben einige grundsätzliche Bedenken bezüglich des beabsichtigten HTAs, welche wir nachfolgend auflisten. Wir verweisen gleichzeitig auch auf die Stellungnahme von Interpharma vom 21. Februar 2023. Vertiefende Ausführungen einzelner Punkte finden Sie zudem auch in den unteren Abschnitten 2-5. Generelle Anmerkungen: 1. Es fehlen klare Rahmenbedingungen sowie transparente Prozessstrukturen für eine Durchführung des HTA bei innovativen Medikamenten, insbesondere ein politisch und gesellschaftlich getragener Schwellenwert der bezüglich Kosteneffizienz herbeigezogen werden kann. 2. Zudem bleibt das genaue Ziel des HTA unklar (siehe auch Kommentar zur Forschungsfrage). Dem Protokoll kann entnommen werden, dass es hauptsächlich auf «Desinvestment» abzielt. Diese vorgängige Zielsetzung verursacht einen gravierenden Bias. Dies steht im Gegensatz zu systematisch durchgeführten unparteiischen HTA Prozessen anderer ausländischer Institute (NICE etc.). 3. Als zu klärendes legales Grundproblem stellt sich uns zudem die Frage, ob und wie im HTA die effektiven Nettopreise der betroffenen Präparate mit vertraulichen Preismodellen berücksichtigt werden. Eine Aussage diesbezüglich fehlt im HTA Protokoll. Eine indirekte Veröffentlichung der	1. We acknowledge the lack of a supported threshold in Switzerland. Nevertheless, presentation of economic results using an ICUR is the standard approach, with the ICUR presented as a function of WTP. 2. The focus of the assessment process (HTA phase) is to evaluate the safety, efficacy and cost-effectiveness of the two CAR T cell therapies to inform future reimbursement decisions. The HTA does not have the aim of disinvestment. 3. As above, confidential tariffs for the CAR T products will not be used in the HTA (i.e. will remain confidential). An external price will be used, and extensive sensitivity analysis in relation to the CAR T product cost undertaken. This will include one-way DSA as well as an exploration of the required product price for the ICUR to meet various threshold values. 4. The HTA will review the different active ingredients (tisa-cel and axi-cel) separately. None of the analyses will combine the two active ingredients. 5. A comparison between tisa-cel and axi-cel is beyond the scope of this HTA. Each CAR T product will be compared, individually, to standard care. 6. The economic evaluation will not compare tisa-cel to axi-

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		vertraulichen Preise durch das BAG im Rahmen eines HTA verstösst aus unserer Sicht gegen den Vertrauensschutz. Die Frage ist angesichts der geplanten Veröffentlichung des HTA wichtig und vor der Vergabe des Auftrags für das HTA zu klären und uns darüber zu informieren. Wir bitten diesbezüglich um eine Klärung. Die CAR-T Zelltherapien sind nicht alle gleich 4. Das HTA Protokoll sieht vor die beiden Therapien Kymriah® und Yescarta® in einem HTA Bericht zu analysieren. Dies steht im Gegensatz zu systematisch durchgeführten HTA Prozessen anderer ausländischer Institute, die die jeweiligen Therapien individuell bewerten. 5. Es gibt keine vergleichenden Studien zwischen den CAR-T Zelltherapien Kymriah® und Yescarta®. Dazu gibt es erhebliche methodische Probleme bei Vergleichen zwischen CAR-Ts, die aussagekräftige Schlussfolgerungen nicht erlauben, insbesondere im Hinblick auf die Wirksamkeit und Sicherheit. Diese Einschränkungen werden in der Publikation von Zhang 2019 diskutiert (https://doi.org/10.6084/m9.figshare.12370136). Aufgrund dieser Probleme 6. unterliegen auch die Kosten-Wirksamkeits-Analysen, die auf studienübergreifender Evidenz basieren, denselben Einschränkungen. Es ist von entscheidender Bedeutung, die mit solchen Analysen verbundenen Einschränkungen zu beachten und solche Ergebnisse bei jeder HTA- Bewertung mit äußerster Vorsicht zu interpretieren. Klinische und	cel. Separate pairwise results for tisa-cel vs standard care and axi-cel vs standard care will be presented. Analyses may be based on cross-study evidence between tisa-cel or axi-cel and standard care studies. Clear commentary around the limitations of such analyses will be provided in the HTA report. 7. The HTA will review the different active ingredients (tisa-cel and axi-cel) separately. None of the analyses will combine the two active ingredients. 8. The clinical evidence review will not attempt to make cross-class comparisons. If no comparative clinical evidence is identified in the literature, single-arm CAR T results will be reported narratively. Indirect, naïve comparison to single-arm studies of comparative interventions will not be conducted, owing to the methodological concerns associated with this approach. Cross-class comparisons may, however, be necessary for the economic evaluation. Previous evaluations based on cross-class comparisons (i.e. CAR T vs standard care) have been published. Care will be taken to ensure the most robust comparisons possible are made, and that limitations in the comparisons are highlighted in the ***HTA report***. 9. We acknowledge the complexities in defining standard care for the populations of interest. To facilitate a comparison, the ***HTA protocol*** details the most representative standard care options in the Swiss setting. These were identified via engagement with Swiss clinical

