Sanofi thanks ICER for the opportunity to comment on their draft evidence report assessing the investigational treatment of tolebrutinib for the treatment of non-relapsing secondary progressive multiple sclerosis. Tolebrutinib is currently under review with the U.S. FDA and is not approved anywhere globally. Tolebrutinib represents hope for persons living with multiple sclerosis (PwMS) who have no treatment options for non-relapsing SPMS. It is always a challenge to assess innovation that has no comparator, so we offer the following comments and recommendations to ICER for their consideration.

Underrepresentation of the importance of slowing disability progression not due to relapses

The traditional cost effectiveness model structures in multiple sclerosis were initially built with relapsing disease in mind because the available treatment options were all for relapsing-remitting forms of the disease. The cost-effective prices derived from these models were heavily driven by the costs and disutility coming from relapse activity. So, treatment options that had larger impacts on relapse suppression would achieve higher prices which was intuitive. However, these models always struggled to capture the full direct and indirect costs of disability progression. This became very clear once treatment options for primary progressive disease showed success in clinical trials. The traditional Markov cost effectiveness structure was adapted by removing relapses from these models but the direct and indirect costs associated with disability progression were not reassessed.

A clear example of the consequences of these choices is ICER's review of ocrelizumab for RRMS and PPMS. Ocrelizumab was the first ever option for primary progressive multiple sclerosis yet ICER's recommended cost effective price for ocrelizumab for RRMS was four times higher than ICER's recommended cost-effective price for ocrelizumab for PPMS despite the many treatment options already available for RRMS.

Recommendation: We recommend that ICER should at a minimum reassess how they are capturing direct and indirect costs of disability progression so options that are first in class are not penalized if they are targeting slowing or reversing disability progression rather than targeting relapse prevention. Alternatively, ICER and all bodies using cost-effectiveness need to assess if this adaptation of the traditional RRMS Markov model structure is the most appropriate way to model treatments for multiple sclerosis that are not solely focused on relapse prevention. The best model for multiple sclerosis treatments might be one that moves away from the traditional phenotype definitions and instead allows the model to appropriately weight and value the impact on relapses and the impact on disability progression in absence of relapses.

Evidence rating for Tolebrutinib

We appreciate ICER's partnership as we continue to provide data from the clinical trial programs once they are fully validated and are ready for dissemination. The GEMINI and HERCULES programs are robust, large programs and analysis was ongoing for several months after the phase 3 readout in September 2024. The data from GEMINI 1 and 2 and HERCULES were published in The New England Journal of Medicine just days before the release of the draft evidence report so we appreciate that ICER did not have full access to the

data prior to the report's release. However, now that more data is available, we believe the P/I assessment rating from ICER does not reflect the true strength of evidence. ICER cited concerns about the lack of improvement in brain atrophy, limb mobility via the 9 hole peg test (9-HPT), and liver monitoring as reasons for their assessment for tolebrutinib.

GEMINI 1 did demonstrate a nominally significant improvement in brain volume loss (BVL). While GEMINI 2 and HERCULES did not demonstrate statistically significant improvements in BVL, the BVL observed in the tolebrutinib arms in GEMINI 1 and 2 and HERCULES (about -0.7% from month 6 to end of study) was approaching what is observed in healthy people. It is important to note that teriflunomide, the active comparator in GEMINI has been shown to have significant benefit in BVL measurements versus placebo. While the importance of BVL in RRMS is fairly well understood, the importance of BVL in SPMS is not as well understood.

Within HERCULES, liver enzyme elevations (>3xULN) were observed in 4.1% of participants receiving tolebrutinib compared with 1.6% in the placebo group, a side effect also reported with other BTK inhibitors in MS. A small (0.5%) proportion of participants in the tolebrutinib group experienced peak ALT increases of >20xULN, all occurring within the first 90 days of treatment. All but one case of liver enzyme elevations resolved without further medical intervention. Prior to the implementation of the revised study protocol with more stringent monitoring, one participant in the tolebrutinib arm experienced hepatotoxicity leading to a liver transplant and died due to post-operative complications. Once we identified a signal for hepatotoxicity in mid-2022, the stringency of monitoring was increased such that weekly monitoring was implemented between weeks 2 and 12, with monthly monitoring from month 3 until month 12 and quarterly monitoring through end of study.

For limb mobility, the upper limb mobility as captured by 9-HPT was not statistically significant. However, lower limb function measured by the 25FWT was nominally significant (statistically significant but lower in the hierarchy than the failed 9-HPT endpoint). Across the full trial population (both treatment arms), only 25% of participants experienced ≥20% worsening in 9-HPT scores.

Recommendation: With the additional data provided separately from these public comments given embargoes and space constraints, we recommend that ICER reassess the evidence rating and the impact of the liver monitoring schedule both on the evidence rating and model.

Costs and other discrepancies in the model, report, and SAP

There appears to be a discrepancy in the costs used between the report, SAP, and model. The SAP referenced Hernandez (2016) interpolation of Kobelt data inflated using US BLS (2023a), however the report mentions the use of Hernandez (2016) interpolation of ICER 2020 Review which are much higher costs than the one mentioned in the SAP. Given the issues mentioned above around the model underrepresenting the costs of disability progression, please ensure the best data is being used and the SAP and report are consistent. There are also small discrepancies between the numbers seen in the model itself versus reported in the report that we cannot trace the source.

Recommendation: Please relook at the costs used in the model in comparison to those in the report and SAP and ensure the correct costs are being used. Please also confirm if the discrepancies between the output tables and the model have been resolved.

Inclusion of CDI in the model

The draft report mentions a desire to include the nominal CDI results in the model structure. We support capturing disease improvements observed in both treatment arms. The London Ontario dataset, while historically valuable, unfortunately does not adequately reflect potential improvements. To address the need for more information about disability improvement, we derived annual transition probabilities using the HERCULES data that can be used as an alternative to individual arm EDSS progression source, in the cost-effectiveness model.

However, this does have a significant limitation (aside from the classical trial duration constraint and restricted patient population limitations). The absence of EDSS 9 observations in HERCULES prevented us from constructing complete transition matrices. In the interest of transparency, Sanofi has provided the transition probabilities for EDSS 1-8 derived from HERCULES. These could be supplemented with London Ontario data for transitions not captured in our trial data.

The advantage of this approach is that it would allow for straightforward modification of the US ICER model, by applying CDP and CDI Hazard ratios in a consistent way, to the relevant elements of the placebo matrix, thereby comprehensively reflecting the treatment's dual benefits: slowing disease progression while effectively capturing additional improvements.

Recommendation: We recommend using the HERCULES placebo derived transition probabilities supplemented with the London Ontario dataset to fill in the EDSS 9 gap and applying the CDP and CDI hazard ratios for tolebrutinib to capture both the impact of tolebrutinib on disability progression slowing and disability improvement.

Major drivers of ICERs from the Cost Effectiveness Model

There are three further issues with the model structure that have a large impact on the resulting ICERs for tolebrutinib that should be revisited. The general mortality used is from 2019 while a 2023 version is available. The medical “unrelated” costs are unclear and no source is provided disclosing where these are from. Finally, there seems not to be any half cycle corrections in the model.

Recommendation: We recommend updating the mortality to the latest version, providing more clarity on the source of the medical “unrelated” costs and perhaps reassessing them in light of the underrepresented costs mentioned above, and applying half cycle corrections in the model.

Thank you for considering these recommendations and we look forward to the next version of the report.