Tabelecleucel for Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease Response to Public Comments on Draft Evidence Report

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#	Comment	Response/Integration
Manufacturers		
Pierre Fabre Pharmaceuticals		

1.	We agree with the following findings in ICER's Draft Evidence Report:
	• A high unmet need is associated with R/R EBV+ PTLD due to limitations of current disease management options, poor survival, and the devastating impact of R/R EBV+ PTLD on patients and caregivers.[1]
	  ○ Patients have limited treatment options and are faced with very poor survival (roughly 3 weeks to 4 months).
	  ○ It imposes tremendous impact on physical, emotional and social functioning as well as a high-cost burden with more than three-fold higher post-transplant costs compared with patients who do not have PTLD.
	  ○ Side effects/adverse outcomes of current management options, such as organ/graft failure, can be severe and affect patient health-related quality of life.
	• Treatment with tabelecleucel appears to induce complete or partial response in at least half of patients, extending survival for patients who otherwise usually die in weeks to months, with few harms. Thus, we have a high certainty of substantial net health benefit (A) for tabelecleucel compared with usual care."[1]
	  ○ Tabelecleucel demonstrated a response rate of 51% with median duration of response of 23 months and median overall survival of 18.4 months. This compares with median overall survival of 0.7 months for hematopoietic stem cell transplant (HSCT) and 4.1 months for solid organ transplant (SOT) in the real-world setting.[2]
	  ○ Very few harms were noted in the Phase 3 ALLELE clinical trial of tabelecleucel compared with severe side effects associated with current treatment options.[2]
		Thank you for your comment.

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2.	We are also pleased that ICER recognizes that tabelecleucel is a treatment that offers a substantial opportunity to improve patient access due to its formulation as an off-the-shelf, cytotoxic T-cell therapy and its flexible site of administration given it can be administered in an outpatient setting. • Due to very poor survival, rapid access to treatment is critical to offer patients the best opportunity for survival. Tabelecleucel, as an off-the-shelf T-cell immunotherapy, offers an opportunity to treat more patients in a timely manner.	Thank you for your comment.
3.	We are also pleased that ICER recognizes that tabelecleucel is a treatment that offers a substantial opportunity to improve patient access due to its formulation as an off-the-shelf, cytotoxic T-cell therapy and its flexible site of administration given it can be administered in an outpatient setting. • Due to very poor survival, rapid access to treatment is critical to offer patients the best opportunity for survival. Tabelecleucel, as an off-the-shelf T-cell immunotherapy, offers an opportunity to treat more patients in a timely manner. While ICER has described tabelecleucel as a donor-derived T-cell therapy in the Draft Evidence Report, we request ICER accurately describe tabelecleucel as an allogeneic, off-the shelf, T-cell therapy, as it appears in the literature.	We appreciate this feedback. We have made changes to the Evidence Report to make the description of tabelecleucel consistent with the literature.
4.	**We ask ICER to further consider these additional important aspects prior to the Final Evidence Report:** **The modified societal perspective should be included as a co-base case instead of a sensitivity analysis since patient community input substantiates the significant impact of EBV+ PTLD on caregivers and society.** ICER stated that it could not conduct a co-base case analysis reflecting the modified societal perspective because there was "no direct data available to inform the analysis" despite vocal feedback from the patient community regarding the significant impact of EBV+ PTLD on caregivers and society. However, as part of Section 5. Benefits Beyond Health and Special Ethical Priorities, ICER acknowledges: "An effective treatment for EBV+ PTLD could produce substantial improvement in caregivers' quality of life since patients could	Thank you for your comment. Although direct data is lacking, we recognize the impact of EBV+ PTLD on caregivers and society. Consistent with our 2023 Value Assessment Framework, we implemented new methods to ensure that cost-effectiveness analyses done according to a modified societal perspective have "non-zero" inputs for impacts on productivity for the patient and caregivers, even when direct data are lacking. As stated in ICER's Reference Case and in the scoping document for this review, the modified societal perspective is considered a "co-base case" only when

