Cost-effectiveness of sacituzumab govitecan (Trodelvy®) for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of sacituzumab govitecan (Trodelvy®). Following assessment of the Applicant's submission, the NCPE recommends that sacituzumab govitecan (Trodelvy®) be considered for reimbursement if cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Gilead Sciences) Health Technology Assessment of sacituzumab govitecan (Trodelvy®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2023**

Summary

In August 2022, Gilead Sciences Ltd submitted a dossier of clinical, safety and economic evidence for sacituzumab govitecan (Trodelvy®) for the treatment of adult patients with unresectable or metastatic triple negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease. Sacituzumab govitecan is a trophoblast cell surface antigen-2 (Trop-2) antibody-drug conjugate. Sacituzumab govitecan is administered by intravenous infusion at a recommended dose of 10mg/kg once weekly on days 1 and 8 of a 21-day treatment cycle. Treatment is continued until disease progression or unacceptable toxicity. The standard of care for the treatment, of this group of patients in Ireland, is dependent on previous therapies and treatment interval, and is expected to predominantly consist of single-agent chemotherapies, including for example, eribulin, capecitabine, gemcitabine and vinorelbine.

1. Comparative effectiveness of sacituzumab govitecan

The efficacy and safety of sacituzumab govitecan was assessed in the ASCENT trial, an international phase 3, multicentre, open-label, randomised study conducted in 529 patients with locally advanced unresectable triple negative breast cancer (TNBC) or mTNBC who had relapsed after at least two prior chemotherapies for breast cancer. All patients received previous taxane treatment in either the adjuvant, neoadjuvant or advanced stage unless contraindicated or intolerant to taxanes. Patients were randomised (1:1) to receive sacituzumab govitecan or Treatment of Physician's Choice (TPC), to include one of the following single-agent regimens: eribulin, capecitabine, gemcitabine or vinorelbine, determined before randomisation. The primary efficacy endpoint was progression-free survival (PFS) in patients without brain metastases at baseline (i.e. BM negative) as measured by a blinded, independent, centralised review (BICR). Secondary efficacy endpoints included PFS by BICR for the overall population, overall survival (OS), objective response rate (ORR) and duration of response (DOR). Treatment was continued until disease progression, unacceptable toxicity, study withdrawal or death. Patient characteristics were generally balanced between arms; median age was 54 (range 27 to 82 years), 99.6% were female and 79% were white. The median number of prior systemic therapies was four. The Applicant submitted initial results from the pre-specified final analysis (data cut-off 11

March 2020, median follow-up 17.7 months), and updated results from the final database lock (data cut-off 25 February 2021, median follow-up 27 months). In the updated results (consistent with the earlier analysis), treatment with sacituzumab govitecan resulted in statistically significant longer median PFS (median PFS was 4.8 months vs 1.7 months, hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.33, 0.52; p-value: <0.0001), and longer median OS (median OS was 11.8 months vs 6.9 months, HR 0.51, 95% CI 0.42, 0.63; p-value:<0.0001) in the intention to treat (ITT) population, compared with TPC. Similar results were observed in the population who were BM negative. Results of the ORR assessment (defined as a complete response or partial response), supported the PFS and OS benefit of sacituzumab govitecan with greater treatment effect in both the ITT population and the population who were BM negative (31% in the ITT population, 35% in the population who were BM negative) compared to the TPC arm (4.2% in the ITT population, 4.7% in the BM negative population). Health-related quality of life (HRQoL), assessed using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) tool, was a secondary outcome in the ASCENT trial. A post-hoc analysis reported superior changes from baseline in global health status (GHS)/quality of life, physical functioning, fatigue, and pain, for sacituzumab govitecan versus TPC. ASCENT was an open-label trial and, as such, there is potential for bias in the measurement of subjective outcomes, particularly patient-reported outcomes e.g. HRQoL outcomes and adverse events (AEs), which may be influenced by knowledge of treatment allocation. A greater percentage of patients in the TPC arm compared with the sacituzumab govitecan arm were randomised but not treated or discontinued treatment due to withdrawal of consent. Due to the open-label study design, this is likely due to patients´ expectations of receiving the intervention treatment, and may have impacted efficacy outcomes. Conservative sensitivity analysis, involving worse-case imputation, was conducted by the Applicant on request from the European Medicines Agency, and provided some reassurance on the robustness of results.

2. Safety

A total of 366 patients with locally advanced unresectable TNBC or mTNBC with at least one dose of sacituzumab govitecan and a median duration of treatment of 4.9 months were included in the safety data. The most commonly reported treatment emergent AEs in the sacituzumab govitecan arm in comparison to the TPC arm were diarrhoea (65.1% vs 17.0%),

neutropenia (64.0% vs 43.8%), nausea (62.4% vs 30.4%), fatigue (51.6% vs 39.7%), alopecia (46.9% vs 16.1%), anaemia (39.5% vs 27.7%), constipation (37.2 % vs 23.2%) and vomiting (33.3 % vs 16.1%). A similar frequency of serious AEs was observed in the sacituzumab govitecan arm (26.7%) and the TPC arm (28.1%). The EMA safety review considered that the safety profile of sacituzumab govitecan is unfavourable compared to the TPC arm, mainly due to high rates of haematological events (severe neutropenia) and gastrointestinal disorders (severe diarrhoea). Nonetheless, the safety profile of sacituzumab govitecan was considered manageable in the proposed indication of a second-line therapy in patients with locally advanced unresectable TNBC or mTNBC and the rate of discontinuations due to AEs was considered low.

