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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

Trodelvy

International non-proprietary name: sacituzumab govitecan

Procedure No. EMA/VR/0000312649

### Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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## List of abbreviations

|                        |                                                                                          |
|------------------------|------------------------------------------------------------------------------------------|
| %CV                    | percentage coefficient of variation                                                      |
| ADA                    | antidrug antibody                                                                        |
| ADC                    | antibody-drug conjugate                                                                  |
| ADR                    | adverse drug reaction                                                                    |
| AE                     | adverse event                                                                            |
| AESI                   | adverse event(s) of special interest                                                     |
| ALT                    | alanine aminotransferase                                                                 |
| ASCO                   | American Society of Clinical Oncology                                                    |
| AST                    | aspartate aminotransferase                                                               |
| AUC                    | area under the curve                                                                     |
| AUC <sub>0-168</sub>   | area under the concentration-time curve within the first week of dosing                  |
| BAS                    | biomarker analysis set                                                                   |
| BICR                   | blinded independent central review                                                       |
| BLQ                    | below limit quantification                                                               |
| BRCA                   | breast cancer susceptibility gene                                                        |
| CAP                    | College of American Pathologists                                                         |
| CL                     | clearance                                                                                |
| C <sub>max1</sub>      | maximum observed concentration of drug after first dose                                  |
| C <sub>max,D1,SG</sub> | maximum observed concentration of drug after first dose of SG                            |
| C <sub>min,C1,SG</sub> | minimum concentration during Cycle 1                                                     |
| C <sub>min,SS,SG</sub> | minimum SG concentration during 1 dosing cycle at steady state                           |
| CHMP                   | Committee for Medicinal Products for Human Use                                           |
| CI                     | confidence interval                                                                      |
| CPS                    | combined positive score                                                                  |
| CR                     | complete response                                                                        |
| DAP                    | data access restriction plan                                                             |
| DAR                    | drug-to-antibody ratio                                                                   |
| DMC                    | data monitoring committee                                                                |
| DOR                    | duration of response                                                                     |
| EBE                    | empirical Bayes estimates                                                                |
| ECL                    | electrochemiluminescence                                                                 |
| ECOG                   | Eastern Cooperative Oncology Group                                                       |
| EMA                    | European Medicines Agency                                                                |
| EORTC QLQ-C30          | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire |
| EOT                    | End of treatment                                                                         |
| E-R                    | exposure-response                                                                        |
| ESMO                   | European Society for Medical Oncology                                                    |
| EU                     | European Union                                                                           |
| FDA                    | Food and Drug Administration                                                             |
| FFPE                   | formalin-fixed paraffin-embedded                                                         |
| GCP                    | Good Clinical Practice                                                                   |
| G-CSF                  | granulocyte colony-stimulating factor                                                    |
| HER2                   | human epidermal growth factor receptor 2                                                 |

|             |                                                                                                         |
|-------------|---------------------------------------------------------------------------------------------------------|
| HR          | hazard ratio                                                                                            |
| HR+         | hormone receptor positive                                                                               |
| IB          | investigator brochure                                                                                   |
| ICH         | International Conference on Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) |
| ICI         | immune checkpoint inhibitors                                                                            |
| IHC         | immunohistochemistry                                                                                    |
| IF          | information fraction                                                                                    |
| IIV         | inter-individual variability                                                                            |
| ISI         | integrated summary of immunogenicity                                                                    |
| ISS         | integrated summary of safety                                                                            |
| IPD         | important protocol deviations                                                                           |
| ITT         | intent to treat                                                                                         |
| IV          | intravenous                                                                                             |
| IWRS        | interactive web response system                                                                         |
| LDH         | lactate dehydrogenase                                                                                   |
| LS          | least-squares                                                                                           |
| mBC         | metastatic breast cancer                                                                                |
| MM          | Michaelis Menton                                                                                        |
| MMRM        | mixed model for repeated measures                                                                       |
| NAb         | neutralizing antibody                                                                                   |
| NR          | Not reached                                                                                             |
| ORR         | objective response rate                                                                                 |
| OS          | overall survival                                                                                        |
| PARP        | poly (adenosine diphosphate-ribose) polymerase                                                          |
| PD          | progressive disease                                                                                     |
| PD-1        | programmed cell death protein 1                                                                         |
| PD-L1       | programmed cell death ligand 1                                                                          |
| PFS         | progression-free survival                                                                               |
| PK          | pharmacokinetic(s)                                                                                      |
| PopPK       | population pharmacokinetics                                                                             |
| PR          | partial response                                                                                        |
| PRO         | patient-reported outcomes                                                                               |
| PT          | preferred term                                                                                          |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumors v1.1                                                       |
| ROPE        | region of practical equivalence                                                                         |
| SAE         | serious adverse event                                                                                   |
| SAP         | statistical analysis plan                                                                               |
| SCS         | Summary of Clinical Safety                                                                              |
| SG          | sacituzumab govitecan                                                                                   |
| $t_{1/2}$   | terminal elimination half-life                                                                          |
| TEAE        | treatment-emergent adverse event                                                                        |
| TNBC        | triple-negative breast cancer                                                                           |
| TTE         | time to event                                                                                           |
| TPC         | treatment of physician's choice                                                                         |
| Trop-2      | trophoblast cell-surface antigen 2                                                                      |
| TTD         | time to deterioration                                                                                   |

|          |                                                 |
|----------|-------------------------------------------------|
| TTR      | time to response                                |
| UGT1A1   | uridine diphosphate glucuronosyltransferase 1A1 |
| US       | United States                                   |
| $V_{ss}$ | volume of distribution at steady state          |
| VPC      | visual predictive check                         |
| WHO      | World Health Organization                       |

# 1. Background information on the procedure

## 1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland Unlimited Company submitted to the European Medicines Agency on 11 November 2025 an application for a variation.

The following changes were proposed:

| Variation(s) requested |                                                                                     | Type              |
|------------------------|-------------------------------------------------------------------------------------|-------------------|
| C.I.6.a                | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication for treatment of adult patients with PD-L1-negative metastatic triple-negative breast cancer or PD-L1-positive metastatic triple-negative breast cancer previously treated with an anti-PD-(L)1 agent in the curative setting for Trolvelvy, based on results from study GS-US-592-6238 (ASCENT-03), which is a phase 3 study of sacituzumab govitecan (IMMU-132) versus treatment of physician's choice (TPC) in Patients With Previously Untreated, Locally Advanced, Inoperable or Metastatic Triple-Negative Breast Cancer Whose Tumors Do Not Express PD-L1 or in Patients Previously Treated With Anti-PD-(L)1 Agents in the Early Setting Whose Tumors Do Express PD-L1. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

## Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0018/2020 on the granting of a product-specific waiver.

## Information relating to orphan market exclusivity

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### Scientific advice

The MAH received Scientific Advice from the CHMP on 11 November 2021 (EMA/SA/0000069358). The Scientific Advice pertained to clinical aspects of the dossier.

## 1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus

PRAC Rapporteur: Bianca Mulder

| Timetable                                                                                | Actual dates     |
|------------------------------------------------------------------------------------------|------------------|
| Submission date                                                                          | 11 November 2025 |
| Start of procedure:                                                                      | 29 November 2025 |
| CHMP Rapporteur's preliminary assessment report circulated on:                           | 23 January 2026  |
| PRAC Rapporteur's preliminary assessment report circulated on:                           | 29 January 2026  |
| PRAC members' comments:                                                                  | N/A              |
| PRAC Rapporteur's updated assessment report circulated on:                               | N/A              |
| PRAC RMP advice and assessment overview adopted by PRAC:                                 | 12 February 2026 |
| CHMP members' comments:                                                                  | 16 February 2026 |
| CHMP Rapporteur's updated assessment report circulated on:                               | 18 February 2026 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 26 February 2026 |
| MAH's responses submitted to the CHMP on:                                                | 20 March 2026    |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:    | 21 April 2026    |
| PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:    | 22 April 2026    |
| PRAC members' comments:                                                                  | N/A              |
| PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:        | N/A              |
| PRAC RMP advice and assessment overview adopted by PRAC:                                 | 7 May 2026       |
| CHMP members' comments:                                                                  | 11 May 2026      |
| CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:        | 13 May 2026      |
| CHMP opinion:                                                                            | 21 May 2026      |

## 2. Scientific discussion

### 2.1. Introduction

#### 2.1.1. Problem statement

The scope of this variation is to add a new therapeutic indication for Trodelvy for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) based on the results of the ASCENT-03 (GS-US-592-6238) study.

## **Disease or condition**

The MAH initially applied for the following indication:

*'Trodely is indicated as monotherapy for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy (see section 5.1).'*

## **Epidemiology and risk factors**

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer death in women globally as of 2022. 2.3 million women globally were diagnosed with breast cancer and 670,000 died from the disease in 2022<sup>1</sup>. Triple negative breast cancer (TNBC) accounts for approximately 15% of invasive breast cancers<sup>2</sup>. TNBC is more common in younger women than in older women and in black persons than in persons of other races and ethnic groups. Other risk factors for the disease include the presence of a breast cancer susceptibility gene (BRCA) mutation, premenopausal status, obesity, and maternal-related factors such as parity and age at first pregnancy (Trivers et al. 2009; Plasilova et al. 2016).

## **Biologic features**

TNBC is defined by a lack of oestrogen receptor, progesterone receptor, and HER2 expression in tumour cells.

## **Clinical presentation, and stage/prognosis**

Compared with hormone receptor-positive and HER2 positive tumours, TNBC is characterized by a more aggressive tumour biology and shorter overall survival with a low 5-year survival rate of approximately 12%<sup>3</sup>.

Historically, the majority of patients with TNBC experience disease recurrence, with studies reporting 25% of patients with metastatic TNBC presenting with de novo metastatic disease<sup>4,5,6</sup>; however, with recent advances in the curative setting, such as treatment with intensive neoadjuvant and adjuvant chemotherapy, anti PD-1 or anti PD-L1 therapy, and PARP inhibitors, more contemporary data suggest a shift to 33% of patients with metastatic TNBC presenting with de novo metastatic disease<sup>7</sup>. TNBC is most commonly associated with visceral metastases affecting the liver, lung, and brain<sup>8</sup>.

## **Management**

Current standard treatment for recurrent/metastatic TNBC varies by subtypes. For patients with de novo metastatic TNBC or recurrence of >6-12 months after the end of (neo)adjuvant immune

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<sup>1</sup> WHO. Breast Cancer. Available at: <https://www.who.int/news-room/fact-sheets/detail/breast-cancer>. Last Updated: 13 March. 2024

<sup>2</sup> Anders et al. The management of early-stage and metastatic triple-negative breast cancer: a review. Hematol Oncol Clin North Am 2013

<sup>3</sup> American Cancer Society. Triple-negative Breast Cancer. Available at: <https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html>. Last Updated: 01 March. 2023

<sup>4</sup> Cardoso F et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). Breast 2018

<sup>5</sup> Skinner KE et al. Real-world effectiveness outcomes in patients diagnosed with metastatic triple-negative breast cancer. Future Oncol 2021

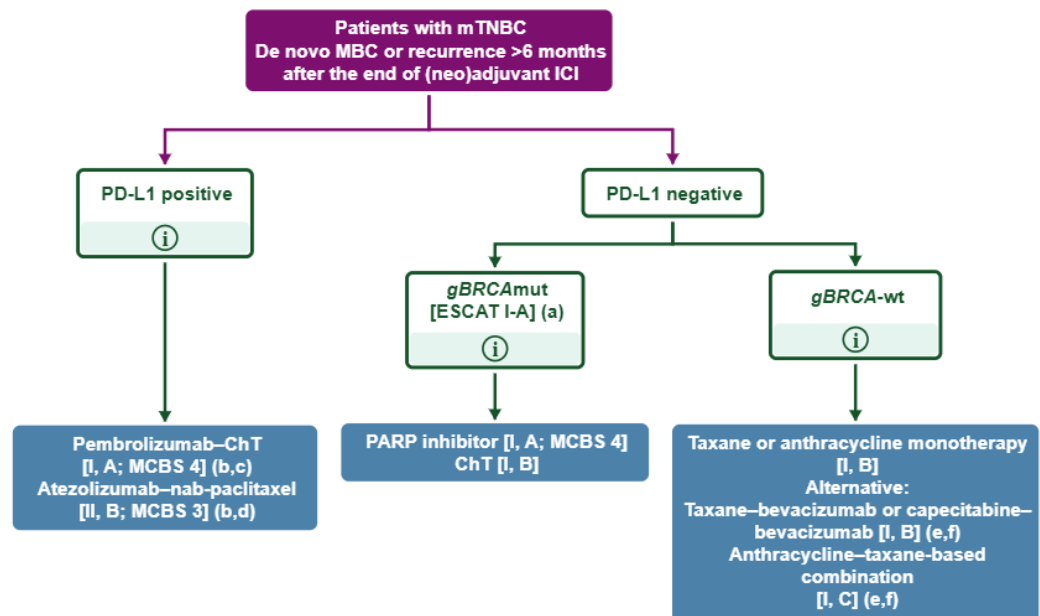
<sup>6</sup> Tan A et al. San Antonio Breast Cancer Symposium (SABCS) Virtual; 2020

<sup>7</sup> Punie K et al. Evolution of characteristics, real-world treatment landscape, and survival outcomes in patients with previously untreated mTNBC in the United States [Abstract]. ESMO Breast Cancer; 2024

<sup>8</sup> O'Reilly D et al. Overview of recent advances in metastatic triple negative breast cancer. World J Clin Oncol 2021

checkpoint inhibitors (ICI) most recent ESMO guidance recommends a combination of chemotherapy with an ICI for PD-L1 positive patients. PD-L1 negative patients with germline BRCA 1/2 mutations should be treated with a PARP inhibitor and gBRCA-wt PD-L1 negative patients should receive chemotherapy (ESMO living guideline<sup>9</sup>).

**Figure 1 De novo MBC or recurrence > 6-12 months after the end of (neo)adjuvant ICI**



(a) ESCAT scores apply to genomic alterations only

(b) Pembrolizumab may be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI

(c) ChT physician's choice of nab-paclitaxel, paclitaxel or gemcitabine–carboplatin

(d) Disease free interval should be  $\geq 12$  months in countries where this indication is approved (EMA approved, not FDA approved)

(e) If not used previously

(f) Preferred if imminent organ failure [V, B]

ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; mut, mutation; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; wt, wild-type.

The subset of patients with PD L1 positive metastatic TNBC (CPS  $\geq 10$ ) accounts for approximately 40% of patients with metastatic TNBC (Cortes et al. 2020). The prevalence of germline BRCA mutations is only 2% to 4% among patients with metastatic breast cancer and 9.3% to 15.4% among patients with TNBC (Armstrong et al. 2019). For the majority of patients, first-line treatment remains chemotherapy which is associated with a short median progression free survival (PFS) of 5.6 months and median overall survival (OS) of 16 months (Cortes et al. 2022). Therefore, there is still a significant unmet need for treatments for the subgroup of patients with TNBC who are not candidates for ICI (or PARPi).

## 2.1.2. About the product

Sacituzumab govitecan is an antibody-drug conjugate (ADC) composed of the following 3 components:

<sup>9</sup> ESMO Living Guideline for Triple-negative metastatic breast cancer; G Curigliano et al., Ann Oncol. 2025.

- The humanized monoclonal antibody hRS7 IgG1κ, which binds to trophoblast cell-surface antigen 2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers.
- The camptothecin-derived agent SN-38, a topoisomerase I inhibitor.
- A hydrolyzable linker, with the company designation as CL2A that links the humanized monoclonal antibody to SN-38.

Binding of Trop 2 by the parental RS7 antibody has been shown to result in internalization and processing of the antibody by the targeted cells. Because of its hydrolyzable linker, sacituzumab govitecan (SG) will release its SN-38 payload both intra- and extracellularly in the tumor microenvironment. SG delivers significantly greater amounts of SN-38 to a Trop 2-expressing tumour than conventional irinotecan chemotherapy. The extracellular release of SN-38 from SG also allows for bystander killing of Trop 2 negative tumour cells. Thus, SG can deliver cytotoxic chemotherapy to tumours, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy and may reduce toxic effects in normal tissues that do not express the target.

Sacituzumab govitecan is approved in the EU 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 (EC decision November 2021) and for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting (Trodelvy EMEA/H/C/005182/II/0020, EC decision July 2023).

### **2.1.3. The development programme/compliance with CHMP guidance/scientific advice**

#### **Scientific advice**

The clinical efficacy and safety of SG for the treatment of adult participants with previously untreated locally advanced unresectable or metastatic TNBC have been evaluated in study GS-US-592-6238 (ASCENT-03). EMA scientific advice regarding the design of the phase 3 study was obtained in November 2021 (EMA/SA/0000069358). The MAH overall followed the CHMP's recommendations.

Related to eligibility criteria, CHMP was critical of the fact that gBRCA1/2 testing was not mandatory and recommended that patients with BRCA mutation should have received prior PARP inhibitor or alternatively, be excluded. -> [This recommendation was not implemented by the MAH.](#)

CHMP further discussed that PD-L1 positive patients might be potentially eligible to ICI retreatment after (neo)adjuvant ICI treatment depending on the disease-free interval; therefore, the rationale for SG or TPC administration instead of using ICI-containing regimen for all patients with prior (neo)adjuvant ICI was not considered justified. -> [This was not considered relevant in view of recruited PD-L1 negative patient population \(see below\).](#)

The proposed comparator and the proposed dosing regimens were considered overall acceptable, but possible differences in baseline characteristics and prognosis between the patients who will receive carboplatin/gemcitabine doublet or taxane could not be excluded and the MAH was encouraged to consider stratification according to TPC. -> [No stratification was implemented but prespecified subgroup analyses by TPC were implemented.](#)

The optional crossover from the control arm at confirmed progression to SG was considered acceptable, since it would mirror the recommended treatment pathway and would likely occur also

outside the study, at least for patients who have received chemotherapy also in the (neo)adjuvant setting. The collection of data on sequencing of treatment, information on post-study treatment in both arms, as well as analysis of PFS2 was recommended. -> PFS2 data were provided by the MAH during the ongoing assessment.

#### **2.1.4. General comments on compliance with GCP**

The assessment of the dossier has not raised concerns regarding GCP compliance of the pivotal study ASCENT-03.