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	return to their prior level of functioning and decrease caregiver burden." *As such, we request that ICER consider the modified societal perspective as a co-base case analysis versus a sensitivity analysis, to reflect the robust input from the EBV+ PTLD community.*	the following three conditions are satisfied: 1) the impact of treatment on indirect costs is judged to be substantial, **2) direct data are available for the impact of treatment on at least one of the indirect cost domains, and** 3) these costs are considered large in relation to health care costs associated with treatment of the condition. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per evLYG or QALY, and/or when the result crosses thresholds of $100,000-$150,000 per evLYG or QALY. For this review, due to the lack of direct data to quantify the impact of treatment on societal cost domains, ICER undertook an indirect approach to valuing patient and caregiver productivity impacts for tabelecleucel compared to standard of care. This indirect approach relies on a published relationship between patient utility scores and time use, which is not specifically developed and validated for patients with EBV+ PTLD. As such, the modified societal perspective is presented as a scenario analysis. Importantly, we also highlighted the potential impact of treatment in improving societal outcomes that are important to patients in the Benefits Beyond Health and Special Ethical Priorities section of our report.
5.	**The eligible population estimate should be decreased based on publicly available data, and the budget impact estimates adjusted accordingly.** In ICER's *Revised Scoping Document* published on May 30, 2024, ICER correctly points out: "Post-transplant lymphoproliferative disease (PTLD) is a rare, serious, often fatal complication of solid organ transplant (SOT) and allogeneic hematopoietic stem cell transplant (HCST), with only several hundred cases per year reported in the US (United States)." This estimate of a few hundred cases in the	Thank you very much for outlining your approach to calculating the potentially eligible patient population of tabelecleucel. We agree that our estimate for the potentially eligible population in the Potential Budget Impact Model was overestimated. Our estimate for the incidence of EBV+ PTLD for solid organ transplant was incorrectly calculated and

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	US is well supported in the published literature. However, ICER's *Draft Evidence Report*[1] includes a budget impact analysis with estimates of 13,319 eligible patients (inclusive of SOT and HSCT) in the US over five years. Based on epidemiologic data derived from the published literature and appropriately weighted for transplant type, the subset of EBV+ PTLD patients (inclusive of SOT and HSCT) in the US who are refractory to first line treatment with rituximab/chemotherapy is approximately 319 patients per year, a number substantially smaller than ICER's estimate. Please see below for our calculation estimates with sources. We assume that there will be approximately 62,500 annual transplant patients in total (SOT 52,818; HCT 9,829). We began with the 2023 transplant incidence rates for SOT and HCT and grew them annually on a compound annual growth rate (CAGR) based on past annual transplant data from 2016-2023 for each organ (kidney, liver, heart, lung, pancreas, intestine, multi-organ) and for allogeneic HCT.[3,4] From 2026 onward, the transplant incidence was grown at the same rate as the US population yearly growth, 0.51%, based on UN population data.[5] Transplant incidence was further split based on adults vs. children for each organ type/HCT. Because EBV+ PTLD incidences vary greatly depending on organ type/HCT and age group (see Table 1 below), we first applied PTLD incidence rates for each organ type/HCT for adult and children rates (SOT blended average 3.2%, dependent on organ type and age group; HCT blended average 3.0%, dependent on age group), gathered across multiple studies.[7-12,14-29] EBV+ incidence was then applied (SOT average 66.5%, dependent on organ type and age group; HCT 95.0%).[18,30-39] First line treatment rates of rituximab +/- chemotherapy were applied at a flat rate of 75% across all groups, based on published literature.[17,22,40-49] Patients eligible for tabelecleucel therapy are relapsed/refractory to the above mentioned first lines of therapy. According to literature, 30% of these patients are refractory to rituximab +/- chemotherapy.[14-16,30,36,50-57] Little literature exists specifically for relapsed patients; therefore, refractory rates were assumed to be relapsed/refractory in the calculations. These inputs yield an estimated 1,594 patients over five years or approximately 319 patients with relapsed/refractory EBV+ PTLD per year.	did not account for proportional weighting of incidence rates according to number of transplants performed for each organ type. Our information was derived from information reported in the Annual Data Report of the US Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR) which are the same primary sources used by the manufacturer. Our incidence estimate for solid organ transplant has been revised to reflect a weighted average of the 5-year incidence rates for kidney, pancreas, liver, intestine, heart, lung, and multi-organ transplants reported by the manufacturer in their accompanying response (Table 1) (i.e., 2.13% for SOT assuming a PTLD incidence of 3.2% and an EBV+ incidence of 66.5%). We have also revised our estimate for the incidence rate for hematopoietic stem cell transplant to capture cases that may occur beyond year 1 and have used the midpoint of the range 1.0 to 3.5% reported in Campagno et al 2020 (i.e., 2.25%). We appreciate the manufacturer sharing a list of sources and the incidence rates for each transplant type and age group and for their additional clarification regarding how the blended averages were calculated. Notably, the references that ICER used in calculating the incidence rates (OPTN/SRTR) aligns with the manufacturer's preferred source for these estimates. To summarize, our key assumptions to estimate the eligible patient population for the Potential Budget Impact Model in the Revised Evidence Report include: Number of SOTs and HSCTs per year (US): 49,187 and 9,299, respectively (no change from draft to revised Evidence report)