3. Cost effectiveness

Methods

A three health-state partitioned survival model was submitted by the Applicant. The treatment effects captured by the cost-effectiveness model (CEM) were the delay of disease progression and death. The key efficacy inputs to the model were PFS and OS. The population characteristics were broadly based on a subset of patients recruited from ex-US (mostly European) countries in the ASCENT trial. The model comparator reflected the TPC arm of the ASCENT trial ITT population, composed of 53.1% eribulin, 19.8% vinorelbine, 14.5% gemcitabine and 12.6% capecitabine. Treatment duration was modelled using parametric survival modelling of time-to-treatment discontinuation data from the ASCENT trial, which predicted a mean treatment duration of 6.09 months and 2.11 months for sacituzumab govitecan and TPC, respectively. A relative dose intensity of 94.2%, reflecting patients' exposure to sacituzumab govitecan in the ASCENT trial, was applied to both arms. Vial sharing, leading to 50% wastage, was assumed by the Applicant. Parametric survival analyses were conducted by fitting survival functions to patient-level PFS and OS data collected in the ITT population of the ASCENT trial to make long-term extrapolations for the model. EQ-5D-3L HRQoL utilities were mapped from the EORTC QLQ-C30 data from the ASCENT trial, using the Longworth mapping algorithm. Treatment-specific utilities were applied to each health state, leading to higher HRQoL for patients receiving sacituzumab govitecan compared with TPC. The Review Group identified a number of limitations in the

Applicant's CEM, which were addressed through changes in the NCPE-adjusted base case. These changes included: alternative parametric model selection for PFS and for OS, based on statistical fit and clinical opinion; adjustment of the HRQoL utilities to account for the potential bias introduced by the open-label design, while acknowledging the clinical plausibility of a higher HRQoL in the progression-free health state, and the lack of evidence for this to continue into the progressed disease health state; removal of the vial sharing assumption; adjustment of sacituzumab drug costs to reflect the distribution of actual body weights observed in the ex-US population of the ASCENT trial; and adjustment of the cost of subsequent treatments which were underestimated in the submitted model. The base case analysis and scenario analyses were conducted from the perspective of the Health Service Executive (HSE) in Ireland, considering only direct medical costs. The model reports life years, quality adjusted life years (QALY) and costs per treatment cohort as well as the incremental cost-effectiveness ratios (ICERs). The analysis was conducted from the perspective of the HSE.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. The probability of cost-effectiveness for sacituzumab govitecan vs TPC (in both the Applicant's base case and the NCPE-adjusted base case analyses) was 0% at a threshold of €20,000/QALY and €45,000/QALY, respectively. Deterministic sensitivity analysis indicated that the most influential parameters in the model related to the choice of parametric model for OS and the progressed-disease health state utility value for both arms.

Table 1: Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC	20,148	0.51	-	-	-
Sacituzumab govitecan [b]	88,527	1.04	68,379	0.53	129,356[c]

TPC: *Treatment of physician's choice;* ***QALY****s: quality adjusted life years;* ***ICER****: incremental cost-effectiveness ratio*

[a] *Corresponding probabilistic ICER using 1000 iterations =€129,158/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.*

[c] *Figures differ from those included in the Applicant submission as the Applicant did not include the Framework Agreement rebate (7.75% at the time of submission) in their costs for sacituzumab govitecan or the comparators (eribulin and vinorelbine). This error has been corrected by the Review Group*

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC	20,067	0.49	-	-	-
Sacituzumab govitecan [b]	95,831	0.84	75,454	0.35	216,138

NCPE: *National Centre for Pharmacoeconomics;* ***TPC:*** *Treatment of physician's choice;* ***QALY****s: quality adjusted life years;* ***ICER****: incremental cost-effectiveness ratio*

[a] *Corresponding probabilistic ICER using 1000 iterations =€215,718/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.*

4. Budget impact

The price to wholesaler for sacituzumab govitecan 10mg/ml powder for concentrate for solution for infusion (200mg vial) is €1,009. The total cost of sacituzumab govitecan and TPC per patient per treatment course (assuming a mean treatment duration of 6.09 months for sacituzumab govitecan and 2.11 months for TPC), is €82,116 and €4,187, respectively. The Applicant submitted a budget impact model estimating the population of eligible patients with locally advanced unresectable TNBC or mTNBC, and the proportion expected to receive treatment with sacituzumab govitecan if reimbursed in Ireland. The budget impact model has been reviewed by the NCPE Review Group, however many of the inputs are very uncertain and there is therefore considerable uncertainty associated with the budget impact estimates. The Applicant predicted that 11 patients will be treated in Year 1 rising to 17 patients in Year 5, resulting in a total of 74 patients receiving treatment over five years. The 5-year cumulative gross drug budget impact of sacituzumab govitecan was an estimated €6.1 million (including VAT). A net drug budget impact resulted in slight cost offsets due to the displacement of lower-cost TPC agents. Clinical opinion obtained by the NCPE Review Group anticipates high levels of uptake in the eligible patient population given limited alternative treatment options. The NCPE Review Group considered that the Applicant's market share may potentially be underestimated.

5. Patient organisation submission

A patient organisation submission was not received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that sacituzumab govitecan be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.