### **2.2. Non-clinical aspects**

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

#### **2.2.1. Ecotoxicity/environmental risk assessment**

The environmental risk assessment (ERA) was previously submitted for Trodelvy® as part of the EU initial MAA. The EMA guideline on the Environmental Risk Assessment (ERA) states that “the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use.” Given the dosing regimen will not change for the extension of indication and that the calculation is thus independent of the indication, an update of the ERA was not deemed warranted by the MAH and hence was not be submitted in the context of this extension of indication variation as the planned indication extension is within the environmental exposure predicted by the prior ERA. This is considered acceptable.

### **2.3. Clinical aspects**

#### **2.3.1. Introduction**

##### **GCP**

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

**Table 1 Conducted clinical studies included in this submission**

| Type of Study                 | Description of Study                                                                                                                                                                                                                                                                                                                                                                 | Data Included in This Submission                        | Study Population/<br>Number of Participants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal Study</b>          |                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| GS-US-592-6238<br>(ASCENT-03) | Phase 3, ongoing, open-label, randomized, multicenter, global study to compare efficacy of SG versus TPC as measured by PFS as determined by BICR using RECIST v1.1                                                                                                                                                                                                                  | Efficacy<br>Safety <sup>a</sup><br>PK<br>Immunogenicity | <p>Participants with previously untreated locally advanced unresectable or metastatic TNBC whose tumors are:</p> <p>PD-L1 negative (tumors with a CPS &lt; 10 using the PD-L1 IHC 22C3 pharmDx assay)</p> <p>OR</p> <p>PD-L1 positive (tumors with a CPS ≥ 10) if the patient previously received an anti-PD-1 or anti-PD-L1 agent in the adjuvant or neoadjuvant setting or if they cannot be treated with an anti-PD-1 or anti-PD-L1 agent due to a comorbidity</p> <p><u>Total</u>: 558 randomized (551 treated)<br/> <u>SG<sup>b</sup></u>: 279 randomized (275 treated)<br/> <u>TPC<sup>c</sup></u>: 279 randomized (276 treated)</p> |
| <b>Supportive Studies</b>     |                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| IMMU-132-09<br>(TROPICS-02)   | Phase 3, open-label, randomized, multicenter, international study to assess and compare the efficacy of SG with TPC as measured by PFS as determined by BICR using RECIST v1.1                                                                                                                                                                                                       | Safety <sup>a</sup><br>PK<br>Immunogenicity             | <p>Participants with locally recurrent inoperable or metastatic HR+/HER2- breast cancer who have been treated with a CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy regimens for metastatic disease (1 of which could be in the neoadjuvant or adjuvant setting if development of unresectable, locally advanced, or metastatic disease occurred within 12 months)</p> <p><u>Total</u>: 543 randomized (517 treated)<br/> <u>SG<sup>b</sup></u>: 272 randomized (268 treated)<br/> <u>TPC<sup>d</sup></u>: 271 randomized (249 treated)</p>                                            |
| IMMU-132-05<br>(ASCENT)       | Phase 3, randomized, open-label, controlled, multicenter study to compare the efficacy of SG with TPC as measured by independently reviewed PFS in participants who were BM-negative at baseline                                                                                                                                                                                     | Safety <sup>a</sup><br>PK<br>Immunogenicity             | <p>Participants with locally advanced or metastatic TNBC who were either refractory or had relapsed after at least 2 prior standard of care chemotherapy regimens.</p> <p><u>Total</u>: 529 randomized (482 treated)<br/> <u>SG<sup>b</sup></u>: 267 randomized (258 treated)<br/> <u>TPC<sup>d</sup></u>: 262 randomized (224 treated)</p>                                                                                                                                                                                                                                                                                                |
| IMMU-132-01                   | <p>Phase 1/2, open-label, single-arm, basket study.</p> <p><u>Phase 1</u>: To evaluate the safety and tolerability of SG as a single agent and to determine a maximum acceptable dose<sup>e</sup> and select cancer types for a continued expanded study in Phase 2.</p> <p><u>Phase 2</u>: To evaluate the safety and efficacy of SG administered at a dose selected in Phase 1</p> | Safety <sup>a</sup><br>PK<br>Immunogenicity             | <p>Participants with metastatic epithelial cancer (except for GBM) that was relapsed or refractory to at least 1 standard therapy for their tumor type.</p> <p><u>Total</u>: 515 enrolled (402 treated)<sup>f</sup></p>                                                                                                                                                                                                                                                                                                                                                                                                                    |
| IMMU-132-06<br>(TROPY-U-01)   | Phase 2, ongoing, open-label study to assess the efficacy and safety of SG in locally advanced unresectable or metastatic UC                                                                                                                                                                                                                                                         | Safety <sup>a</sup><br>Immunogenicity                   | <p>Cohort 1: participants with locally advanced unresectable or metastatic UC that progressed after prior platinum-containing and anti-PD-1 or anti-PD-L1-based therapies</p> <p>Total: 141 enrolled (113 treated)<sup>g</sup></p> <p>Cohort 2: participants with platinum-ineligible locally advanced unresectable or metastatic UC that progressed after prior anti-PD-1 or anti-PD-L1-based therapy</p> <p>Total: 54 enrolled (38 treated)<sup>g</sup></p>                                                                                                                                                                              |

BICR = blinded independent central review; BM = bone marrow; CDK = cyclin-dependent kinase; CPS = combined positive score; GBM = glioblastoma multiforme; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; IHC = immunohistochemistry; IV = intravenous; mUC = metastatic urothelial cancer; nab = nanoparticle albumin-bound; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; UC = urothelial cancer

a The integrated safety dataset includes all available data up to the data cutoff dates from Studies GS-US-592-6238 (02 April 2025) and IMMU-132-06 (28 February 2023), and final safety data from Studies IMMU-132-09 (15 December 2023), IMMU-132-01 (02 April 2021), and IMMU-132-05 (25 February 2021).

b Participants received SG 10 mg/kg IV infusion on Days 1 and 8 of a 21-day treatment cycle.

c TPC was paclitaxel, nab-paclitaxel, or gemcitabine with carboplatin administered per standard of care.

d TPC was eribulin, capecitabine, gemcitabine, or vinorelbine administered per standard of care.

e Starting doses of 8, 10, 12, and 18 mg/kg were evaluated during the dose escalation phase (Phase 1) of Study IMMU-132-01.

f Of the 515 participants enrolled in Study IMMU-132-01, 495 participants were included in the Overall Safety Population. The population included the following tumor types: ovarian, endometrial, cervical, TNBC, HR+/HER2- metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, non-small-cell lung cancer, small-cell lung cancer, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and mUC. Participants with GBM were also eligible but were not required to have metastatic disease.

g Study is ongoing and data up to the data cutoff date of 28 February 2023 were included in the integrated safety analysis

### 2.3.2. Pharmacokinetics

With this application for extension of indication, the MAH is seeking approval of sacituzumab govitecan (SG, Trodelvy), a trophoblast cell-surface antigen-2 (Trop-2)-directed ADC, for locally advanced unresectable or metastatic triple-negative breast cancer (TNBC) patients who have not received previous systemic therapy for advanced disease and who were not candidates for programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors.

The recommended dose of SG is 10 mg/kg administered intravenously (IV) once weekly on Days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity and thus is equal to the approved posology.

PK, and immunogenicity of SG were evaluated based on data from study GS-US-592-6238 and from 3 additional completed studies: Study IMMU-132-01, Study IMMU-132-05, and Study IMMU-132-09, whereas ongoing Study IMMU-132-06 contributed data to the immunogenicity package.

The PK of total antibody, free SN 38, and conjugated SN-38 was characterized in participants with solid tumors using an integrated PopPK model. The integrated PopPK model was also used to evaluate the effect of various intrinsic and extrinsic factors on the exposure of total antibody, SG, and free SN-38. Data from Studies IMMU-132-01, IMMU 132-05, IMMU-132-09, and GS-US-592-6238 were used to develop the model.

Pharmacokinetics of SG have been characterized throughout the initial marketing authorization procedure. In this variation assessment report, only summarized data on sacituzumab govitecan ADME, dose proportionality, special populations and interaction studies are presented.

In the pivotal Study GS-US-592-6238, serum samples for PK analyses were collected only for participants receiving SG. Collection times for PK samples were predose and after the end of infusion on Day 1 and Day 8 of Cycle 1; Day 8 of Cycles 2, 6, and 10. Thereafter, predose samples were collected on Day 8 of every 8 cycles after Cycle 10 (e.g. Cycle 18 Day 8, Cycle 26 Day8); and at the end of treatment (EOT) visit.

## Analytical methods

### Bioanalytical methods

Bioanalytical methods for the quantitation of total SN-38, free SN-38, SN-38G, and total antibody (hRS7-IgG and HRS7-SN38) in human serum were developed and fully validated at KCAS, LLC [Shawnee, Kansas, USA]) and then transferred and validated at Novotech Laboratory Services (formerly PPC-China Clinical Research Co., Ltd; Shanghai, China).

According to the MAH, all bioanalytical method validations, cross-validation between laboratories, and sample analysis reports supporting clinical studies were conducted according to the United States (US) Food and Drug Administration Bioanalytical Method Guidelines (2018) (U. S. Department of Health & Human Services (DHHS) 2018), International Council for Harmonisation (ICH)-M10 Bioanalytical Method Validation and Study Sample Analysis Guidance for Industry (2022) (International Council for Harmonisation (ICH) 2022, U.S. Department of Health and Human Services (DHHS) 2022), and European Medicines Agency Guidelines on Bioanalytical Method Validation (2011) (European Medicines Agency (EMA) 2011).

**Table 2 Summary of Bioanalytical Methods for Individual Studies**

| Study Number   | Matrix      | Analyte               | Current Validation Report <sup>a</sup> | Calibrated Range | Sample Analysis Report                                                                   |
|----------------|-------------|-----------------------|----------------------------------------|------------------|------------------------------------------------------------------------------------------|
| IMMU-132-01    | Human Serum | Total SN-38           | VIMME1701E1 A3                         | 5-2500 ng/mL     | <a href="#">BIMME1704E2_revision_1</a><br>Project numbers:<br>BIMME1704E2<br>BIMME1802E2 |
|                |             | Free SN-38 and SN-38G | VIMME1700E2 A3                         | 1-500 ng/mL      | <a href="#">BIMME1704E1_revision_1</a><br>Project numbers:<br>BIMME1704E1<br>BIMME1802E1 |
|                |             | Total Antibody        | VIMME1706E1 A2                         | 374-3049 ng/mL   | <a href="#">BIMME1708E1_revision_1</a><br>Project numbers:<br>BIMME1708E1<br>BIMME1801E1 |
| IMMU-132-05    | Human Serum | Total SN-38           | VIMME1701E1 A3                         | 5-2500 ng/mL     | <a href="#">BIMME1803E2</a>                                                              |
|                |             | Free SN-38 and SN-38G | VIMME1700E2 A3                         | 1-500 ng/mL      | <a href="#">BIMME1803E1</a>                                                              |
|                |             | Total Antibody        | VIMME1706E1 A2                         | 374-3049 ng/mL   | <a href="#">BIMME1804E1</a>                                                              |
| IMMU-132-09    | Human Serum | Total SN-38           | VIMME1701E1 A3                         | 5-2500 ng/mL     | <a href="#">B1101809E2</a>                                                               |
|                |             | Free SN-38 and SN-38G | VIMME1700E2 A3                         | 1-500 ng/mL      | <a href="#">B1101809E1</a>                                                               |
|                |             | Total Antibody        | VIMME1706E1 A2                         | 374-3049 ng/mL   | <a href="#">B1101809E3</a>                                                               |
| GS-US-592-6238 |             |                       | VIMME1701E1 A3                         | 5-2500 ng/mL     | <a href="#">B1102202E2</a>                                                               |

|  |             |                |                    |                |                                      |
|--|-------------|----------------|--------------------|----------------|--------------------------------------|
|  | Human Serum | Total SN-38    | VR0327001-ENv01-A1 | 5-2500 ng/mL   | <a href="#">BRCN23-3051-01-ENv01</a> |
|  |             | Free SN-38     | V1102206E1         | 1-500 ng/mL    | <a href="#">B1102202E1</a>           |
|  |             | Free SN-38     | VR0333001-ENv01-A1 | 1-500 ng/mL    | <a href="#">BRCN23-3051-02-ENv01</a> |
|  |             | Total Antibody | VIMME1706E1 A2     | 374-3049 ng/mL | <a href="#">B1102202E3</a>           |
|  |             |                | VR0326001-ENv01-A2 | 374-3049 ng/mL | <a href="#">BRCN23-3051-03-ENv01</a> |

- a The most current versions of the validation reports and sample analysis reports are listed and are cumulative for all previous versions. Validation reports and sample analysis reports cited in the corresponding clinical study reports (CSRs) were those in effect at the time of CSR approval.

In study GS-US-592-6238, serum concentrations of total SN-38 and total antibody (hRS7-IgG and HRS7-SN38) were measured by using previously reported bioanalytical methods (validation report: VIMME1701E1-A3, and VIMME1706E1-A2, respectively) validated at KCAS Bio; by using a bioanalytical method that was partially validated at KCAS Bio (method TP-80150) for the determination of only free SN-38 (validation report: V1102206E1) and by using bioanalytical methods (validation report: VR0327001-ENv01-A1 [total SN-38], VR0333001-ENv01-A1 [free SN-38], and VR0326001-ENv01-A2 [total antibody]) that were transferred to and validated at Novotech Laboratory Services.

The submitted bioanalytical methods for determination of total SN-38, free SN-38 and SN-38G, and total antibody (hRS7-IgG and HRS7-SN38) validated at KCAS Bio were already assessed during previous procedures and found to be adequately validated and overall acceptable for their intended purpose. Therefore, these methods are not listed and assessed in this report.

However, for the method validation VIMME1701E1 A3 (total SN-38) an Amendment No3 has been submitted, which included further long-term stability results (up to 1982 days at -80°C) and the evaluation of co-medication effects (domvanalimab, zimberelimab, and etrumadenant with its two metabolites A0304481 and A0003642) on the LC-MS/MS method for determination of free SN-38 and SN-38G. The pre-defined acceptance criteria and acceptance criteria of the ICH M10 on bioanalytical method validation (EMA/CHMP/ICH/172948/2019) were met. The updated results are considered acceptable.

The assessment of the partially- (validation report: V1102206E1), transferred- (validation reports: VR0327001-ENv01-A1, VR0333001-ENv01-A1, and VR0326001-ENv01-A2) and cross-validated bioanalytical methods, which were newly submitted with this application, is described below.

### **Validation results**

- Method V1102206E1 for free SN-38

The bioanalytical method TP-80150 was partially validated at KCAS Bio (Olathe, Kansas, USA) under KCAS Project Number V1102206E1 and was performed for the determination of free SN-38 in human serum. KCAS method TP-80150 is an LC-MS/MS method identical to KCAS method TP70467 with the exception of SN-38G being removed from the preparations and analysis. Thus, the purpose of this partial validation was to remove SN-38 glucuronide from the existing test procedure showing that free SN-38 analysis is equivalent without SN-38 glucuronide. The assay was analyzed in the range of 1.00 – 500 ng/mL and is for use on human serum samples obtained during clinical trials.

The cross validation consists of evaluation of the following parameters:

1. Accuracy and Precision for SN-38 only

2. Cross validation of TP70467 with TP-80150. Analysis of pooled subject samples from clinical study will be run using both test procedures. Results were compared for cross validation. A total of 84 samples with reportable SN-38 concentrations were chosen to create a pool of 21 samples.

- Method validation report VR0327001-Env01-A1 for total SN-38

The bioanalytical method AM0327001-ENV01 was validated at Novotech Laboratory Services (Shanghai, China) under Novotech validation report VR0327001-ENV01. Novotech method AM0327001-ENV01 is an LC-MS/MS method, and total SN-38 is defined as the combined amounts of free SN-38 in solution (unbound to the ADC [hRS7-SN-38]) and acid-dissociated (hydrolyzed) SN-38. Following hydrolysis, total SN-38 is extracted from human serum by protein precipitation and is quantified by reverse-phase HPLC-MS/MS with SN-38-d3 as an internal standard.

- Method validation report VR0333001-Env01-A1 for free SN-38 and SN-38G

The bioanalytical method AM0333001-ENV01 was validated at Novotech Laboratory Services (Shanghai, China) under Novotech validation report VR0333001-ENV01. Novotech method AM0333001-ENV01 is an LC-MS/MS method, where free SN-38 and SN-38G (i.e. both unconjugated to the SG antibody) are extracted from human serum by solid-phase extraction under yellow light and are quantified by reverse-phase HPLC-MS/MS, using SN-38-d3 and SN-38G-13C6 as internal standards.

- Method VR0326001-Env01-A2 for total antibody

The bioanalytical method AM0326001-ENV01 was validated at Novotech Laboratory Services (Shanghai, China) under Novotech validation report VR0326001-ENV01 for the determination of SG total antibody (hRS7 unconjugated or conjugated with SN-38) in human serum. Novotech method AM0326001-ENV01 is an electrochemiluminescence (ECL) immunoassay that captures SG total antibody with anti-hRS7-IgG monoclonal antibody (mAb), and the complex is detected using a biotinylated anti-human IgG-Fc antibody followed by Sulfo-TAG Streptavidin.

#### ***Laboratory Cross-Validation results of KCAS, LLC [Shawnee, Kansas, USA] and Novotech Laboratory Services***

Cross-validation of bioanalytical methods for the determination of total SN-38, free SN-38 and SN-38G, and total antibody using spiked blank matrix and pooled clinical samples was conducted at KCAS Bio and Novotech to establish interlaboratory comparability.

The percentage difference of the mean cross-validation QCs (excluding low QC of Total SN-38) and the pooled clinical study samples (for total SN-38 and total antibody (hRS7 SN38 and hRS7-IgG)) met the pre-defined acceptance criteria. For free SN-38, no pooled clinical study samples were tested due to the limited freeze/thaw stability data for free SN-38. However, the assessment of bias (e.g. by Bland - Altman plots or Deming regression) was not presented.

#### **ADA assay**

Immunogenicity of SG or its components was assessed in clinical studies by evaluating and characterizing antidrug antibody (ADA) response using a semiquantitative electrochemiluminescence (ECL) immunoassay format to detect anti-SG antibodies and a multitiered approach that includes domain specificity testing. A competitive ligand-based ECL neutralizing antibody (NAb) assay method was developed and validated to evaluate the ability of ADAs to interfere with the activity of SG or its components.

These assay methods to detect the presence of ADAs and Nabs were developed and validated in accordance with agency guidance (European Medicines Agency (EMA) 2017, U.S. Department of Health & Human Services (DHHS) 2019), as stated by the MAH.