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Table 1. PTLD and EBV+ incidences, by transplant type and age group

Transplant type	PTLD incidence	EBV+ incidence
HCT	Adults: 2% Children: 4%	Adults: 95% Children: 95%
Kidney	Adults: 1.5% Children: 10.1%	Adults: 55% Children: 90%
Liver	Adults: 3% Children: 4%	Adults: 80% Children: 90%
Heart	Adults: 6% Children:15%	Adults: 50% Children: 90%
Lung	Adults: 5% Children: 15%	Adults: 80% Children: 90%
Multi-organ	Adults: 12.5% Children: 25%	Adults: 79% Children: 90%
Pancreas	Adults: 9% Children: 9%	Adults: 50% Children: 90%
Intestine	Adults: 10% Children: 10%	Adults: 60% Children: 90%

Note: Incidence rates were gathered for each transplant type and age group across multiple sources of literature to determine the appropriate incidence rate to use in calculations. These rates were applied over the respective transplant type and age groups.

Therefore, the estimate for eligible patients in ICER's budget impact analysis should be revised from 13,319 eligible patients to 1,594 eligible patients over five years (equating to approximately 319 patients per year in the US). A lower budget impact typically correlates with broader patient access to an important new treatment option, which is particularly important in this situation given there are currently no FDA-approved treatments for this ultra-rare disease with poor prognosis and high mortality rates.

We ask that ICER lower the estimate of eligible patients and associated budget impact for tabelecleucel to 1,594 eligible patients over five years based on these public sources and calculations.

Incidence of EBV+ PTLD: 2.13% (SOT) and 2.25% (HSCT) (revised from draft to revised Evidence report)

Percentage of patients who receive first line treatment with rituximab +/- chemotherapy: 75% (revised from draft to revised Evidence Report to reflect literature suggesting that 50%-100% of patients receive rituximab +/- chemotherapy first-line).

Percentage of patients who are relapsed or refractory to first line rituximab +/- chemotherapy: 50% (no change from draft to revised Evidence report)

Our estimated eligible patient population for the potential budget impact model in the Revised Evidence Report has been revised to 2,355 patients over five years (or 471 patients per year).

6. **ICER should incorporate available long-term efficacy data from the tabelecleucel expanded access protocol into its assessment to more accurately reflect the impact of tabelecleucel on longer-term outcomes.**

Thank you for this suggestion. The most recent data from the ALLLELE study and EAP has been incorporated into the Section 3.2, under the Overall Survival section. However, a common milestone for cancer patients is 5-year overall