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		politische Entscheidungen sollten nicht auf solch einer Grundlage getroffen werden. Eine falsche Interpretation solcher Ergebnisse könnte erhebliche Auswirkungen auf den Zugang der Patienten haben. 7. Das BAG nimmt in dem HTA Protokoll an, dass die beiden CAR-Therapien per se gleich sind. Obgleich die klinischen Daten das Gegenteil beweisen: Nicht nur haben beide Therapien unterschiedliche molekulare Eigenschaften (z.B. Signaldomäne oder unterschiedliche Gen- Editing-Vektoren), unterschiedliche Herstellprozesse und Umgang mit den Zellkulturen (z.B. die Möglichkeit der Kryokonservierung), sondern zeigen auch unterschiedliche Studiendaten hinsichtlich Wirksamkeits- und Verträglichkeitsprofil. <u>Komplexität der CAR-T Zelltherapien sprengt den Rahmen</u> 8. Als Kern-Problematik des geplanten HTA erachten wir die Tatsache, dass mit einem «klassenübergreifenden» HTA die Komplexität der Beurteilung derart steigt, dass schlussendlich keine validen Aussagen und Resultate generiert werden können (siehe Ausführungen unter PICO). 9. Insbesondere die Therapie des diffus großzellige B-Zell-Lymphom (DLBCL) aber auch der pädiatrischen akuten Leukämie und die Therapieschemata sind derart individuell, so dass jeder Patient je nach Vorgeschichte, Metastasierung etc. unterschiedlich behandelt wird. 10. Die Zulassungsstudien der CAR-T Zelltherapien weisen Unterschiede bezüglich der eingeschlossenen	experts, who were provided a list of potential comparators and asked to identify the 1 or 2 most relevant or most commonly used (and asked to nominate specific regimens if salvage chemotherapy was selected). The complexities of defining standard care for the populations of interest will be highlighted in the ***HTA report***. 10. As above, the HTA will review the different active ingredients (tisa-cel and axi-cel) separately. None of the analyses will combine the two active ingredients. 11. As above, the HTA will review the different active ingredients (tisa-cel and axi-cel) separately, based on the indications for use of each product specified in Appendix 1 of the Health Insurance Benefits Ordinance. 12. Relevant literature will be identified in the systematic literature review. This includes selection of studies relating to ethical, legal, social or organisational issues around CAR T therapy use. 13. The highest quality and most up-to-date evidence available at the search data will be considered. Upcoming evidence will be discussed in the additional issues section of the HTA (informed by a search of clinical trial registries). 14. PICO criteria are defined for 3 separate populations in the ***HTA protocol*** (based on the indications for use listed in Appendix 1 of the Health Insurance Benefits Ordinance). These criteria will guide study selection. The process of study selection is described in ***Section 6.2*** (e.g. screening