To assess the immunogenicity of SG or its components, all clinical samples from studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, and GS-US-592-6238, that were available for analysis, were analyzed using the ADA method validated under V1101906E1\_A1. All ADA confirmed positive clinical samples using the ADA method validated under V1101906E1\_A1 were analyzed for neutralizing activity using the NAb method validated under RSY2.

**Table 3 Summary of method validation reports**

| Report No.                 | Report Title                                                                                                                                                                                                  | Analytes                             |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| VIMME1712E1                | Bioanalytical Method Validation Report for the Detection of Anti-hRS7-SN8 Antibodies in Human Serum by Electrochemiluminescence (ECL) Assay                                                                   | Antibodies to hRS7-SN38              |
| V1101906E1_A1 <sup>a</sup> | Validation of an Electrochemiluminescent Assay Method TP70641 for the Screening, Confirmation, Titration, and Assessment of hRS7 Domain Specificity of Anti-hRS7-SN8 (Anti-GS-0132) Antibodies in Human Serum | Antibodies to hRS7-SN38              |
| RSYP2 <sup>a</sup>         | Validation of an Electrochemiluminescent Ligand Binding Assay Method for the Detection of Anti-GS-0132 Neutralizing Antibodies in Human serum                                                                 | Neutralizing antibodies to hRS7-SN38 |

<sup>a</sup> Denotes methods used to generate the results provided in this Integrated Summary of Immunogenicity document.

These submitted bioanalytical methods for determination of ADA (V1101906E1\_A1) and Nab (RSYP2) were already assessed during previous procedures (e.g. grouping of variations EMEA/H/C/005182/II/0018/G). No new information is provided with the current dossier, as there is no change in these bioanalytical methods. The bioanalytical methods to detect the presence of ADAs (V1101906E1\_A1) and NAb (RSYP2) will therefore not be further discussed in this report.

## Population PK

### *Rationale for developing an integrated PopPK model and context of use*

The popPK of SG, free SN-38, and TAb (conjugated and unconjugated anti-Trop-2 antibody), have been previously characterized using the combined concentration-time data from participants with different types of epithelial cancers (study IMMU-132-01), participants with metastatic TNBC (study IMMU-132-05), and from participants with HR+/HER2– metastatic breast cancer (mBC) (study IMMU-132-09).

The current analysis applied an integrated model structure with the measured PK data of three analytes: TAb, free SN-38 and total SN-38. In addition to the data included from three clinical studies in the previously developed popPK model, this analysis included additional data from the phase 3 study GS-US-592-6238 (ASCENT-03) in first-line patients with unresectable locally advanced or metastatic TNBC. The PK of SG were now derived based on model-estimated kinetics of conjugated SN-38 and potential change in drug-to-antibody ratio (DAR) over time. In contrast, for the purpose of the previous popPK analysis, SG concentrations were calculated based on an assumed DAR of 8 and the molecular weights for free SN-38 and the loaded hRS7 antibody of 392 Da and 161 kDa, respectively.

Compared to the previous three popPK models (2-compartment models) that were developed separately for each analyte, the integrated model was developed to provide a more mechanistic and flexible structure to describe the dynamic change of TAb and free SN-38 at first cycle and at steady state. Covariate assessment for each analyte was performed during the model development. The PopPK model was also used to identify the effect of intrinsic and extrinsic factors on the exposure to SG, free SN-38, and TAb and to predict individual exposures of SG, TAb and free SN-38 for subsequent exposure-response analyses.

## PK Data Set and Methods

The PopPK analysis dataset included a total of 1063 participants contributing with 8396, 8487, and 8482 observations of total antibody, total SN-38, and free SN-38, respectively, from 4 clinical studies in participants with solid tumours: IMMU-132-01 (phase 1/2), IMMU-132-05 (phase 3), IMMU-132-09 (phase 3), and GS-US-592-6238 (phase 3). The pooled analysis dataset included all participants treated with SG and for whom dosing time and associated concentrations (from at least one post dose visit) were available. For observed Tab, 8260 of 8396 samples were included in the dataset after accounting for inconsistencies, outliers and below limit quantification (BLQ) samples (0.64%). From 8487 observed samples of total SN-38, 7654 were included in the final data set. Most of the excluded observation were classified BLQ (8.5%) and were also excluded prior to model development. For free SN-38, data handling resulted in 8415 samples that were included in the final data set for model development – 5438 quantifiable observations and 2977 BLQ samples (35%). Below the limit of quantification (BLQ) observations were flagged in the popPK analysis dataset and a likelihood-based approach (M3) was implemented.

The popPK analysis was conducted via nonlinear mixed-effects modelling (NONMEM) software, Version 7.5 (ICON Development Solutions, Dublin, UK). Data manipulation, postprocessing, summaries, and plotting were performed using R 4.2 or above.

Population and individual model parameters were estimated using the stochastic approximation expectation maximization (SAEM) method followed by importance sampling Monte Carlo (IMP). The 95% CI of parameter estimates were derived from the covariance matrix of the estimates (NONMEM \$COV step).

## Model structure

The structural model was built on prior knowledge from previous modelling and incorporates several assumptions. Conjugated SN-38 and TAb are assumed to share the same PK parameters of clearances and volume of distributions since kinetics are expected to be driven by the monoclonal antibody. Both linear and nonlinear clearance pathways were tested to investigate the necessity of their inclusion in the model. The compartmental model further accounts for the formation kinetics of free SN-38 whose formation kinetics were driven by the deconjugation process - characterized by the deconjugation rate constant ( $K_{dec}$ ) - from the conjugated SN-38. The model defined a mass balance such that the sum of free SN-38 and conjugated SN-38 amount corresponded to the observed total SN-38. Both 1-compartment and 2-compartment models were assessed for free SN-38 PK, as well as linear and nonlinear elimination pathways.

The concentration of SG ( $C_{SG}$ ) was calculated as the ratio of conjugated SN-38 concentration to the time-varying drug-antibody ratio (DAR):

$$C_{SG} = \frac{C_{\text{Conjugated SN-38}}}{DAR}$$

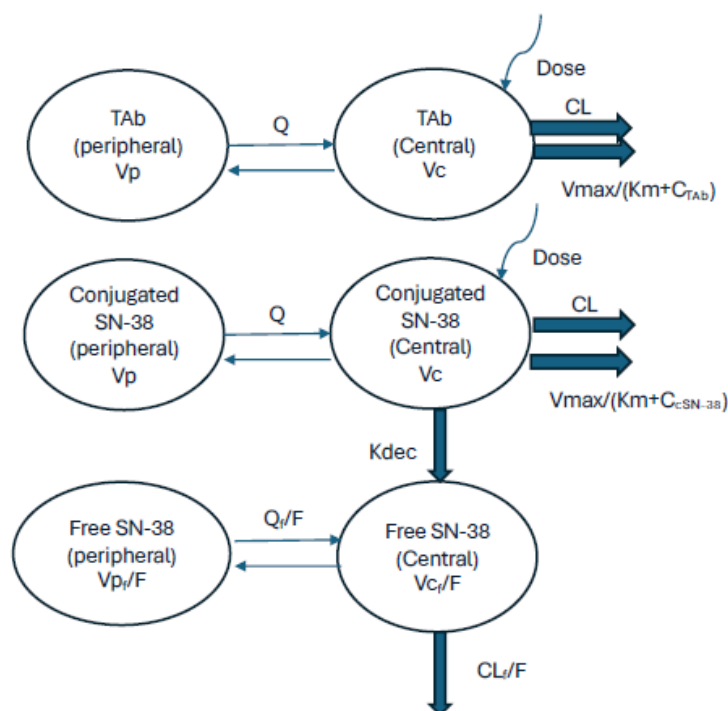
where DAR changes over time:

$$DAR = 1 + 7e^{-K_{dec} \times TAD}$$

TAD represents time after each SG dose. All concentrations are represented in molar units. The DAR at time zero equals 8 and changes with time. As the concentration of SG was the fraction of conjugated SN-38 over DAR, DAR should not take values below 1. A value less than 1 would suggest lack of conjugated SN-38 and the ratio would not be numerically meaningful. Therefore, a minimum DAR of 1

was assumed to be present for the entire duration of conjugated SN-38 exposure throughout deconjugation.

**Figure 2 Integrated model structure**



Dose of SG is in molar units. CL: linear clearance of TAB and conjugated SN-38, Km: the exposure eliciting half of the maximum effect, Vmax: maximal Michaelis-Menten clearance, Q: intercompartmental clearance of TAB and conjugated SN-38, Vc: central volume of distribution of TAB and conjugated SN-38, Vp: peripheral volume of distribution of TAB and conjugated SN-38,  $CL_r/F$ : apparent clearance of free SN-38,  $Q_r/F$ : apparent intercompartmental clearance of free SN-38,  $V_{c_f}/F$ : apparent central volume of distribution of free SN-38,  $V_{p_f}/F$ : apparent peripheral volume of distribution of free SN-38,  $K_{dec}$ : first order deconjugation rate constant.

### Covariate model and model evaluation

Covariates screened for inclusion into the popPK model were based on mechanistic plausibility, exploratory analysis, and clinical interest. The effects of these covariates on clearance parameters (of both TAB and free SN-38) were included in the full model. The conjugated SN-38 and TAB shared the same PK parameters for clearances and volume of distributions. The covariates, therefore, apply to both analytes. The potential effect of anti-drug antibody (ADA) presence during the SG treatment on clearance was explored.

**Table 4 Covariates to assess impact of exposures to total antibody, free, SN-38, and SG**

| Factors     | Covariates Included                                                                                                                                                                                                                                        |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Demographic | Sex (male or female), age, race (Asian, White, Black or African American, or other), and body weight.                                                                                                                                                      |
| Disease     | Tumor type (TNBC, HR+/HER2- mBC, or other), ECOG (0 or $\geq 1$ ), number of prior cancer treatments (0, 1, 2, 3, 4, or $\geq 5$ ), and baseline tumor size.                                                                                               |
| Participant | Serum albumin, hepatic impairment based on NCI-ODWG classification (normal, mild, moderate, or missing), renal function or impairment (based on eGFR estimated using MDRD equation), and UGT1A1 genotype (*1/*1, *1/*28, *28/*28, *1/*6, *6/*6, or other). |

ECOG = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; MDRD = Modification of Diet in Renal Disease; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

A full covariate modelling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented. The full model was reduced to the final model by removing covariates with 95% CIs of their estimated effects falling within the region of practical equivalence (ROPE), which is commonly defined as 80% to 125% of the null value.

Final model performance was evaluated by visual predictive check (VPC). Post hoc empirical Bayes estimates (EBEs) from the final models were used to calculate exposure metrics (C<sub>max1</sub>, AUC<sub>0-168</sub>, and C<sub>trough</sub>) of total antibody, free SN-38, and SG. Forest plots were generated with simulations informed by model parameter sets and dataset covariates. A total of 1000 sets of parameters were sampled from distributions based on parameter estimates and the associated variance-covariance matrix of the final model. The influence of each covariate was compared against a reference individual PK parameter. Uncertainty was computed as a 95% CI for each exposure metric.

### **Final popPK model and Results**

The PK of the TAb and conjugated SN-38 were described by a two-compartment model with linear and nonlinear (Michaelis-Menten [MM]) clearance pathways. Free SN-38 PK were described by a two-compartment model with linear clearance.

Estimates for the effects of age, sex, tumour type, hepatic function, albumin, Eastern Cooperative Oncology Group performance status (ECOG), baseline tumour size, and number of prior lines of therapy in the full covariate model fell within the ROPE for area under the AUC<sub>0-168</sub> and C<sub>max1</sub> of total antibody, free SN-38, and SG. These effects were considered not statistically significant or clinically meaningful and, therefore, not included in the final model. In the final model, the effects of body weight on clearances and volumes were included using allometric scaling with estimated coefficients. The effects of race, renal function, and UGT1A1 genotype were estimated on the clearances on total antibody and free SN-38.

**Table 5 Population Pharmacokinetic model parameters – fixed and random effects**

|                                                    |               |                                                                      | Estimate | 95% CI           |
|----------------------------------------------------|---------------|----------------------------------------------------------------------|----------|------------------|
| <b>Structural model parameters</b>                 |               |                                                                      |          |                  |
| CL (L/hr)                                          | $\theta_1$    | Total antibody/conjugated SN-38 clearance                            | 0.0113   | 0.0107, 0.0119   |
| Vc (L)                                             | $\theta_2$    | Total antibody/conjugated SN-38 central volume                       | 2.83     | 2.80, 2.86       |
| Q (L/hr)                                           | $\theta_3$    | Total antibody/conjugated SN-38 inter-compartmental clearance        | 0.00845  | 0.00817, 0.00872 |
| Vp (L/hr)                                          | $\theta_4$    | Total antibody/conjugated SN-38 peripheral volume                    | 1.79     | 1.70, 1.88       |
| $CL_f/F$ (L/hr)                                    | $\theta_5$    | Apparent free SN-38 clearance                                        | 3.89     | 3.52, 4.26       |
| $Vc_f/F$ (L)                                       | $\theta_6$    | Apparent free SN-38 central volume                                   | 1.97     | 1.49, 2.44       |
| $Q_f/F$ (L/hr)                                     | $\theta_7$    | Apparent free SN-38 inter-compartmental clearance                    | 1.02     | 0.781, 1.27      |
| $Vp_f/F$ (L)                                       | $\theta_8$    | Apparent free SN-38 peripheral volume                                | 16.0     | 13.3, 18.7       |
| Kdec (1/hr)                                        | $\theta_9$    | Deconjugation rate constant                                          | 0.0417   | 0.0413, 0.0421   |
| Vmax (uM/hr)                                       | $\theta_{10}$ | Total antibody/conjugated SN-38 maximal Michaelis-Menten elimination | 0.00211  | 0.00188, 0.00235 |
| KM (uM)                                            | $\theta_{11}$ | Total antibody/conjugated SN-38 half-inhibitory concentration        | 0.0217   | 0.0178, 0.0255   |
| <b>Covariate effect parameters: total antibody</b> |               |                                                                      |          |                  |
| CL ~ body weight                                   | $\theta_{12}$ | body weight effect on CL and Q                                       | 0.428    | 0.358, 0.498     |
| CL ~ black and other race                          | $\theta_{16}$ | race effect on CL                                                    | 0.0368   | -0.0385, 0.112   |
| CL ~ Asian race                                    | $\theta_{17}$ | race effect on CL                                                    | 0.0850   | -0.00968, 0.180  |
| CL ~ eGFR category                                 | $\theta_{33}$ | eGFR 60 - <90 effect on CL                                           | -0.0646  | -0.107, -0.0220  |
| CL ~ eGFR category                                 | $\theta_{34}$ | eGFR <60 effect on CL                                                | -0.0382  | -0.116, 0.0393   |
| CL ~ UGT1A1 genotype                               | $\theta_{39}$ | UGT1A1 *1/*28 effect on CL                                           | -0.00899 | -0.0574, 0.0394  |
| CL ~ UGT1A1 genotype                               | $\theta_{40}$ | UGT1A1 *28/*28 effect on CL                                          | 0.0577   | -0.0265, 0.142   |
| CL ~ UGT1A1 genotype                               | $\theta_{41}$ | UGT1A1 *1/*6+*6/*6+all others effect on CL                           | 0.0847   | -0.0597, 0.229   |
| CL ~ UGT1A1 genotype                               | $\theta_{42}$ | UGT1A1 missing effect on CL                                          | -0.0748  | -0.144, -0.00504 |
| Vc ~ body weight                                   | $\theta_{47}$ | body weight effect on Vc and Vp                                      | 0.523    | 0.472, 0.574     |
| <b>Covariate effect parameters: free SN-38</b>     |               |                                                                      |          |                  |
| $CL_f/F$ – body weight                             | $\theta_{13}$ | body weight effect on SN-38 CL and Q                                 | 0.458    | 0.277, 0.639     |
| $CL_f/F$ – black and other race                    | $\theta_{18}$ | race effect on SN-38 CL                                              | -0.0380  | -0.179, 0.103    |
| $CL_f/F$ – Asian race                              | $\theta_{19}$ | race effect on SN-38 CL                                              | 0.222    | -0.00824, 0.453  |
| $CL_f/F$ – eGFR category                           | $\theta_{35}$ | eGFR 60 - <90 effect on SN-38 CL                                     | -0.0715  | -0.158, 0.0152   |
| $CL_f/F$ – eGFR category                           | $\theta_{36}$ | eGFR <60 effect on SN-38 CL                                          | -0.108   | -0.249, 0.0337   |
| $CL_f/F$ – UGT1A1 genotype                         | $\theta_{43}$ | UGT1A1 *1/*28 effect on SN-38 CL                                     | -0.00706 | -0.107, 0.0930   |
| $CL_f/F$ – UGT1A1 genotype                         | $\theta_{44}$ | UGT1A1 *28/*28 effect on SN-38 CL                                    | -0.0318  | -0.185, 0.121    |
| $CL_f/F$ – UGT1A1 genotype                         | $\theta_{45}$ | UGT1A1 *1/*6+*6/*6+all others effect on SN-38 CL                     | 0.305    | -0.0735, 0.683   |

|                            |               |                                       | Estimate | 95% CI          |
|----------------------------|---------------|---------------------------------------|----------|-----------------|
| $CL_f/F$ – UGT1A1 genotype | $\theta_{46}$ | UGT1A1 missing effect on SN-38 CL     | -0.127   | -0.262, 0.00817 |
| $Vc_f/F$ – body weight     | $\theta_{48}$ | body weight effect on SN-38 Vc and Vp | 0.444    | 0.0530, 0.834   |

Abbreviations: eGFR = estimated Glomerular Filtration Rate; UGT1A1 = uridine diphospho-glucuronosyl transferase 1A1; CI = confidence intervals