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	ICER expressed uncertainty about the long-term durability of response for tabelecleucel based on the data from the ALLELE study. However, there are recently published longer-term data from the expanded access protocol that can be used to assess the longer-term benefits of tabelecleucel.[58] While these data represent a smaller cohort than studied in the phase 3 ALLELE study, they provide important insights that reinforce the longer-term safety and efficacy of tabelecleucel for patients with R/R EBV+ PTLD. ○ The estimated one- and two-year overall survival (OS) rates were both 70.0% (95% confidence interval [CI], 46.5-84.7) overall, both 61.5% (95% CI, 30.8-81.8) in HCT, and both 81.5% (95% CI, 43.5-95.1) in SOT (median follow-up: 8.2, 2.8, and 22.5 months, respectively). Patients responding to tabelecleucel had higher one- and two-year OS rates (94.1%) than nonresponders (0%).[58] *We request that ICER incorporate this published longer-term efficacy data into its assessment.*	survival, and it appears these data have not yet been reported for the cohort in the ALLELE study or EAP. Additionally, because treatment with tabelecleucel carries the risk of severe adverse events such as GvHD, which may take time to develop, the long-term safety of treatment would be important data for the assessment of overall harms and benefits of tabelecleucel. We have revised the report to more clearly reflect these points.
7.	**The costs and quality of life impacts associated with organ/graft rejection among patients with EBV+ PTLD who are treated with chemotherapy should be accounted for in the cost-effectiveness analysis, particularly given that organ/graft rejection due to reduction of immunosuppression is a major adverse outcome in chemotherapy patients, leading to devastating transplant failure with substantial cost and QALY implications.** There were no cases of organ/graft rejection attributable to tabelecleucel therapy reported in the ALLELE study. However, Socie et al. reported that 1-3% of patients in a real-world comparator arm experience organ/graft rejection.[59] Graft failure is associated with substantial costs and quality of life impacts. For example, Sussell et al. reported that for the average kidney transplant patient, graft failure would impose additional medical costs of $78 079 (95% confidence interval [CI] $41 074, $112 409) and a loss of 1.66 QALYs (95% CI 1.15, 2.18).[60] *We request that ICER incorporate the above-mentioned cost and consequences of organ/graft failure for the usual care arm to accurately reflect the costs and consequences of organ/graft failure due to reduction of immunosuppression among chemotherapy patients with EBV+ PTLD.*	Thank you for your suggestion and for providing relevant data. The team has discussed this matter with clinical experts to determine whether it is appropriate to consider organ/graft rejection. Based on our discussions with various clinical experts, we concluded that organ/graft rejection is not a relevant consideration in this context, as stated in the report: *"Although graft-versus-host disease and organ rejection are adverse events of special interest, they were not modeled because clinical experts have suggested that these events do not have a causal relationship with the comparator, and there is still limited tabelecleucel-specific evidence for these events.as the available data does not provide sufficient evidence to suggest that the incidence of organ/graft rejection differs between the two arms. "* Specifically, clinical experts indicated that there is nono causal relationship is

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		expected between chemotherapy use and organ/graft rejection. Organ/graft rejection is rather associated with a reduction in immunosuppression, but there is no evidence suggesting that the reduction in immunosuppression differs significantly between the two treatment armsbetween tabelecleucel and standard of care. Additionally, the study by Nikiforow (2024) in Blood Advances reported a few cases of graft-versus-host disease in patients treated with tabelecleucel, which were considered possibly related to the treatment. Consequently, although we did not include it in the model, we cannot rule out the possibility that there would be This complicates our ability to conclude that there will be no incidence ofcases of organ/graft rejection in the treatment tabelecleucel arm. Lastly, the incidence rates of organ/graft rejection reported with chemotherapy in in the ALLELE trial and by Socie (2024) are unadjusted estimates, and relying on these unadjusted figures may introduce confounding bias.

#	Comment	Response/Integration
Other		
Partnership to Improve Patient Care		
1.	**Caregiver impact should be included in the model.**	Thank you for highlighting the impact on caregivers.

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	ICER chooses not to include caregiver costs in the model, despite acknowledging in the opening of the report that caregiver burden is high given the severity of disease and the side effects of currently available treatments. The literature supports this assertion that caregiver burden for PTLD is substantial. The modified societal perspective ICER employs uses a proxy version of caregiver cost, while neglecting to incorporate caregiver quality-of-life. PIPC asserts that ICER should be incorporating both directs costs and caregiver quality of life and that both should be included in ICER's base case model.	Our draft Evidence Report captured the impact on caregivers productivity in our modified societal perspective analysis. We also recognize the significance of caregiver burden in this context, however, there is a lack of data specific to EBV+ PTLD following transplantation or similar diseases to inform caregiver quality of life impacts comprehensively and accurately. We have added the following text in the **Uncertainty and Controversies section** of the Revised Evidence Report to acknowledge this limitation: *"We were unable to incorporate caregiver quality of life impacts in our modified societal perspective analysis due to data limitations. While qualitative and anecdotal evidence suggests that caregiver quality of life may decrease both mentally and physically, we could not include this impact due to insufficient data to accurately reflect how treatment affects the quality of life of caregivers throughout the course of EBV+ PTLD."*
2.	**ICER's model does not reflect the reported results in the trial data it has chosen to use.** The ICER model assumes that the survival benefit for tabelecleucel is the same for patients with hematopoietic stem cell transplantation (HCST) and solid organ transplant (SOT). However, the evidence the report relies on clearly states that the survival benefit is different. The ALLELE RCT reports Median survival was 18.4 months in all patients and 16.4 months in SOT, which suggests survival would be higher in HSCT.	Thank you for your comment. Based on the current evidence, we are unable to conclude that there is a differential survival benefit between the SOT and HSCT populations. More data are still needed to understand whether there may be clinically important differences in subgroup treatment effects between the two groups. Although the HSCT population appears to have higher survival rates, current data from the ALLELE study shows similar overall and complete response rates between the HSCT and SOT groups. This may, in part, be due to the heterogeneity of the SOT group, as the underlying survival rate of that group also depends on the type of transplant. Furthermore, since the ALLELE trial is a single-arm study, it does not provide the survival benefit of tabelecleucel compared to the standard of care. Therefore, we were unable to use the trial data directly to model the differential survival benefit