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		Patientenpopulationen auf, was die Vergleichbarkeit der Studiendaten und - resultate stark limitiert. Die Durchführung und Analyse von Multi-HTAs (mehrere verschiedene Wirkstoffe in einem HTA) erfordert konsistente und vergleichbare Studiendaten zu den individuellen Interventionen und Vergleichstherapien. Diese Voraussetzung ist im vorliegenden HTA nicht gegeben. In anderen Ländern wurde jedes CAR-T Produkt jeweils konsequent separat beurteilt. 11. Stattdessen würden wir vorschlagen, die Untersuchungsfrage auf spezifische Patientenpopulation und CAR-T Produkt zu limitieren und getrennte HTA Untersuchungen durchzuführen. 12. Bei der CAR-T Zelltherapie sind viele Akteure involviert, die im Hinblick auf den Faktor Zeit den Behandlungserfolg (Outcome) beeinflussen können. Aus der Literatur (Chen et al. 2020; Thornton Snider et al. 2019; Tully et al. 2019) geht hervor, dass die Wartezeit einen erheblichen Einfluss auf den Outcome der CAR-T Zelltherapie haben kann. Die HTA-Bewertung sollte die Wartezeit in ihre Analyse einbeziehen. Zu den Akteuren gehören der überweisende Arzt, das Behandlungszentrum, die Krankenversicherer, das Zelllabor und die Zulassungsinhaberin in Bezug auf die Herstellung. All diese Akteure können zu einem Bias führen, was in der HTA-Analyse berücksichtigt werden muss. Berücksichtigung aktuellster und relevanter Daten 13. Bei der CAR-T Zelltherapie handelt es sich um eine neue, hoch-innovative Therapie, zu der fortlaufend neue Daten generiert werden. Deshalb sollten für jedes Produkt jeweils die	will be undertaken by 2 reviewers; training samples will be used to ensure that the inclusion criteria are interpreted consistently between reviewers). 15. Experts were included on the premise of anonymity. Names will not be disclosed (nor sub-specialty expertise due to the risk of identification); however, their general field of expertise was relevant (e.g. oncology). 16. The draft HTA report is submitted to all stakeholders (including the marketing authorization holders) for consultation. Subsequently, the HTA report is finalized and published on the FOPH website together with the comments of the stakeholders and the authors'/FOPH's responses to the stakeholders' comments.

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		aktuellen Daten (z.B. klinsche Daten, Guidelines, gesundheitsökonomische Daten) herangezogen werden. Zudem werden jährlich z.B. am American Society of Hematology-Congress (ASH) im Dezember aktuelle Daten vorgestellt. Diese sollten im HTA berücksichtigt werden. Fehlende Definitionen 14. Im HTA Protokoll werden nur teilweise und nicht abschliessende Angaben gemacht, wie und weshalb gewisse Studien ein und/oder ausgeschlossen werden. Dies führt unweigerlich zu einem potentiellen «Bias», welcher zusammen mit dem hohen Grad an Komplexität durch die Vermischung aller Studienpopulationen, fehlenden Definitionen, mangelnder Zielführung und unklarer Prozessbeschreibung des HTAs eine Anpassung des Protokolls erfordert. HTA-Prozess 15. Der Einbezug von Experten wird an verschiedenen Stellen im Protokoll erwähnt. Grundsätzlich begrüsst Novartis den Einbezug von Experten, allerdings sollten die Auswahlkriterien der Experten, deren Auflistung (Name und Fachrichtung) sowie die ausgehändigten Dokumente (z.B. Fragebogen und Auswahl der Alternativtherapien) im Rahmen des Protokolls ausgewiesen werden, um die Prozesstransparenz sowie die Validität des HTAs zu erhöhen. 16. Das Protokoll sieht nicht vor weitere Stakeholder in den HTA Prozess einzubeziehen. Die Zulassungsinhaberinnen sind wichtige Akteure bei der Herstellung der patientenindividuellen	

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		CAR-T Zelltherapie. Gerne stellt sich Novartis dem BAG für einen kollaborativen Austausch zur Verfügung. Darüber hinaus ist anzumerken, dass das Protokoll keine Angaben enthält, zu welchen Fragen und Bereichen die Zulassungsinhaberinnen konsultiert werden. Es ist wichtig, dass Kommentare der Zulassungsinhaberinnen zu dem HTA von der jeweiligen HTA-Stelle behandelt und rechtzeitig veröffentlicht werden. --- We have some general concerns about the proposed HTA, which we list below. At the same time, we also refer to Interpharma's statement of February 21, 2023. You will also find detailed explanations of individual points in sections 2-5 below. <u>General Notes:</u> 1. There is a lack of clear framework conditions and transparent process structures for carrying out the HTA for innovative medicines, in particular a politically and socially supported threshold value that can be used with regard to cost efficiency. 2. In addition, the exact goal of the HTA remains unclear (see also the comment on the research question). From the protocol it can be seen that it mainly aims at «disinvestment». This prior objective causes a serious bias. This is in contrast to the systematically conducted impartial HTA processes of other foreign institutes (NICE etc.). 3. As a basic legal problem that needs to be clarified, we also have to ask whether and how the effective net prices of the affected preparations are taken into account in the HTA using confidential price models. A statement in this regard is missing	