Confidence intervals = estimate  $\pm 1.96 \cdot SE$

Source code: final-param-table.R

Source file: pk-param-final-fixed.tex

|                                              |                    | Estimate               | 95% CI           | Shrinkage (%) |
|----------------------------------------------|--------------------|------------------------|------------------|---------------|
| <b>Interindividual variance parameters</b>   |                    |                        |                  |               |
| IIV-CL                                       | $\Omega_{(1,1)}$   | 0.113 [CV%=34.6]       | 0.0964, 0.130    | 20.8          |
| IIV-Vc                                       | $\Omega_{(2,2)}$   | 0.0284 [CV%=17.0]      | 0.0251, 0.0317   | 12.6          |
| IIV-Q                                        | $\Omega_{(3,3)}$   | 0.0429 [CV%=20.9]      | 0.0314, 0.0544   | 18.7          |
| IIV-Vp                                       | $\Omega_{(4,4)}$   | 0.163 [CV%=42.1]       | 0.134, 0.192     | 37.1          |
| IIV- $CL_f/F$                                | $\Omega_{(5,5)}$   | 0.317 [CV%=61.0]       | 0.257, 0.376     | 24.1          |
| IIV- $Vc_f/F$                                | $\Omega_{(6,6)}$   | 1.41 [CV%=176]         | 1.09, 1.74       | 42.4          |
| IIV- $Q_f/F$                                 | $\Omega_{(7,7)}$   | 1.00 [CV%=131]         | FIXED            | 68.1          |
| IIV- $Vp_f/F$                                | $\Omega_{(8,8)}$   | 1.00 [CV%=131]         | FIXED            | 37.0          |
| IIV-Vmax                                     | $\Omega_{(10,10)}$ | 0.385 [CV%=68.6]       | 0.302, 0.468     | 34.2          |
| IIV-KM                                       | $\Omega_{(11,11)}$ | 0.194 [CV%=46.2]       | 0.0483, 0.339    | 78.3          |
| <b>Interindividual covariance parameters</b> |                    |                        |                  |               |
| CL - Vc                                      | $\Omega_{(2,1)}$   | 0.0266 [Corr=0.469]    | 0.0210, 0.0321   | -             |
| CL - Q                                       | $\Omega_{(3,1)}$   | 0.0163 [Corr=0.233]    | 0.00691, 0.0256  | -             |
| Vc - Q                                       | $\Omega_{(3,2)}$   | 0.0319 [Corr=0.914]    | 0.0255, 0.0382   | -             |
| CL - Vp                                      | $\Omega_{(4,1)}$   | -0.0370 [Corr=-0.273]  | -0.0545, -0.0195 | -             |
| Vc - Vp                                      | $\Omega_{(4,2)}$   | 0.0305 [Corr=0.449]    | 0.0217, 0.0393   | -             |
| Q - Vp                                       | $\Omega_{(4,3)}$   | 0.0604 [Corr=0.723]    | 0.0462, 0.0746   | -             |
| $CL_f/F$ - $Vc_f/F$                          | $\Omega_{(6,5)}$   | -0.0330 [Corr=-0.0494] | -0.115, 0.0486   | -             |
| <b>Residual errors</b>                       |                    |                        |                  |               |
| SD of RUV-free SN-38 (study 5926238)         | $\theta_{49}$      | 0.834                  | 0.794, 0.874     | 11.7          |
| SD of RUV-free SN-38 (study 13201)           | $\theta_{50}$      | 0.584                  | 0.558, 0.609     | 11.7          |
| SD of RUV-free SN-38 (study 13205)           | $\theta_{51}$      | 0.671                  | 0.582, 0.761     | 11.7          |
| SD of RUV-free SN-38 (study 13209)           | $\theta_{52}$      | 0.549                  | 0.524, 0.575     | 11.7          |
| RUV-total antibody                           | $\Sigma_{(1,1)}$   | 0.0642 [SD=0.253]      | 0.0619, 0.0665   | 5.32          |
| RUV-total SN-38                              | $\Sigma_{(3,3)}$   | 0.0457 [SD=0.214]      | 0.0438, 0.0475   | 7.12          |

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; IIV = inter-individual variability; RUV = residual unexplained variability

CV% of log-normal omegas =  $\sqrt{\exp(\text{estimated variance}) - 1} \cdot 100$

CV% of sigma = estimate  $\cdot 100$

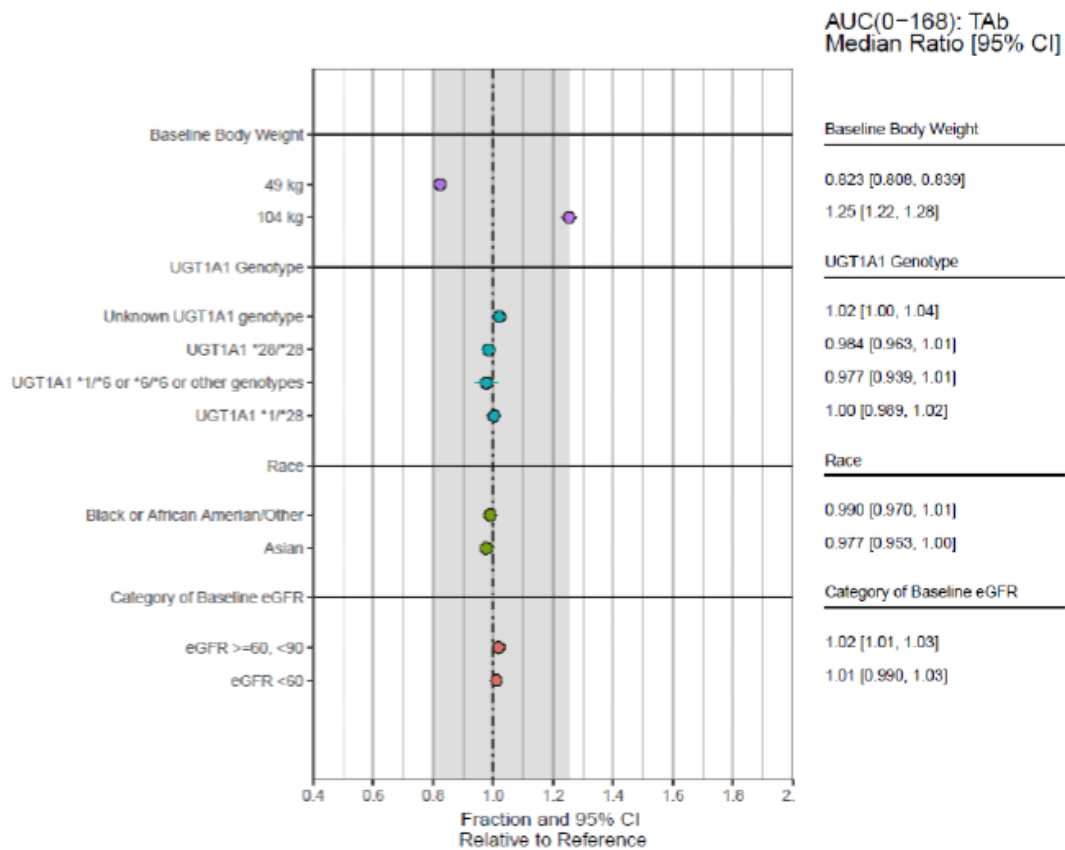
Source code: final-param-table.R

Source file: pk-param-final-random.tex

### Impact of Covariates on Exposure

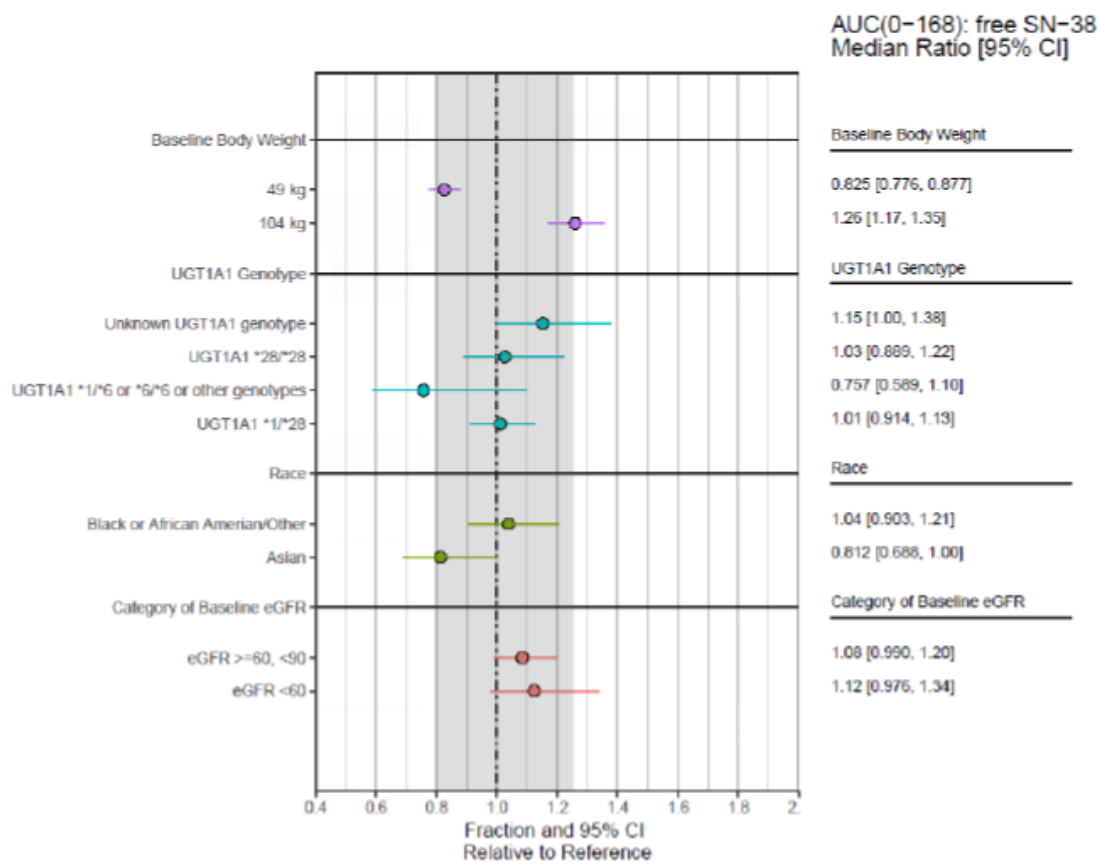
Forest plots depict the impact of the estimated covariate effects on exposure ( $AUC_{0-168}$  and  $C_{max1}$ ) presenting the ratio of exposures of TAB, free SN-38 and model-derived SG, given a covariate effect, relative to the exposure from a reference subject. The reference range was equivalent to a 20% change on the log scale. The reference subject is a 69 kg White participant with first line advanced or metastatic TNBC,  $eGFR \geq 90$  mL/min/1.73m<sup>2</sup>, UGT1A1 genotype of \*1/\*1, and receiving SG dose of 10 mg/kg.

**Figure 3 Forest Plot of Estimated Covariate Effects on AUC0-168 in Final Model: Total Antibody**



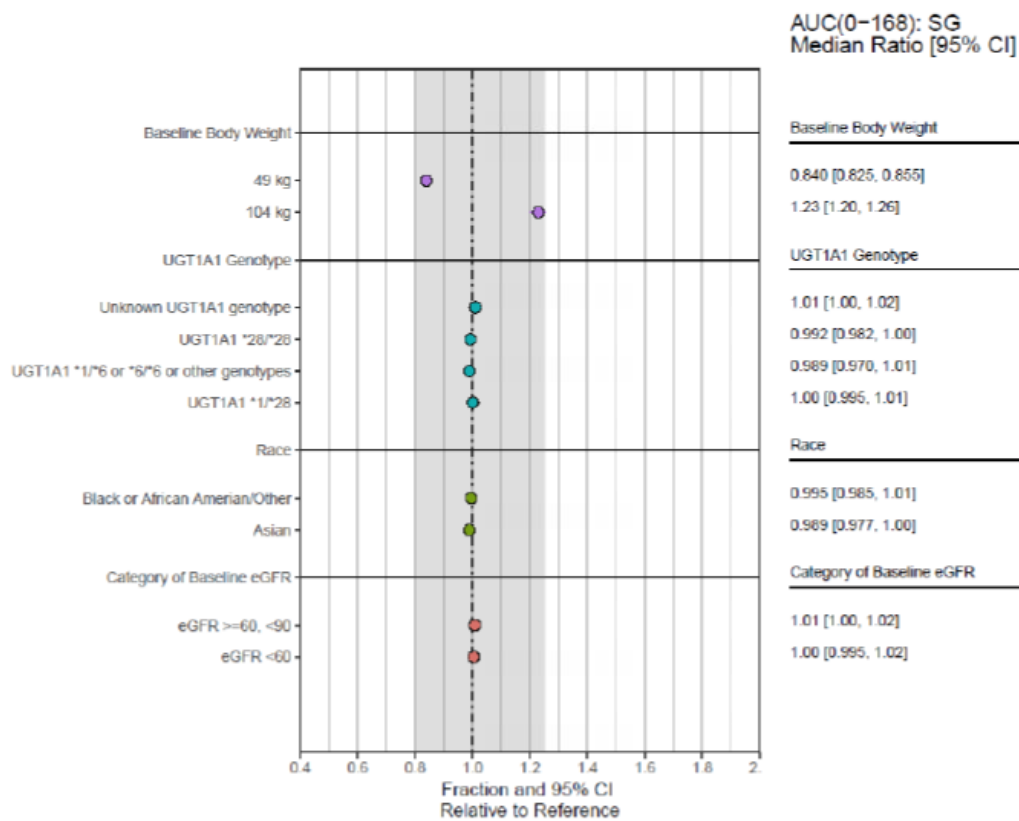
eGFR = estimated glomerular filtration rate; SG = sacituzumab govitecan; TAB = total antibody; TNBC = triple-negative breast cancer; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1  
Reference participant is 69 kg, White,  $eGFR \geq 90$  mL/min/1.73 m<sup>2</sup>, UGT1A1 genotype of \*1/\*1, receiving SG dose of 10 mg/kg. Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects.

Figure 4 Forest Plot of Estimated Covariate Effects on AUC<sub>0-168</sub> in Final Model: Free SN-38



eGFR = estimated glomerular filtration rate; SG = sacituzumab govitecan; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1  
Reference participant is 69 kg, White, eGFR ≥ 90 mL/min/1.73 m², UGT1A1 genotype of \*1/\*1, receiving SG dose of 10 mg/kg.  
Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects.

Figure 5 Forest Plot of Estimated Covariate Effects on AUC<sub>0-168</sub> in Final Model: SG

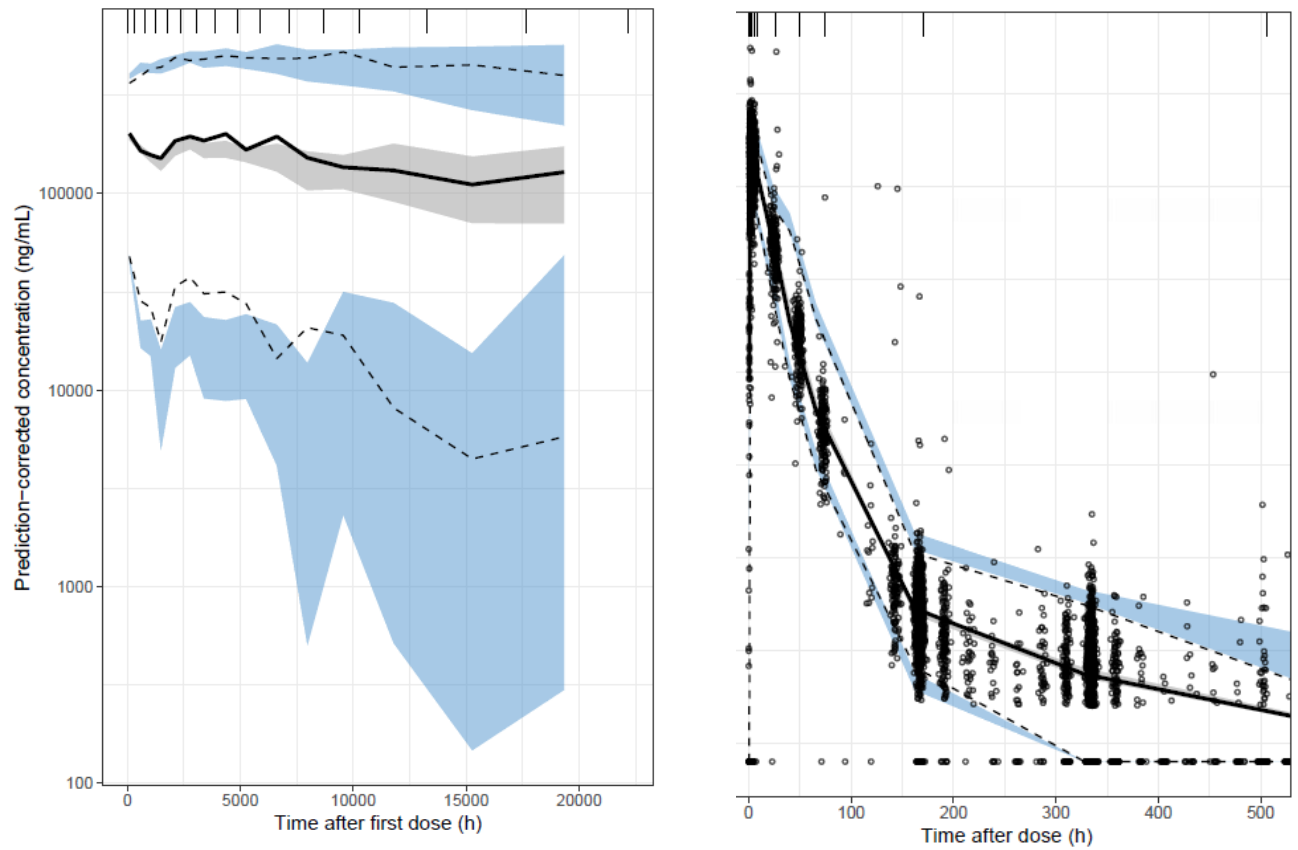


eGFR = estimated glomerular filtration rate; SG = sacituzumab govitecan; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1  
Reference participant is 69 kg, White, eGFR ≥ 90 mL/min/1.73 m<sup>2</sup>, UGT1A1 genotype of \*1/\*1, receiving SG dose of 10 mg/kg.  
Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects

Model evaluation

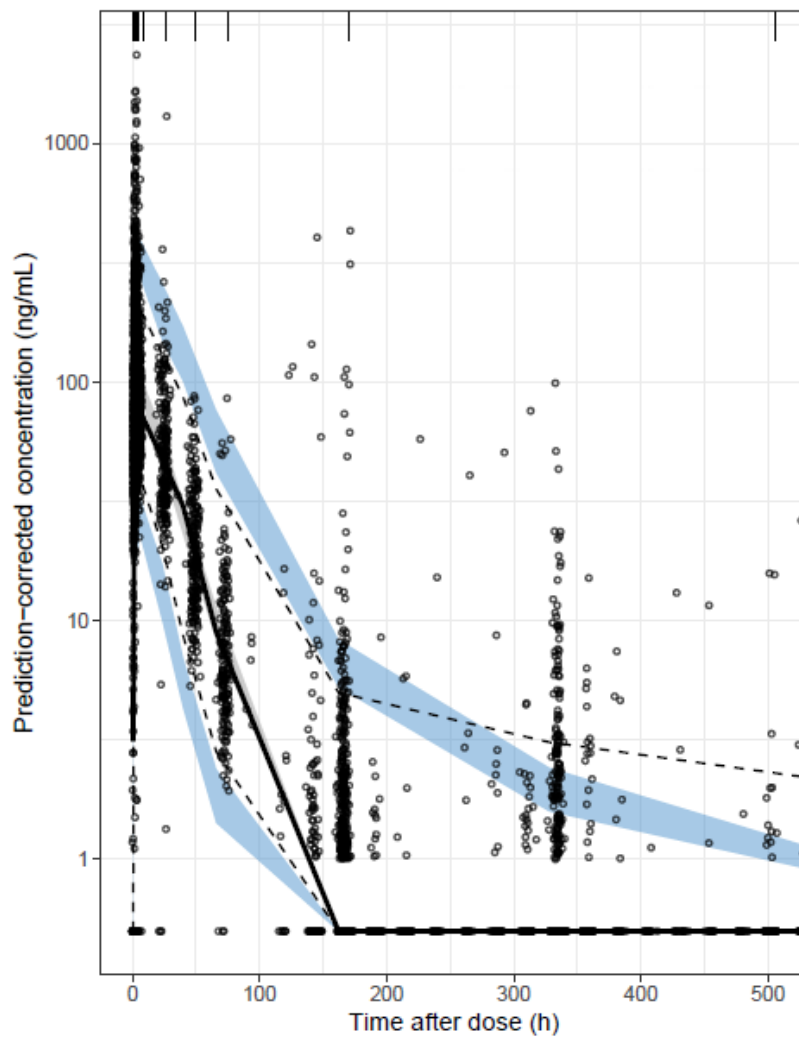
Simulation-based model diagnostics (VPCs) were generated to investigate the predictive performance of the integrated popPK model. Observed data of the three analytes and the model-simulated median, fifth, and 95<sup>th</sup> percentiles for the final model are opposed.