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		of tabelecleucel. Instead, we referenced Barlev 2024, a comparative effectiveness study that reported the adjusted survival benefit of the treatment. This study, however, reported the hazard ratio for overall survival for the combined SOT and HSCT population, not separately for each population. Since we don't have sufficient data to differentiate the survival benefit of tabelecleucel between the SOT and HSCT populations, we used the same hazard ratio for overall survival for both populations, but with different underlying survival curves for which the treatment benefit is applied. Please note that we also highlighted this as an area of uncertainty in the **Uncertainty and Controversies section** of our report as follows: *"We attempted to address the heterogeneity by modeling patients with EBV+ PTLD following SOT and HSCT separately, based on the clinical evidence presented in the ALLELE trial and other literature, and suggestions from clinical experts. Due to the lack of population-specific data for key model parameters, such as the survival benefit of tabelecleucel, there remains a high level of uncertainty in the results for individual populations. Notably, based on our assessment of the clinical validity of the survival estimates compared to those reported in the ALLELE trial, we suspect that our model overestimates the survival benefit for SOT and underestimates it for HSCT (we did not have stratified data available to estimate survival benefit separately). Therefore, our primary analysis was based on a weighting of results according to the proportions of patients with a SOT and HSCT in the ALLELE trial."*
3.	ICER should adhere to the rates of utilization in the trial data it has chosen to use instead of extrapolating its own assumption about dosing. The ICER report states that all patients given tabelecleucel are assumed to receive 3 cycles	The number of cycles or doses of tabelecleucel used in the model was based on the ALLELE trial. In the trial, the median number of treatment cycles was 2 (IQR: 1-

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	of treatment. The source of the efficacy data suggests all patients that received at least 1 cycle of tabelecleucel - with a maximum of 3 - were included in the trial results. despite this data, the ICER model assumes *all* patients received all 3 cycles. The dosing in the model should reflect the source of the efficacy data. If the mean/median dosage for those patients treated was between 1 and 3 cycles, then the costs should reflect that, as the efficacy data reflects the actual, not preferred, rate of utilization/dosing. We urge ICER to revisit the model to reflect the actual level of utilization that generated the efficacy results from the RCT, not a hypothetical treatment regimen.	3) for the SOT population and 3 (IQR: 2-4) for the HSCT population. We used these median values for the base-case analysis, stratified by population, and applied the IQR to establish the upper and lower bounds in the sensitivity analysis. Please refer to **Table E2.9** for the values used in the base-case analysis and **Section E4** for the lower and upper bounds for the number of cycles for each population.
4.	**ICER's oversimplification risks distorting the actual costs of the treatment being evaluated versus that of usual care.** In the description of the ICER model the report states that they assume that '*after treatment failure with tabelecleucel (or usual care) there is only one subsequent treatment.*' It is not reasonable to apply this rule equally with respect to subsequent treatment costs for patients who remain alive after successful treatment with tablecleucel and usual care. The basic assumption is not accurate based on the literature suggesting that only a fraction of patients undergo subsequent treatments upon treatment failure in usual care. This assumption is contrary to the goal of assessing the treatment's clinical efficacy. The reason cost of treatment will accrue more rapidly for patients being treated with tabelecleucel is that a much higher proportion of patients being treated remain alive at each timepoint throughout the time horizon of the model than those in the usual care arm. The goal should be to keep patients alive for longer, so a modeling construct should not work against that goal.	As detailed in our Draft Evidence Report, the proportion of patients receiving subsequent treatments is different between the tabelecleucel and standard of care arms and is based on a patient's response to treatment using data from the ALLELE trial. The ALLELE trial found that 14% of responders and 52% of non-responders received subsequent therapy. Since there was a higher percentage of responders in the tabelecleucel arm compared to standard of care, the percentage of patients receiving subsequent therapy with tabelecleucel was lower than that of standard of care. Please see **Table 4.1** and **Section E2** (Drug Utilization) for details.
5.	**ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.** Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions, and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives	Thank you for your comments. Here are some materials explaining ICER's use of cost-effectiveness measures including the QALY and the evLY: • A patient-focused explanation of these measures. • A peer-reviewed academic explanation of these measures. • ICER's reports are consistent with federal guidelines that detail how