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		in the HTA protocol. In our view, an indirect publication of the confidential prices by the BAG as part of an HTA violates the protection of legitimate expectations. The question is important in view of the planned publication of the HTA and must be clarified and informed before the HTA is commissioned. We ask for clarification on this. <u>CAR-T cell therapies are not all the same</u> 4. The HTA protocol provides for analyzing the two therapies Kymriah® and Yescarta® in an HTA report. This is in contrast to the systematically conducted HTA processes of other foreign institutes, which evaluate the respective therapies individually. 5. There are no comparative studies between the CAR-T cell therapies Kymriah® and Yescarta®. In addition, there are significant methodological problems with comparisons between CAR-Ts that do not allow meaningful conclusions, especially with regard to efficacy and safety. These limitations are discussed in Zhang's 2019 publication (https://doi.org/10.6084/m9.figshare.12370136). Because of these problems 6. Cost-effectiveness analyzes based on cross-study evidence are subject to the same limitations. It is crucial to note the limitations associated with such analyzes and to interpret such results with extreme caution in any HTA assessment. Clinical and policy decisions should not be made on such a basis. Misinterpreting such results could have a significant impact on patient access. 7. The BAG assumes in the HTA protocol that the two CAR therapies are the same per se. Although the clinical data prove	

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		the opposite: Not only do both therapies have different molecular properties (e.g. signaling domains or different gene editing vectors), different production processes and handling of the cell cultures (e.g. the possibility of cryopreservation), but also show different study data with regard to efficacy - and tolerance profile. <u>The complexity of CAR-T cell therapies is beyond the scope</u> 8. We consider the core problem of the planned HTA to be that with a "Cross-class" HTA, the complexity of the assessment increases to such an extent that ultimately no valid statements and results can be generated (see explanations under PICO). 9. In particular, the therapy of diffuse large B-cell lymphoma (DLBCL) but also of pediatric acute leukemia and the therapy schemes are so individual that each patient is treated differently depending on their history, metastasis, etc. 10. The approval studies of CAR-T cell therapies show differences in the patient populations included, which severely limits the comparability of the study data and results. The implementation and analysis of multi-HTAs (several different active ingredients in one HTA) requires consistent and comparable study data on the individual interventions and comparative therapies. This requirement is not met in the present HTA. In other countries, each CAR-T product was consistently assessed separately. 11. Instead, we would propose to limit the research question to specific patient population and CAR-T product and conduct separate HTA studies. 12. CAR-T cell therapy involves many actors who can influence the	

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		success of the treatment (outcome) with regard to the time factor. The literature (Chen et al. 2020; Thornton Snider et al. 2019; Tully et al. 2019) shows that the waiting time is a significant influence the outcome of CAR-T cell therapy. The HTA assessment should include the waiting time in its analysis. The stakeholders include the referring physician, the treatment center, the health insurers, the cell laboratory and the marketing authorization holder related to manufacturing. All of these actors can lead to bias, which needs to be taken into account in the HTA analysis. <u>Consideration of the latest and relevant data</u> 13. CAR-T cell therapy is a new, highly innovative therapy for which new data is constantly being generated. Therefore, the current data (e.g. clinical data, guidelines, health economic data) should be used for each product. In addition, current data is presented annually, e.g. at the American Society of Hematology Congress (ASH) in December. These should be taken into account in the HTA. <u>Missing definitions</u> 14. The HTA protocol provides only partial and non-conclusive information as to how and why certain studies are included and/or excluded. This inevitably leads to a potential "bias", which, together with the high degree of complexity caused by the mixing of all study populations, missing definitions, lack of target guidance and unclear process description of the HTA, requires an adjustment of the protocol. <u>HTA process</u>	

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		15. The involvement of experts is mentioned at various points in the minutes. In principle, Novartis welcomes the involvement of experts, but the selection criteria for the experts, their list (name and specialty) and the documents handed out (e.g. questionnaire and selection of alternative therapies) should be shown in the protocol in order to ensure process transparency and the validity of the HTA increase. 16. The protocol does not provide for the involvement of other stakeholders in the HTA process. The marketing authorization holders are important players in the manufacture of patient-specific CAR-T cell therapy. Novartis is happy to make itself available to the BAG for a collaborative exchange. It should also be noted that the protocol does not contain any information on which questions and areas the authorization holders are consulted. It is important that comments from marketing authorization holders on the HTA are dealt with by the relevant HTA body and published in a timely manner.	