**Figure 6 Final model: Prediction-corrected VPC of TAb (left) and total (free and conjugated) SN-38 (right)**



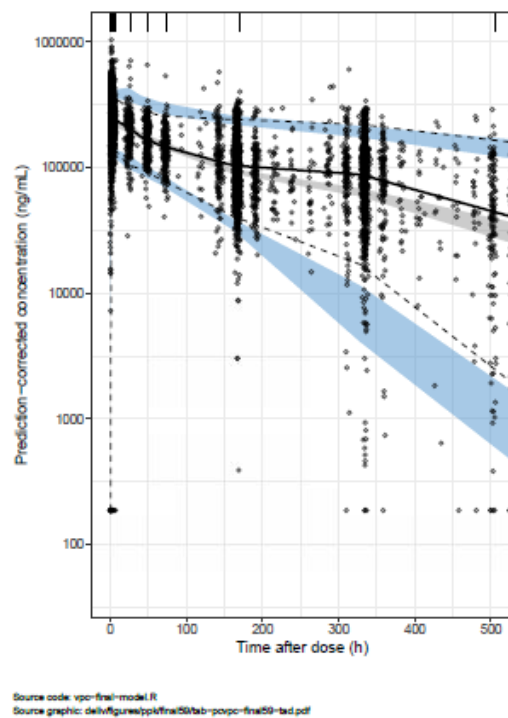
Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

**Figure 7 Final model: Prediction-corrected VPC of free SN-38.**



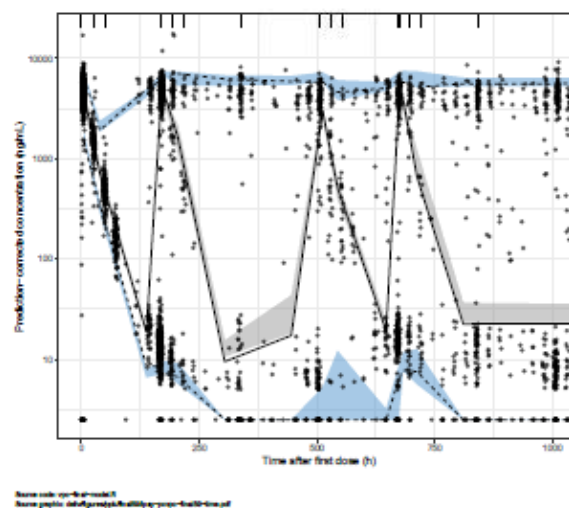
Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

**Figure 8 Final model: Prediction-corrected VPC of total antibody vs time after dose.**



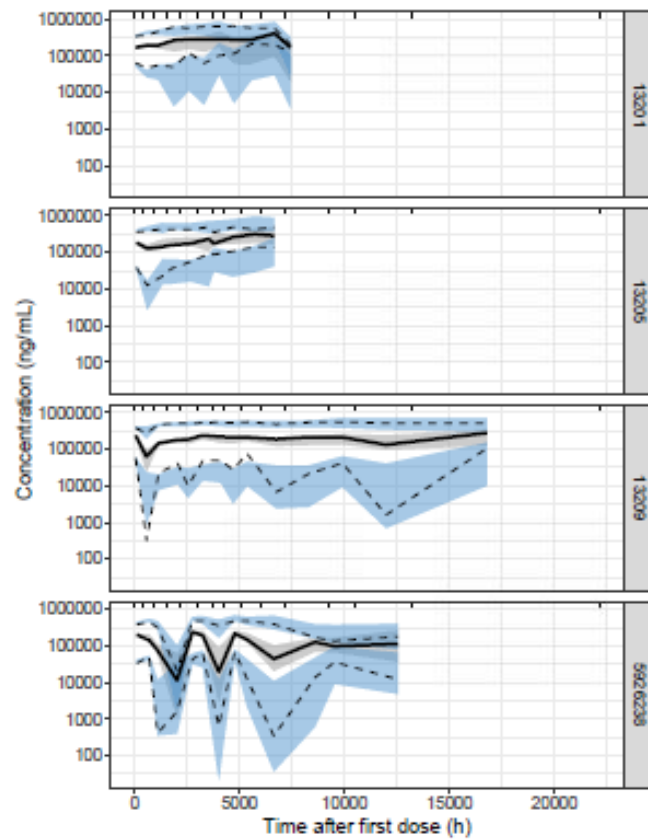
Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

**Figure 9 Final model: Prediction-corrected VPC of total (free and conjugated) SN-38 vs time**



Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

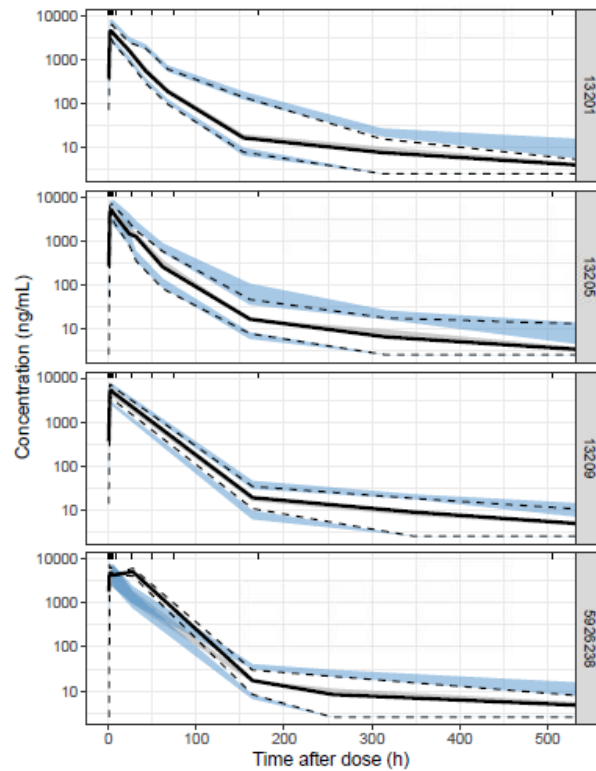
**Figure 10 Final model: VPC of total antibody at 10 mg/kg by study**



Source code: vpc-final-model.R  
Source graphic: delivfiguresppt/final50/tab-vpc-final50-time-10mgkg-study.pdf

Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

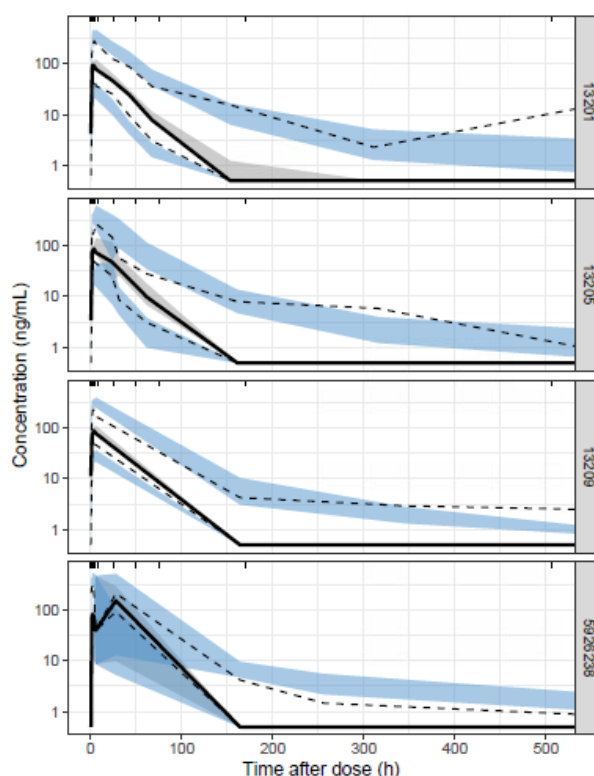
**Figure 11 Final model: VPC of total (free and conjugated) SN-38 at 10 mg/kg by study.**



Source code: vpc-final-model.R  
Source graphic: deliv/figures/ppk/final59/tpay-vpc-final59-tad-10mg/kg-study.pdf

Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

**Figure 12 Final model: VPC of free SN-38 at 10 mg/kg by study**



Source code: vpc-final-model.R  
Source graphic: deliv\figures\pop\final59\upay-vpc-final59-lad-10mgkg-study.pdf

Observed data points are represented by black circles, and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).

## ADME

The PK of total antibody (hRS7 unconjugated or conjugated with SN-38), free SN-38, and conjugated SN-38 was characterized in participants with solid tumours using an integrated PopPK model (including data from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238).

Final model EBEs were used to calculate PK parameters and exposure metrics in participants included in the analysis population and receiving IV SG 10 mg/kg on Days 1 and 8 of 21-day treatment cycles.

## Absorption

Sacituzumab govitecan is administered via IV infusion. No studies characterizing absorption via other routes of administration have been conducted with SG; thus, drug absorption is not applicable. The T<sub>max</sub> of SG occurred at the end of SG infusion across all clinical studies.

## Distribution

Based on the PopPK analyses using data from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238, the estimated volume of distribution at steady state (V<sub>ss</sub>) for SG is 4.62 L.

The mean (%CV) of estimated central volume distribution of both total antibody and SG is 2.86 L (19.7%).

## Metabolism

No metabolism studies with sacituzumab govitecan have been conducted. The metabolism of SG is expected to be mediated by both catabolism of hRS7 IgG1κ into small peptides and amino acids in a manner similar to endogenous immunoglobulin (Ig)G. SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1.

## Elimination

The median (range) elimination half-life ( $t_{1/2}$ ) of sacituzumab govitecan and free SN 38, based on population pharmacokinetic analysis was 155 hours (95.8-555) and 21.5 hours (16.0-259), respectively.

The mean (%CV) terminal elimination half-life of SG is 161 hours (23.2%) and the mean (%CV) apparent half-life of free SN-38 is 23.5 hours (50%).

The mean (%CV) of clearance of total antibody and SG is 0.0117 L/hr (29.4%) and 0.132 L/hr (19.8%), respectively.

No excretion studies have been conducted with SG. SN-38 and SN-38G are reported to be primarily excreted through the hepatobiliary route, with lesser amounts detected in the urine.

## Dose proportionality and time dependencies

Final model EBEs were used to calculate PK parameters and exposure metrics in participants included in the analysis population and receiving IV SG 10 mg/kg on Days 1 and 8 of 21-day treatment cycles.

Model-predicted concentration-time courses indicated minimal accumulation of SG and free SN-38, while the accumulation of total antibody was moderate.

**Table 6 Summary (Mean [%CV]) of model-derived exposure during cycles 1 and 6**

| Exposure Metric          | Cycle | Free SN-38      | SG                  | Total Antibody      |
|--------------------------|-------|-----------------|---------------------|---------------------|
| $C_{max}^a$ (ng/mL)      | 1     | 108.3919 (39.4) | 257107.0 (17.9)     | 228685.4 (17.7)     |
| $AUC_{0-168}$ (ng/mL*h)  |       | 3510.164 (62.6) | 1.204950e+07 (18.5) | 2.244466e+07 (20.3) |
| $C_{trough,168}$ (ng/mL) |       | 1.312253 (417)  | 5109.174 (26.3)     | 73282.84 (28.5)     |
| $C_{max}^a$ (ng/mL)      | 6     | 109.0591 (39.8) | 257645.0 (17.9)     | 321193.1 (23.3)     |
| $AUC_{0-168}$ (ng/mL*h)  |       | 3596.678 (68.7) | 1.239468e+07 (18.6) | 3.592178e+07 (29.4) |
| $C_{trough,168}$ (ng/mL) |       | 1.700268 (421)  | 7416.349 (26.2)     | 143040.3 (38.6)     |

CV = coefficient of variation; SG = sacituzumab govitecan

a  $C_{max,0-168}$  is equivalent to  $C_{max,1}$ , which is the maximum concentration after the first dose.

## Pharmacokinetics in target population

### Study GS-US-592-6238

Of the 279 participants who were randomized to receive SG in study GS-US-592-6238, PK samples were available from 272 participants.

Serum samples for PK analyses were collected only for participants receiving SG. Collection times for PK samples were predose and after the end of infusion on Day 1 and Day 8 of Cycle 1; Day 8 of Cycles 2, 6, and 10. Thereafter, predose samples were collected on Day 8 of every 8 cycles after Cycle 10 (e.g. Cycle 18 Day 8, Cycle 26 Day8); and at the end of treatment (EOT) visit.

In study GS-US-592-6238 the mean  $C_{max}$  for total antibody, total SN-38, and free SN-38 ranged from approximately 226,000 to 342,000 ng/mL, 4470 to 4930 ng/mL, and 85.6 to 129 ng/mL, respectively.

For total SN-38 or free SN-38, mean  $C_{max}$  appeared to reach steady state approximately by Cycle 2.

For total antibody,  $C_{max}$  slightly increase over time (up to Cycle 10).

No apparent accumulation over time was observed for total antibody, total SN-38 or free SN-38.

**Table 7 GS-US-592-6238: Mean serum PK parameters of total antibody, total SN-38, and free SN-38 by visit (PK analysis set)**

|                       | C1D1    | C1D8    | C2D8    | C6D8    | C10D8   | C18D8   | C26D8   |
|-----------------------|---------|---------|---------|---------|---------|---------|---------|
| <b>Total Antibody</b> |         |         |         |         |         |         |         |
| N                     | 250     | 231     | 218     | 138     | 77      | NA      | NA      |
| $C_{max}$ (ng/mL)     | 226,000 | 276,000 | 294,000 | 325,000 | 342,000 | NA      | NA      |
| N                     | 252     | 235     | 228     | 143     | 84      | 18      | 3       |
| $C_{trough}$ (ng/mL)  | NA      | 63,700  | 91,900  | 130,000 | 125,000 | 117,000 | 133,000 |
| <b>Total SN-38</b>    |         |         |         |         |         |         |         |
| N                     | 253     | 236     | 219     | 145     | 80      | NA      | NA      |
| $C_{max}$ (ng/mL)     | 4930    | 4810    | 4600    | 4470    | 4560    | NA      | NA      |
| N                     | 261     | 240     | 230     | 151     | 83      | 19      | 3       |
| $C_{trough}$ (ng/mL)  | NA      | 102     | 37.4    | 70.4    | 80.1    | 41.3    | 21.9    |
| <b>Free SN-38</b>     |         |         |         |         |         |         |         |
| N                     | 253     | 232     | 216     | 145     | 80      | NA      | NA      |
| $C_{max}$ (ng/mL)     | 110     | 129     | 98.3    | 103     | 85.6    | NA      | NA      |
| N                     | 262     | 239     | 230     | 150     | 84      | 19      | 3       |
| $C_{trough}$ (ng/mL)  | NA      | NA      | NA      | NA      | NA      | NA      | NA      |

BLQ = below the limit of quantitation; C = cycle; D = day; NA = not applicable; PK = pharmacokinetic; SG = sacituzumab govitecan;

Pharmacokinetic (PK) Analysis Set includes randomized participants who received  $\geq 1$  SG dose and have  $\geq 1$  measurable posttreatment SG concentration.

$C_{trough}$ : PK concentration collected at pre-dose at each visit;  $C_{max}$ : PK concentration collected at end of infusion at each visit.

Lower limit of quantitation was defined as 374 ng/mL for Total Antibody, 5 ng/mL for Total SN-38, and 1 ng/mL for Free SN-38.

Values BLQ were treated as 0 for pre/post dose summary statistics.

PK Data Cut Date: 29 July 2024

## Special populations

### Effect of Intrinsic Factors

The PopPK analysis was used to evaluate the broader potential impact of demographic and disease-related factors on PK as covariates from all 4 studies across various cancer types.