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	of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments. The recent nondiscrimination regulations governing Section 504 of the Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance. We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities. It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color. With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.	to use these measures while protecting those with disabilities.
6.	**ICER continues to assume a linear relationship between severity of disease and utility increments. This is an outdated approach to cost-effectiveness analysis.** As PIPC has included in past ICER comments, the field of cost-effectiveness analysis is evolving. If ICER seeks to provide credible assessments, it is imperative that its methods also evolve. There has been a widespread questioning of several of the assumptions that cost utility analysis is built on. This argument has been most prominent with respect to the reliance on the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value. In other words, a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden. In fact, several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very	Thank you for your comment. We are aware of the active methods exploration regarding the impact of underlying disease severity on the value of health gains from treatment. Notably, the GRACE framework has been developed to introduce the concept of diminishing returns to health in recent years. As stated in our 2023 Value Assessment Framework update, we are committed to working with experts to independently assess the merits, challenges, and suitability of this framework for HTA processes and recommendation development. [1,2] We also acknowledge that some HTA agencies in the England and Europe employ a "modifier" approach to weight health gains and/or adjust thresholds for what

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	reason, and incorporate the role of severity adjacent to the results to make a more context-relevant models. A system of evaluation that treats therapeutic innovations in these disease spaces as of similar relative value for unit of health gain in less severe conditions - and for patients who have minimal disease burden - is thought by many to be inherently unfair and skewed in the wrong direction. This has obvious relevance to patients with EBV+PTSLD as the health utility value of non-responder states is below 0.4 – which is severe disease.	those health systems should pay for treatments that target severe diseases. While we believe these evolving approaches merit further consideration, a full assessment of their benefits, limitations, and implementation challenges, as well as a discussion of their implications in multi-stakeholder settings, are required before adoption in ICER reviews can be considered. We would like to carefully consider the criticisms that have come in response to the use of severity modifiers in England, the Netherlands, Norway, and other settings. For example, these methods have been criticized for arbitrary cut-offs of calculated QALY "shortfall" data used to discriminate among severity categories, the use of these systems to increase payments for treatments for severe conditions without commensurate reductions in payment for milder diseases, and the breadth of the severity categories themselves, which may violate fundamental principles of horizontal and vertical equity.[3,4] These challenges have been noted and discussed over several decades, with particular emphasis on the notion that over-simplified approaches may be easier to understand but not necessarily representative of patient or public preferences.[5] [6] Indeed, no sooner had England's National Institute for Health and Clinical Excellence (NICE) published a report concluding that their severity modifier was working as intended when the Association of the British Pharmaceutical Industry (ABPI) published a critique of the approach as overly conservative, claiming that certain diseases rated as moderately severe were actually much more serious.[7] Although the GRACE approach is theoretically promising and may address some criticisms of the modifier approaches described above, concerns remain regarding the validity and

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		compatibility of methods to estimate new parameters such as relative risk aversion and marginal rate of substitution between life expectancy and quality of life across patients with different health states and in various therapeutic areas.[4,8,9] In addition, the possible substantial variation in the threshold for considering cost-effectiveness across conditions may be problematic to operationalize in HTA settings. Perhaps most importantly, the cultural implications of this type of severity adjustment, including lower cost-effectiveness thresholds for diseases deemed "less severe", have not been socialized with the patient and caregiver communities in the US that may be disadvantaged by such categorizations. We note that ICER's approach already includes qualitative consideration of disease severity and level of unmet need as part of its public deliberation on benefits beyond health and special ethical priorities, consideration that is informed by the same type of shortfall data described above and further informed by testimony from patients, caregivers, and other stakeholders. Any attempt to move from qualitative consideration to a quantitative approach will require validation of the evolving methods and careful consideration of their potential social and cultural implications.

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