**Figure 13 Full model: Forest plot for covariate effects on AUC0-168 of TAb**

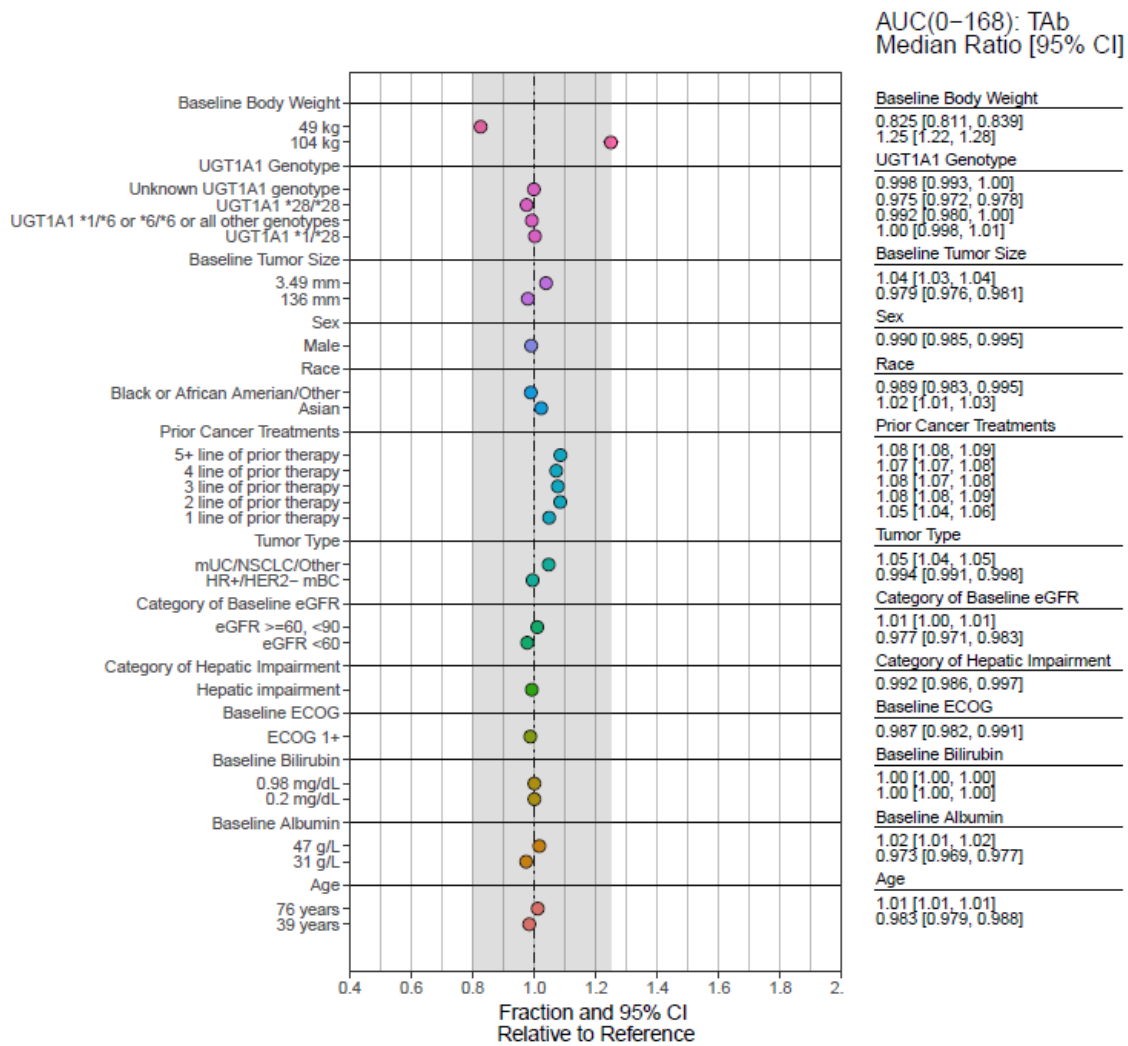


Figure 14 Full model: Forest plot for covariate effects on AUC0-168 of free SN-38

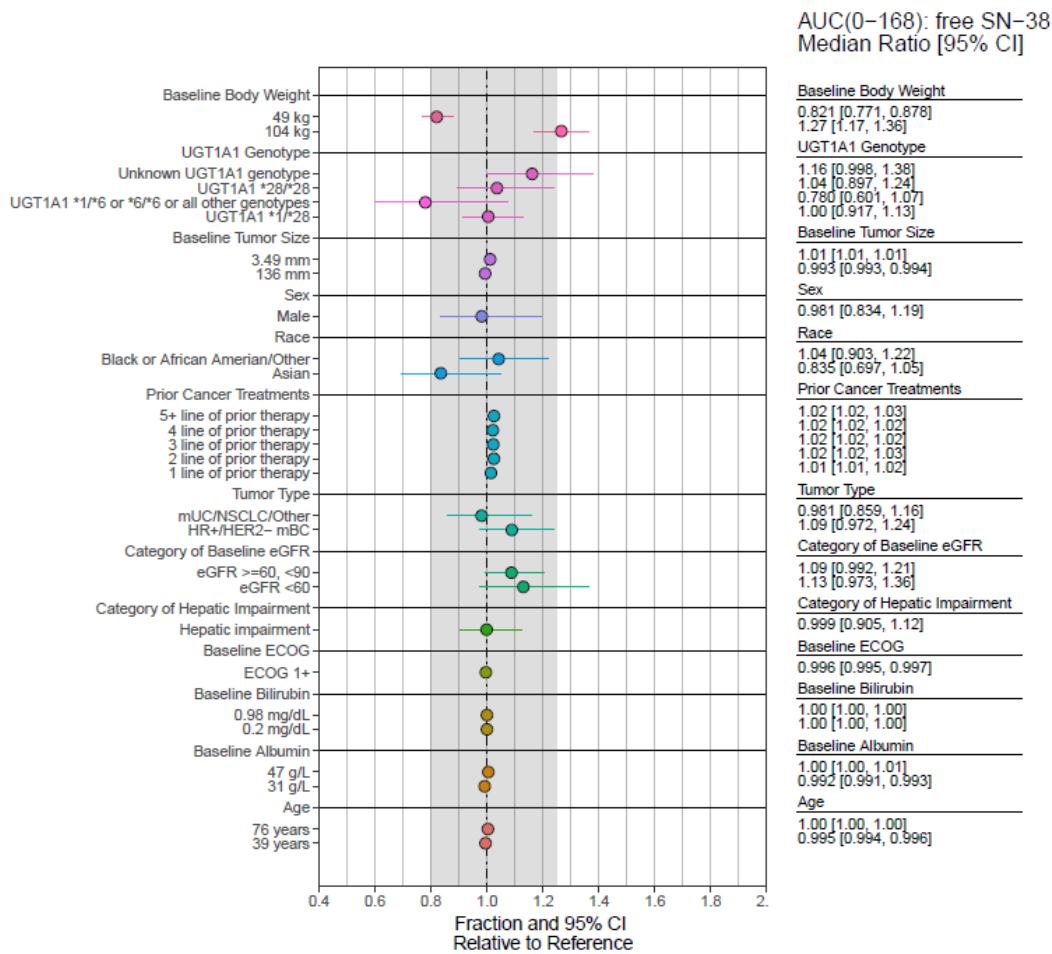
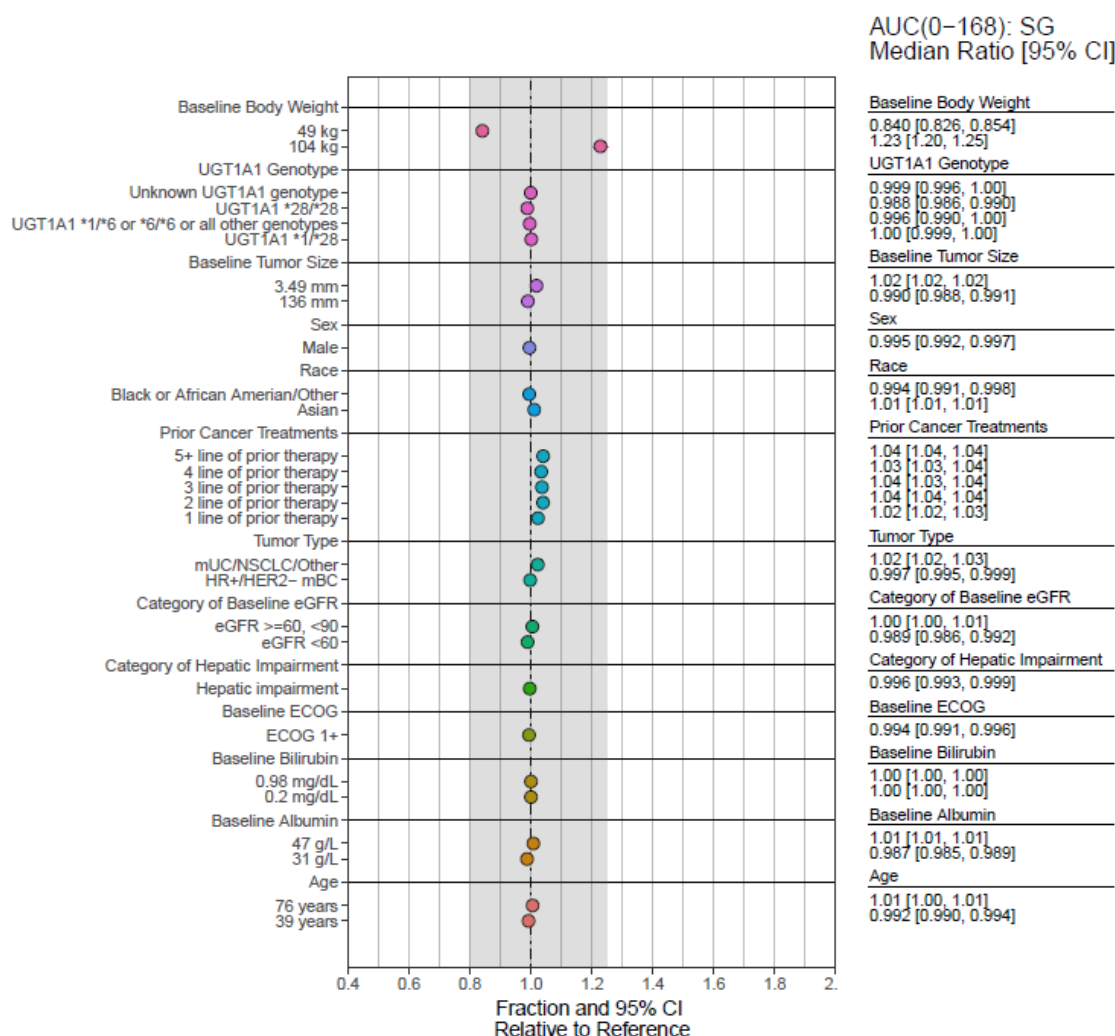


**Figure 15 Full model: Forest plot for covariate effects on AUC0-168 of SG**



### Renal impairment

Mild (n = 464) and moderate (n = 91) renal impairment had no clinically relevant effect on SG, free SN-38, or total antibody exposure compared with participants with normal (n = 506) renal function for the population included in the PopPK analysis. The potential effect of severe (n = 2) renal impairment could not be appropriately estimated due to the low number of participants included in the analysis dataset.

### Hepatic impairment

Mild (n = 317) hepatic impairment had no clinically relevant effect on SG, free SN-38, or total antibody exposure compared with participants with normal (n = 742) hepatic function for the population included in the PopPK analysis. Moderate (n = 4) hepatic impairment also indicated no clinically meaningful effect; however, this assessment should be interpreted with caution as the number of participants included in the dataset are limited.

### Age

Age had no effect on total antibody, free SN-38, or SG exposure for the overall population.

### Sex

Sex (male/female) had no effect on total antibody, free SN-38, or SG exposure for the overall population.

### Body Weight

For total antibody, free SN-38, and SG, the model-predicted AUC<sub>0-168</sub> for a body weight of 49 kg (5th percentile) and a body weight of 104 kg (95th percentile) were estimated to be 17.7%, 17.5%, and 16% lower and 25%, 26%, and 23% higher for the participants with metastatic TNBC when compared with a typical participant (having body weight of 69 kg) with metastatic TNBC, respectively.

### Race

Race had no effect on SG, free SN-38, or total antibody exposure for the overall population.

### UGT1A1 Genotype

No significant differences in total antibody, free SN-38, or SG exposure were observed in participants with the UGT1A1\*28/\*28 (n = 112) or UGT1A1\*1/\*28 (n = 410) genotype compared with participants with the UGT1A1\*1/\*1 (n = 413). Due to low frequency of occurrence for UGT1A1\*1/\*6 (n = 13) and UGT1A1\*6/\*6 (n = 2) alleles, these genotypes were combined with all other genotypes. There was a potential impact of these genotypes on SN-38 exposures; however, given the low sample size these conclusions should be treated with caution.

### Tumor Type

No significant differences in total antibody, SN-38, or SG exposure were observed by tumour type.

## **Pharmacokinetic interaction studies**

### **Effect of Extrinsic Factors**

No drug-drug interaction studies have been conducted with SG.

Concomitant administration of SG with UGT1A1 inhibitors may increase the incidence of adverse reactions due to the potential increase in systemic exposure to SN-38. Exposure to SN-38 may be reduced in participants concomitantly receiving UGT1A1 enzyme inducers.

Among the 1063 participants assessed in the PopPK analyses, only a few participants received either UGT1A1 inhibitors (N = 15) or inducers (N = 7) during SG treatment.

## **2.3.3. Pharmacodynamics**

### **Mechanism of action**

Sacituzumab govitecan (SG) is a trophoblast cell-surface antigen-2 (Trop-2)-directed antibody-drug conjugate (ADC) consisting of a humanized anti-Trop-2 monoclonal antibody (hRS7) conjugated with the active metabolite of irinotecan (SN-38) by a hydrolysable linker (CL2A). SG binds to Trop 2-expressing tumour cells and is internalised with the subsequent release of SN 38 from a hydrolysable linker. SN 38 interacts with topoisomerase I and prevents re ligation of topoisomerase I induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

## Primary and secondary pharmacology

### Immunogenicity

#### Study GS-US-592-6238

In study GS-US-592-6238, collection times for immunogenicity (ADA) samples were at predose on Day 1 (Cycle 1); Day 8 (Cycles 2, 6, and 10); and predose on Day 8 of every 8 cycles after Cycle 10 (e.g. Cycle 18 Day 8, Cycle 26 Day 8); at the EOT visit.

The immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 264 and 247 participants, respectively. Of the participants evaluated for ADA prevalence, 1 participant (0.4%) had ADAs to SG at baseline. Of the participants evaluated for ADA incidence, 3 participants (1.2%) had treatment-emergent ADAs to SG. All 3 participants with treatment-emergent ADAs were classified as having persistent ADA responses. No participant had treatment-boosted ADAs.

The maximum reportable ADA titer for participants with ADA-positive samples was 90.

All 3 participants who had treatment-emergent persistent ADAs also had positive NAb assessments.

**Table 8 GS-US-592-6238: Summary of ADA Response to SG (Immunogenicity Analysis Set)**

|                                                                                 | Sacituzumab<br>Govitecan<br>(N = 264) |
|---------------------------------------------------------------------------------|---------------------------------------|
| Evaluable for ADA prevalence                                                    | 264                                   |
| Any ADA positive (baseline or post-baseline)                                    | 4 (1.5%)                              |
| ADA positive at baseline                                                        | 1 (0.4%)                              |
| ADA not detected post-baseline and positive at baseline                         | 1 (0.4%)                              |
| ADA positive post-baseline                                                      | 3 (1.1%)                              |
| Evaluable for ADA incidence                                                     | 247                                   |
| ADA incidence (Treatment Emergent) <sup>a</sup>                                 | 3 (1.2%)                              |
| ADA positive post-baseline and not positive at baseline (treatment-induced ADA) | 3 (1.2%)                              |
| Persistent Positive <sup>b</sup>                                                | 3 (1.2%)                              |
| Transient Positive <sup>c</sup>                                                 | 0                                     |
| ADA positive post-baseline and positive at baseline                             | 0                                     |
| Treatment-boosted ADA <sup>d</sup>                                              | 0                                     |
| NAb Incidence (Treatment Emergent) <sup>e</sup>                                 | 3 (1.2%)                              |

ADA = antidrug antibody; NAb = neutralizing antibody; SG = sacituzumab govitecan

a ADA incidence (Treatment Emergent ADA): the sum of both treatment induced and treatment boosted ADA.

b Persistent positive ADA: positive at > 1 postdose assessments (with ≥ 16 weeks between first & last positive) or positive at last assessment.

c Transient positive ADA: having > 1 postdose ADA positive assessment and not fulfilling the conditions of persistent positive ADA.

d Treatment-boosted ADA: baseline positive ADA titer that was boosted to a 9-fold (2 step dilutions) or higher level following drug administration.

e NAb incidence (Treatment Emergent) is defined as NAb positive assessment on treatment emergent ADA positive samples.

Evaluable for ADA prevalence population includes participants who have at least one evaluable non-missing ADA result.

ADA Data Cut Date: 29Jul2024.

Evaluable for ADA incidence population includes participants who have at least one evaluable non-missing post-baseline ADA result.

#### Integrated summary of immunogenicity across studies

An overall summary and cross-study comparison of ADA responses to SG in participants who received at least 1 dose of SG 10 mg/kg are presented the table below. Immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 1157 and 1058 participants, respectively, across studies IMMU-132-01, IMMU-132-05, IMMU-132-06 (Cohorts 1 and 2), IMMU-132-09, and GS-US-592-6238.

15 of 1157 participants evaluable for ADA prevalence (1.3%) had positive-ADA results. Among these, 2 participants (0.2%) were ADA positive only at baseline and 13 participants (1.1%) had positive postbaseline ADA results.

13 of 1058 participants evaluable for ADA incidence (1.2%) had treatment-emergent ADAs to SG. 12 participants (1.1%) were classified as having persistent ADA responses and 1 participant (< 0.1%) was classified as having a transient ADA response to SG. Among participants with treatment-emergent ADAs, the onset of ADAs was observed at their last visit (10 of 13 participants; range: 22 to 245 days after first SG dose for participants with onset at the last visit).

The maximum reportable ADA titer observed across the studies ranged from 10 to 90.

No participant had treatment-boosted ADAs.

Ten of the 13 participants with treatment-emergent ADAs also had positive NAb assessments.

**Table 9 Summary of Antidrug Antibody Response to Sacituzumab Govitecan (GS-US-592-6238 ISI Populations)**

|                                                                                | IMMU-132-01<br>SG (10 mg/kg)<br>(N = 221) | IMMU-132-05<br>SG (10 mg/kg)<br>(N = 258) | IMMU-132-06<br>SG (10 mg/kg)<br>(N = 150) | IMMU-132-09<br>SG (10 mg/kg)<br>(N = 265) | GS-US-592-6238<br>SG (10 mg/kg)<br>(N = 264) | Overall mBC<br>SG (10 mg/kg)<br>(N = 893) | All Treated<br>SG (10 mg/kg)<br>(N = 1158) |
|--------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|----------------------------------------------|-------------------------------------------|--------------------------------------------|
| Evaluable for ADA prevalence                                                   | 221                                       | 258                                       | 150                                       | 264                                       | 264                                          | 892                                       | 1157                                       |
| Any ADA positive (baseline or postbaseline)                                    | 2 (0.9%)                                  | 4 (1.6%)                                  | 5 (3.3%)                                  | 0                                         | 4 (1.5%)                                     | 9 (1.0%)                                  | 15 (1.3%)                                  |
| ADA positive at baseline                                                       | 1 (0.5%)                                  | 0                                         | 0                                         | 0                                         | 1 (0.4%)                                     | 2 (0.2%)                                  | 2 (0.2%)                                   |
| ADA not detected postbaseline and positive at baseline                         | 1 (0.5%)                                  | 0                                         | 0                                         | 0                                         | 1 (0.4%)                                     | 2 (0.2%)                                  | 2 (0.2%)                                   |
| ADA positive postbaseline                                                      | 1 (0.5%)                                  | 4 (1.6%)                                  | 5 (3.3%)                                  | 0                                         | 3 (1.1%)                                     | 7 (0.8%)                                  | 13 (1.1%)                                  |
| Evaluable for ADA incidence                                                    | 210                                       | 242                                       | 123                                       | 236                                       | 247                                          | 823                                       | 1058                                       |
| ADA incidence (treatment emergent) <sup>a</sup>                                | 1 (0.5%)                                  | 4 (1.7%)                                  | 5 (4.1%)                                  | 0                                         | 3 (1.2%)                                     | 7 (0.9%)                                  | 13 (1.2%)                                  |
| ADA positive postbaseline and not positive at baseline (treatment-induced ADA) | 1 (0.5%)                                  | 4 (1.7%)                                  | 5 (4.1%)                                  | 0                                         | 3 (1.2%)                                     | 7 (0.9%)                                  | 13 (1.2%)                                  |
| Persistent Positive <sup>b</sup>                                               | 1 (0.5%)                                  | 3 (1.2%)                                  | 5 (4.1%)                                  | 0                                         | 3 (1.2%)                                     | 6 (0.7%)                                  | 12 (1.1%)                                  |
| Transient Positive <sup>c</sup>                                                | 0                                         | 1 (0.4%)                                  | 0                                         | 0                                         | 0                                            | 1 (0.1%)                                  | 1 (<0.1%)                                  |
| ADA positive postbaseline and positive at baseline                             | 0                                         | 0                                         | 0                                         | 0                                         | 0                                            | 0                                         | 0                                          |
| Treatment-boosted ADA <sup>d</sup>                                             | 0                                         | 0                                         | 0                                         | 0                                         | 0                                            | 0                                         | 0                                          |
| NAb Incidence (treatment emergent) <sup>e</sup>                                | 1 (0.5%)                                  | 3 (1.2%)                                  | 3 (2.4%)                                  | 0                                         | 3 (1.2%)                                     | 6 (0.7%)                                  | 10 (0.9%)                                  |

ADA = antidrug antibody; ISI = Integrated Summary of Immunogenicity; NAb = neutralizing antibody; SG = sacituzumab govitecan

a ADA incidence (treatment-emergent ADA): the sum of both treatment-induced and treatment-boosted ADA.

a Persistent ADA: treatment-induced ADA at  $\geq 2$  samples during the treatment (with  $\geq 16$  weeks between first and last positive) or treatment-induced ADA in the last sample or with < 16 weeks before an ADA-negative last sample.

b Transient ADA: treatment-induced ADA that does not meet the definition of persistent ADA.

c Treatment-Boosted ADA: positive baseline and  $(\text{Imax titer of the postbaseline ADA}) / (\text{titer of baseline ADA}) \geq 9$ .

d NAb incidence: proportion of participants with  $\geq 1$  positive NAb result based on the total N evaluable for ADA incidence as denominator.

**Table 10 Summary of time to onset of ADA positivity for participants with treatment-emergent ADAs to SG (GS-US-592-6238 ISI Population)**

| Participant ID                  | Time After First Dose of SG (Days) |
|---------------------------------|------------------------------------|
| [****]                          | 49                                 |
| [****]                          | 78                                 |
| [****]                          | 94                                 |
| [****]                          | 71                                 |
| [****]                          | 22                                 |
| [****]                          | 72                                 |
| [****]                          | 36                                 |
| [****]                          | 152                                |
| [****]                          | 245                                |
| [****]                          | 46                                 |
| [****]                          | 55                                 |
| [****]                          | 54                                 |
| [****]                          | 66                                 |
| Median Across ADA+ Participants | 66                                 |

ADA = antidrug antibody; ADA+ = ADA positive; SG = sacituzumab govitecan

**Impact of Antidrug Antibodies on Sacituzumab Govitecan or Total Antibody Pharmacokinetics**

The impact of immunogenicity on the PK of free SN-38, total SN-38, and total antibody was evaluated in the population PK (PopPK) analysis based on available serum concentration and ADA data in the PopPK analysis population from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238.

Of the 13 participants with treatment-emergent ADAs, PK data were available for 7 participants (n = 4 from study IMMU-132-05; n = 3 from study GS-US-592-6238). In addition, PK data were also available for 1 participant with baseline positive ADAs from study GS-US-592-6238 that was included in the PopPK analysis dataset.

**Figure 16 Studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238: Free SN-38, total SN-38, and total antibody serum concentrations versus time since last dose by ADA status based on pooled data**

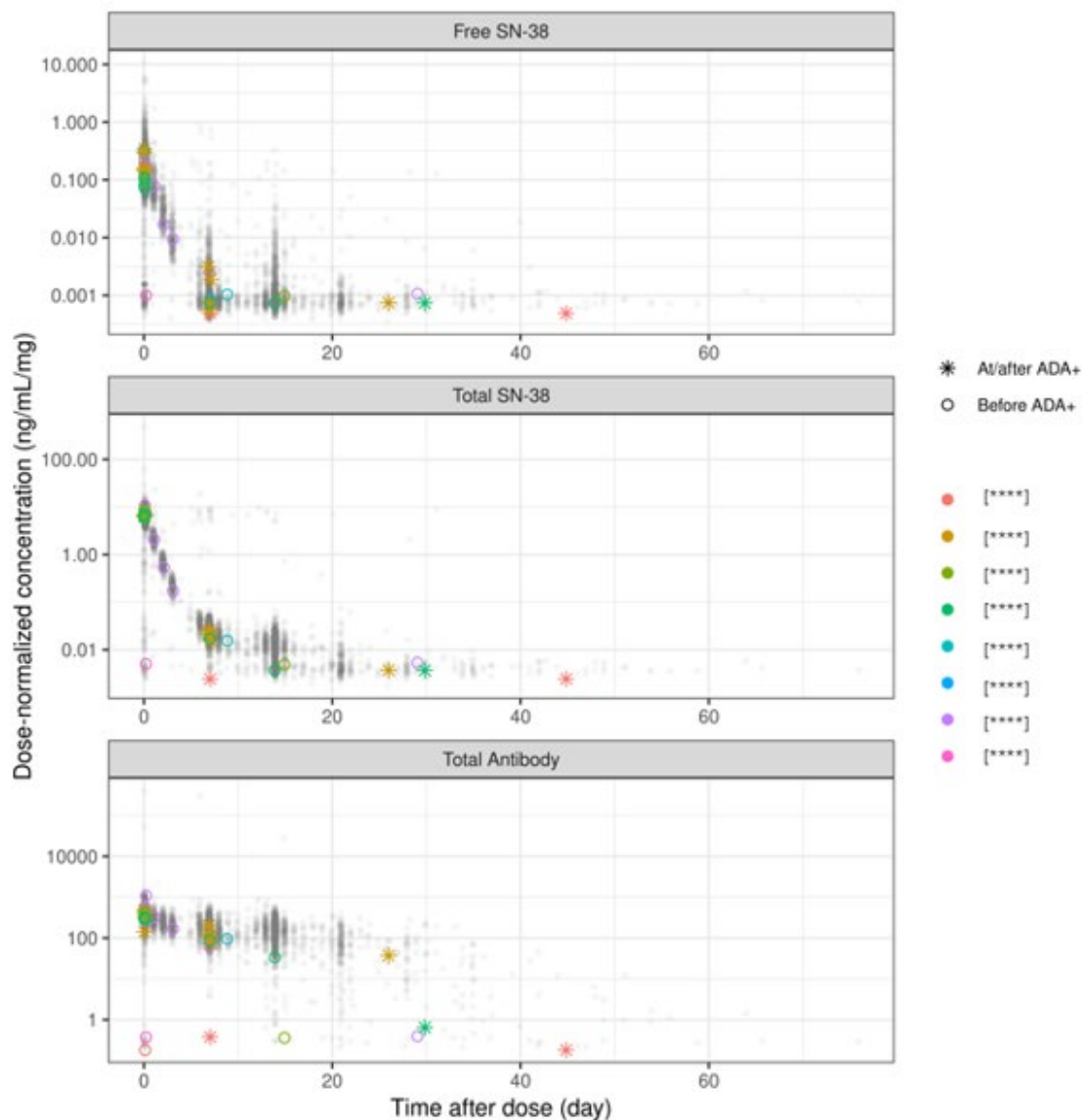


**Table 11 Summary of Exposure by ADA status**

| PK Parameter                         | Groups                  | Free SN-38      | SG                  | Total Antibody      |
|--------------------------------------|-------------------------|-----------------|---------------------|---------------------|
| C <sub>max,0-168</sub> , ng/mL (%CV) | Negative (N = 740)      | 108.8836 (39.4) | 257646.1 (17.4)     | 229114.5 (17.2)     |
|                                      | Positive (N = 7)        | 80.87776 (46.1) | 232828.6 (20.4)     | 206994.3 (19.8)     |
|                                      | No ADA samples (N = 80) | 106.2519 (38.3) | 254244.4 (21.8)     | 226614.3 (21.6)     |
| AUC <sub>0-168</sub> , ng/mL*h (%CV) | Negative (N = 740)      | 3530.248 (61.7) | 1.207866e+07 (17.9) | 2.251567e+07 (19.6) |
|                                      | Positive (N = 7)        | 2205.276 (47.8) | 1.045131e+07 (15.8) | 1.795840e+07 (11.2) |
|                                      | No ADA samples (N = 80) | 3438.569 (70.1) | 1.191959e+07 (23.1) | 2.218032e+07 (25.9) |

ADA = antidrug antibody; %CV = percentage coefficient of variation; SG = sacituzumab govitecan

### Impact of Antidrug Antibodies on Efficacy

Across the studies, 5 participants who were ADA positive had a stable disease, 2 participants had progression disease and one participant had a partial response. 3 participants were not assessed/not available for best overall response assessment and for two participants the best overall response was not evaluable per independent review assessment. The progression-free survival in ADA positive patients ranged from 1.1 to 5.0 months and the overall survival ranged from 1.41 to 20.3 months.

Due to the small number of participants with positive ADA responses to SG across studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, and GS-US-592-6238, no formal analysis was performed by the applicant to assess the impact of ADAs on the efficacy of SG.

**Table 12 Summary of efficacy for participants with a positive ADA response to SG in Studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238**

| Participant ID  | Best Overall Response per Independent Review Assessment | Progression-Free Survival (Months) | Overall Survival (Months) |
|-----------------|---------------------------------------------------------|------------------------------------|---------------------------|
| IMMU-132-01     |                                                         |                                    |                           |
| [****]          | NA                                                      | 5                                  | 5                         |
| IMMU-132-05     |                                                         |                                    |                           |
| [****]          | PD                                                      | 1.31                               | 9.4                       |
| [****]          | SD                                                      | 2.73                               | 17.22                     |
| [****]          | SD                                                      | 1.48                               | 4.44                      |
| [****]          | NE <sup>a</sup>                                         | 1.41                               | 1.41                      |
| IMMU-132-06     |                                                         |                                    |                           |
| [****]          | NA <sup>a</sup>                                         | 1.4                                | 3.4                       |
| [****]          | NE <sup>a</sup>                                         | 1.1                                | 5.6                       |
| [****]          | SD                                                      | 2.8                                | 11.9                      |
| [****]          | PR                                                      | 5.0                                | 16.5                      |
| [****]          | NA <sup>a</sup>                                         | 2.7                                | 3.2                       |
| IMMU-132-09     |                                                         |                                    |                           |
| No participants | —                                                       | —                                  | —                         |
| GS-US-592-6238  |                                                         |                                    |                           |
| [****]          | SD                                                      | 1.41                               | 20.3                      |
| [****]          | SD                                                      | 3.15                               | 3.15                      |
| [****]          | PD                                                      | 1.51                               | 4.86                      |

ADA = antidrug antibody; mUC = metastatic urothelial carcinoma; NA = not assessed/not available; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; SG = sacituzumab govitecan

a Participants [\*\*\*\*], [\*\*\*\*], and [\*\*\*\*] had a best overall response of PD by investigator assessment.  
Participant [\*\*\*\*] had a best overall response of SD by investigator assessment.

**Table 13 Progression-Free Survival by Blinded Independent Central Review by ADA Status (GS-US-592-6238 ISI Population)**

|                                                    | IMMU-132-01<br>SG (All Doses)<br>(N = 223) |                      | IMMU-132-05<br>SG (10 mg/kg)<br>(N = 258) |                      | IMMU-132-06<br>SG (10 mg/kg)<br>(N = 150) |                      | IMMU-132-09<br>SG (10 mg/kg)<br>(N = 265) |                      | GS-US-592-6238<br>SG (10 mg/kg)<br>(N = 264) |                       |
|----------------------------------------------------|--------------------------------------------|----------------------|-------------------------------------------|----------------------|-------------------------------------------|----------------------|-------------------------------------------|----------------------|----------------------------------------------|-----------------------|
|                                                    | ADA+<br>(N = 1)                            | ADA-<br>(N = 211)    | ADA+<br>(N = 4)                           | ADA-<br>(N = 238)    | ADA+<br>(N = 5)                           | ADA-<br>(N = 118)    | ADA+<br>(N = 0)                           | ADA-<br>(N = 236)    | ADA+<br>(N = 3)                              | ADA-<br>(N = 244)     |
| Number (%) of Participants with Available PFS data | 1 (100.0%)                                 | 211 (100.0%)         | 4 (100.0%)                                | 238 (100.0%)         | 5 (100.0%)                                | 118 (100.0%)         | 0                                         | 236 (100.0%)         | 3 (100.0%)                                   | 244 (100.0%)          |
| Number (%) of Participants with Events             | 1 (100.0%)                                 | 183 (86.7%)          | 3 (75.0%)                                 | 171 (71.8%)          | 1 (20.0%)                                 | 78 (66.1%)           | 0                                         | 157 (66.5%)          | 2 (66.7%)                                    | 143 (58.6%)           |
| Disease Progression (PD)                           | 0                                          | 162 (76.8%)          | 2 (50.0%)                                 | 163 (68.5%)          | 1 (20.0%)                                 | 72 (61.0%)           | 0                                         | 137 (58.1%)          | 1 (33.3%)                                    | 137 (56.1%)           |
| Death                                              | 1 (100.0%)                                 | 21 (10.0%)           | 1 (25.0%)                                 | 8 (3.4%)             | 0                                         | 6 (5.1%)             | 0                                         | 20 (8.5%)            | 1 (33.3%)                                    | 6 (2.5%)              |
| Number (%) of Participants Censored                | 0                                          | 28 (13.3%)           | 1 (25.0%)                                 | 67 (28.2%)           | 4 (80.0%)                                 | 40 (33.9%)           | 0                                         | 79 (33.5%)           | 1 (33.3%)                                    | 101 (41.4%)           |
| Kaplan-Meier Estimate of PFS (Months) (95% CI)     |                                            |                      |                                           |                      |                                           |                      |                                           |                      |                                              |                       |
| Median                                             | 5.00<br>(NEst, NR)                         | 5.70<br>(5.30, 6.90) | 2.07 (1.31, NR)                           | 5.59<br>(4.30, 6.34) | 4.99<br>(NEst, NR)                        | 5.68<br>(5.36, 7.92) |                                           | 5.75<br>(4.73, 7.36) | 2.33<br>(1.51, NR)                           | 9.82<br>(8.34, 12.35) |

ADA = antidrug antibody; CI = confidence interval; ISI = integrated summary of immunogenicity; NEst = not estimable; NR = not reached; PD = progressive disease;

PFS = progression-free survival; SG = sacituzumab govitecan

PFS (months) = (date of events or censoring - date of randomization + 1)/30.4375.

Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA-" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.

Denominator of percentages is the number of participants for each ADA status in each study included in the GS-US-592-6238 ISI Populations.

Median PFS is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.

PFS by investigator assessment was summarized for IMMU-132-01 across multiple dose levels (SG 8 mg/kg and 10 mg/kg) and indications, PFS by Blinded Independent Central Review (BICR) was summarized for other studies.

**Table 14 Overall Survival by ADA Status (GS-US-592-6238 ISI Population)**

|                                                   | IMMU-132-01<br>SG (All Doses)<br>(N = 223) |                         | IMMU-132-05<br>SG (10 mg/kg)<br>(N = 258) |                         | IMMU-132-06<br>SG (10 mg/kg)<br>(N = 150) |                         | IMMU-132-09<br>SG (10 mg/kg)<br>(N = 265) |                         | GS-US-592-6238<br>SG (10 mg/kg)<br>(N = 264) |                      |
|---------------------------------------------------|--------------------------------------------|-------------------------|-------------------------------------------|-------------------------|-------------------------------------------|-------------------------|-------------------------------------------|-------------------------|----------------------------------------------|----------------------|
|                                                   | ADA+<br>(N = 1)                            | ADA-<br>(N = 211)       | ADA+<br>(N = 4)                           | ADA-<br>(N = 238)       | ADA+<br>(N = 5)                           | ADA-<br>(N = 118)       | ADA+<br>(N = 0)                           | ADA-<br>(N = 236)       | ADA+<br>(N = 3)                              | ADA-<br>(N = 244)    |
| Number (%) of Participants with Available OS data | 1 (100.0%)                                 | 211 (100.0%)            | 4 (100.0%)                                | 238 (100.0%)            | 5 (100.0%)                                | 118 (100.0%)            | 0                                         | 236 (100.0%)            | 3 (100.0%)                                   | 244 (100.0%)         |
| Number (%) of Participants with Events (Death)    | 1 (100.0%)                                 | 151 (71.6%)             | 3 (75.0%)                                 | 175 (73.5%)             | 5 (100.0%)                                | 92 (78.0%)              | 0                                         | 181 (76.7%)             | 3 (100.0%)                                   | 116 (47.5%)          |
| Number (%) of Participants Censored               | 0                                          | 60 (28.4%)              | 1 (25.0%)                                 | 63 (26.5%)              | 0                                         | 26 (22.0%)              | 0                                         | 55 (23.3%)              | 0                                            | 128 (52.5%)          |
| Kaplan-Meier Estimate of OS (Months) (95% CI)     |                                            |                         |                                           |                         |                                           |                         |                                           |                         |                                              |                      |
| Median                                            | 5.00<br>(NEst, NR)                         | 13.70<br>(11.90, 16.90) | 6.92 (1.41, NR)                           | 13.11<br>(11.17, 14.32) | 5.55 (3.22, NR)                           | 14.29<br>(11.10, 16.66) |                                           | 15.70<br>(14.06, 17.54) | 4.86<br>(3.15, NR)                           | 22.64<br>(20.14, NR) |

ADA = antidrug antibody; CI = confidence interval; ISI = integrated summary of immunogenicity; NEst = not estimable; NR = not reached; OS = overall survival;

PD = progressive disease; SG = sacituzumab govitecan

OS (months) = (date of death or censoring - date of randomization + 1)/30.4375.

Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA-" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.

Denominator of percentages is the number of participants for each ADA status in each study included in the GS-US-592-6238 ISI Populations.

Median OS is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.

OS for IMMU-132-01 was summarized across multiple dose levels (SG 8 mg/kg and 10 mg/kg) and indications.

**Table 15 Objective Response Rate by Blinded Independent Central Review by ADA Status (GS-US-592-6238 ISI Population)**

|                                                    | IMMU-132-01<br>SG (All Doses)<br>(N = 223) |                         | IMMU-132-05<br>SG (10 mg/kg)<br>(N = 258) |                         | IMMU-132-06<br>SG (10 mg/kg)<br>(N = 150) |                         | IMMU-132-09<br>SG (10 mg/kg)<br>(N = 265) |                         | GS-US-592-6238<br>SG (10 mg/kg)<br>(N = 264) |                         |
|----------------------------------------------------|--------------------------------------------|-------------------------|-------------------------------------------|-------------------------|-------------------------------------------|-------------------------|-------------------------------------------|-------------------------|----------------------------------------------|-------------------------|
|                                                    | ADA+<br>(N = 1)                            | ADA-<br>(N = 211)       | ADA+<br>(N = 4)                           | ADA-<br>(N = 238)       | ADA+<br>(N = 5)                           | ADA-<br>(N = 118)       | ADA+<br>(N = 0)                           | ADA-<br>(N = 236)       | ADA+<br>(N = 3)                              | ADA-<br>(N = 244)       |
| Number (%) of Participants with Available ORR data | 0                                          | 206 (97.6%)             | 4 (100.0%)                                | 238 (100.0%)            | 5 (100.0%)                                | 118 (100.0%)            | 0                                         | 236 (100.0%)            | 3 (100.0%)                                   | 244 (100.0%)            |
| Objective Response Rate (ORR) (95% CI)             | 0.0%                                       | 35.1%<br>(28.6%, 41.9%) | 0.0%                                      | 34.9%<br>(28.8%, 41.3%) | 20.0% (0.5%, 71.6%)                       | 36.4%<br>(27.8%, 45.8%) | —                                         | 24.2%<br>(18.8%, 30.1%) | 0.0%                                         | 52.0%<br>(45.6%, 58.5%) |
| Responders (CR + PR)                               | 0                                          | 74 (35.1%)              | 0                                         | 83 (34.9%)              | 1 (20.0%)                                 | 43 (36.4%)              | 0                                         | 57 (24.2%)              | 0                                            | 127 (52.0%)             |
| Non-responders (SD + PD + NE)                      | 0                                          | 132 (62.6%)             | 4 (100.0%)                                | 155 (65.1%)             | 4 (80.0%)                                 | 75 (63.6%)              | 0                                         | 179 (75.8%)             | 3 (100.0%)                                   | 117 (48.0%)             |

ADA = antidrug antibody; CI = confidence interval; CR = complete response; ISI = integrated summary of immunogenicity; ORR = objective response rate; PD = progressive disease; PR = partial response; NE = not evaluable; SD = stable disease

Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA-" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.

Denominator of percentages is the number of participants for each ADA status in each study included in the GS-US-592-6238 ISI Populations.

ORR is the proportion of participants who achieved best overall response of CR/PR. The 95% CI is based on Clopper-Pearson method.

ORR by investigator assessment was summarized for IMMU-132-01 across multiple dose levels (SG 8 mg/kg and 10 mg/kg) and indications, ORR by Blinded Independent Central Review (BICR) was summarized for other studies.

## Impact of Antidrug Antibodies on Safety

An evaluation of immunogenicity and safety for participants with treatment-emergent ADAs to SG has been evaluated in studies IMMU-132-01, IMMU-132-05, IMMU-132-06, and GS-US-592-6238.

All 13 of 1058 participants (1.2% incidence) with treatment-emergent ADAs received a starting dose of SG 10 mg/kg. None of these participants experienced a serious treatment-emergent AE (TEAE) that was considered related to SG.

**Table 16 Overall summary of treatment-emergent AEs by ADA status (GS-US-592-6238 ISI Population)**

|                                                            | IMMU-132-01<br>SG (All Doses)<br>(N = 223) |                   | IMMU-132-01 mBC<br>SG (10 mg/kg)<br>(N = 106) |                  | IMMU-132-05<br>SG (10 mg/kg)<br>(N = 258) |                   | IMMU-132-06<br>SG (10 mg/kg)<br>(N = 150) |                   |
|------------------------------------------------------------|--------------------------------------------|-------------------|-----------------------------------------------|------------------|-------------------------------------------|-------------------|-------------------------------------------|-------------------|
|                                                            | ADA+<br>(N = 1)                            | ADA-<br>(N = 211) | ADA+<br>(N = 0)                               | ADA-<br>(N = 98) | ADA+<br>(N = 4)                           | ADA-<br>(N = 238) | ADA+<br>(N = 5)                           | ADA-<br>(N = 118) |
| Number (%) of Participants with Any                        |                                            |                   |                                               |                  |                                           |                   |                                           |                   |
| TEAE                                                       | 1 (100.0%)                                 | 211 (100.0%)      | 0                                             | 98 (100.0%)      | 4 (100.0%)                                | 238 (100.0%)      | 5 (100.0%)                                | 118 (100.0%)      |
| TEAE with Grade 3 or Higher                                | 1 (100.0%)                                 | 155 (73.5%)       | 0                                             | 72 (73.5%)       | 3 (75.0%)                                 | 171 (71.8%)       | 5 (100.0%)                                | 100 (84.7%)       |
| TEAE Related to SG                                         | 0                                          | 210 (99.5%)       | 0                                             | 97 (99.0%)       | 4 (100.0%)                                | 233 (97.9%)       | 5 (100.0%)                                | 116 (98.3%)       |
| TEAE Related to SG with Grade 3 or Higher                  | 0                                          | 130 (61.6%)       | 0                                             | 67 (68.4%)       | 2 (50.0%)                                 | 152 (63.9%)       | 2 (40.0%)                                 | 80 (67.8%)        |
| Serious TEAE <sup>a</sup>                                  | 1 (100.0%)                                 | 64 (30.3%)        | 0                                             | 26 (26.5%)       | 1 (25.0%)                                 | 59 (24.8%)        | 3 (60.0%)                                 | 52 (44.1%)        |
| TEAE Leading to SG Dose Reduction                          | 0                                          | 0                 | 0                                             | 0                | 1 (25.0%)                                 | 54 (22.7%)        | 1 (20.0%)                                 | 57 (48.3%)        |
| TEAE Leading to SG Interruption                            | 0                                          | 108 (51.2%)       | 0                                             | 44 (44.9%)       | 1 (25.0%)                                 | 151 (63.4%)       | 4 (80.0%)                                 | 77 (65.3%)        |
| TEAE Leading to SG Discontinuation                         | 0                                          | 9 (4.3%)          | 0                                             | 2 (2.0%)         | 0                                         | 10 (4.2%)         | 0                                         | 17 (14.4%)        |
| Any Hypersensitivity or Immune-mediated TEAE               | 0                                          | 50 (23.7%)        | 0                                             | 26 (26.5%)       | 0                                         | 41 (17.2%)        | 0                                         | 18 (15.3%)        |
| Any Hypersensitivity or Immune-mediated TEAE Related to SG | 0                                          | 34 (16.1%)        | 0                                             | 22 (22.4%)       | 0                                         | 25 (10.5%)        | 0                                         | 11 (9.3%)         |
| TEAE Leading to Death                                      | 0                                          | 4 (1.9%)          | 0                                             | 0                | 0                                         | 0                 | 0                                         | 3 (2.5%)          |
| All Deaths <sup>b</sup>                                    | 1 (100.0%)                                 | 168 (79.6%)       | 0                                             | 81 (82.7%)       | 3 (75.0%)                                 | 175 (73.5%)       | 5 (100.0%)                                | 92 (78.0%)        |

| (Continued)                                                | IMMU-132-09<br>SG (10 mg/kg)<br>(N = 265) |                   | GS-US-592-6238<br>SG (10 mg/kg)<br>(N = 264) |                   | Overall mBC<br>SG (10 mg/kg)<br>(N = 893) |                   | All Treated<br>SG (10 mg/kg)<br>(N = 1158) |                    |
|------------------------------------------------------------|-------------------------------------------|-------------------|----------------------------------------------|-------------------|-------------------------------------------|-------------------|--------------------------------------------|--------------------|
|                                                            | ADA+<br>(N = 0)                           | ADA-<br>(N = 236) | ADA+<br>(N = 3)                              | ADA-<br>(N = 244) | ADA+<br>(N = 7)                           | ADA-<br>(N = 816) | ADA+<br>(N = 13)                           | ADA-<br>(N = 1045) |
| TEAE                                                       | 0                                         | 236 (100.0%)      | 3 (100.0%)                                   | 243 (99.6%)       | 7 (100.0%)                                | 815 (99.9%)       | 13 (100.0%)                                | 1044 (99.9%)       |
| TEAE with Grade 3 or Higher                                | 0                                         | 168 (71.2%)       | 3 (100.0%)                                   | 156 (63.9%)       | 6 (85.7%)                                 | 567 (69.5%)       | 12 (92.3%)                                 | 748 (71.6%)        |
| TEAE Related to SG                                         | 0                                         | 233 (98.7%)       | 3 (100.0%)                                   | 241 (98.8%)       | 7 (100.0%)                                | 804 (98.5%)       | 12 (92.3%)                                 | 1031 (98.7%)       |
| TEAE Related to SG with Grade 3 or Higher                  | 0                                         | 151 (64.0%)       | 2 (66.7%)                                    | 144 (59.0%)       | 4 (57.1%)                                 | 514 (63.0%)       | 6 (46.2%)                                  | 655 (62.7%)        |
| Serious TEAE <sup>a</sup>                                  | 0                                         | 60 (25.4%)        | 2 (66.7%)                                    | 54 (22.1%)        | 3 (42.9%)                                 | 199 (24.4%)       | 7 (53.8%)                                  | 287 (27.5%)        |
| TEAE Leading to SG Dose Reduction                          | 0                                         | 83 (35.2%)        | 1 (33.3%)                                    | 95 (38.9%)        | 2 (28.6%)                                 | 232 (28.4%)       | 3 (23.1%)                                  | 289 (27.7%)        |
| TEAE Leading to SG Interruption                            | 0                                         | 161 (68.2%)       | 3 (100.0%)                                   | 164 (67.2%)       | 4 (57.1%)                                 | 520 (63.7%)       | 8 (61.5%)                                  | 659 (63.1%)        |
| TEAE Leading to SG Discontinuation                         | 0                                         | 11 (4.7%)         | 1 (33.3%)                                    | 5 (2.0%)          | 1 (14.3%)                                 | 28 (3.4%)         | 1 (7.7%)                                   | 52 (5.0%)          |
| Any Hypersensitivity or Immune-mediated TEAE               | 0                                         | 25 (10.6%)        | 1 (33.3%)                                    | 20 (8.2%)         | 1 (14.3%)                                 | 112 (13.7%)       | 1 (7.7%)                                   | 154 (14.7%)        |
| Any Hypersensitivity or Immune-mediated TEAE Related to SG | 0                                         | 16 (6.8%)         | 1 (33.3%)                                    | 14 (5.7%)         | 1 (14.3%)                                 | 77 (9.4%)         | 1 (7.7%)                                   | 100 (9.6%)         |
| TEAE Leading to Death                                      | 0                                         | 3 (1.3%)          | 0                                            | 2 (0.8%)          | 0                                         | 5 (0.6%)          | 0                                          | 11 (1.1%)          |
| All Deaths <sup>b</sup>                                    | 0                                         | 201 (85.2%)       | 2 (66.7%)                                    | 84 (34.4%)        | 5 (71.4%)                                 | 541 (66.3%)       | 11 (84.6%)                                 | 719 (68.8%)        |

ADA = antidrug antibody; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ISI = Integrated Summary of Immunogenicity; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event

a No participant with treatment-emergent ADAs experienced a serious TEAE that was considered related to SG.

b All Deaths include deaths not due to AEs.

Percentages are based on ADA (N) in column header.

Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA-" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.

A participant with ≥ 2 AEs in each row is counted only once. A participant may be counted in multiple categories.

Adverse events leading to dose reduction were not collected in Study IMMU-132-01; study participants were excluded in pooled percentage calculations.

Adverse events were coded per MedDRA Version 27.1. Severity grades were defined per CTCAE Version 5.0.

One of the 13 participants (7.7%) with treatment-emergent ADAs experienced a TEAE that led to premature discontinuation of study drug. The TEAE was in the AESI hypersensitivity category (a Grade 2 infusion-related reaction that resolved the same day) and did not recur upon receiving an additional dose of SG. This participant also had a positive NAb assessment.

No participant had treatment-emergent immune-mediated AEs.

## 2.3.4. PK/PD modelling

### Exposure-Response Relationships

Using an integrated population pharmacokinetic (popPK) model that characterized 1) total SN-38, 2) free SN-38, and 3) total SG antibody (tAb) concentrations following SG administration, exposure-response (E-R) analyses were conducted to characterize the relationships between exposure and efficacy and safety endpoints of clinical interest. Individual empirical Bayes estimates (EBE) of PK parameters from this popPK model were used to calculate the exposure metrics of tAb, SG and free SN-38, which were tested in the presented E-R analyses. In total, up to 26 metrics were considered for E-R analyses regarding efficacy and 12 additional metrics (for SN38) for E-R analyses regarding safety.

Exposure-response (E-R) for efficacy analyses were conducted using data from a total of 272 participants with metastatic TNBC from study GS-US-592-6238, and exposure-safety analyses were conducted using data from a total of 1063 participants with solid tumours who received SG in studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238.

### Exposure-response (E-R) analysis for efficacy

Exposure-efficacy relationships were evaluated in participants with locally advanced unresectable or metastatic TNBC who received a starting dose of SG 10 mg/kg on Days 1 and 8 of a 21-day cycle in study GS-US-592-6238. The exposure-efficacy analysis dataset included a total of 272 participants

with locally advanced unresectable or metastatic TNBC from study GS-US-592-6238 who had estimated exposure metrics based on PopPK model and data for respective efficacy endpoints.

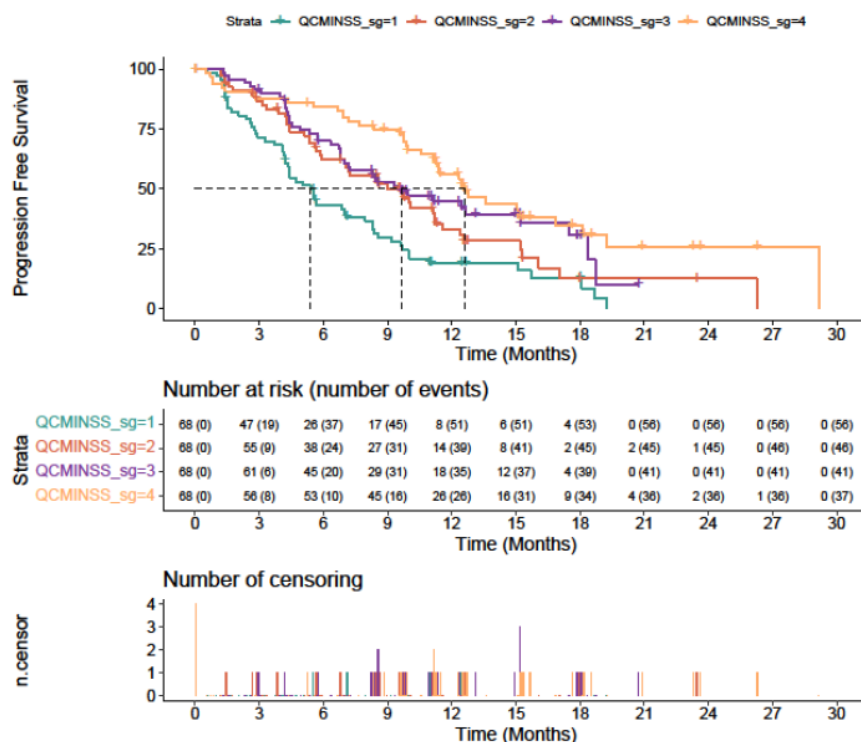
The evaluated efficacy endpoints included PFS and ORR.

The exposure-efficacy relationships were analyzed using binomial logistic regression models for ORR and parametric time-to-event (TTE) models for PFS.

- *Exposure-PFS*

The exposure-efficacy relationships were analyzed using parametric time-to-event (TTE) models for PFS (N=272). For PFS,  $C_{min,SS,SG}$  was identified as the most significant exposure metric and implemented as an Emax drug effect on the baseline hazard.

**Figure 17 GS-US-592-6238: Kaplan-Meier Curves of PFS Stratified by Quartiles of  $C_{min,SS,SG}$**



PFS = progression-free survival; QCMINSS\_sg = quartiles of  $C_{min,SS,SG}$

The vertical dashed lines indicate the median survival time (corresponding to a survival probability of 0.5) associated with each exposure quartile.

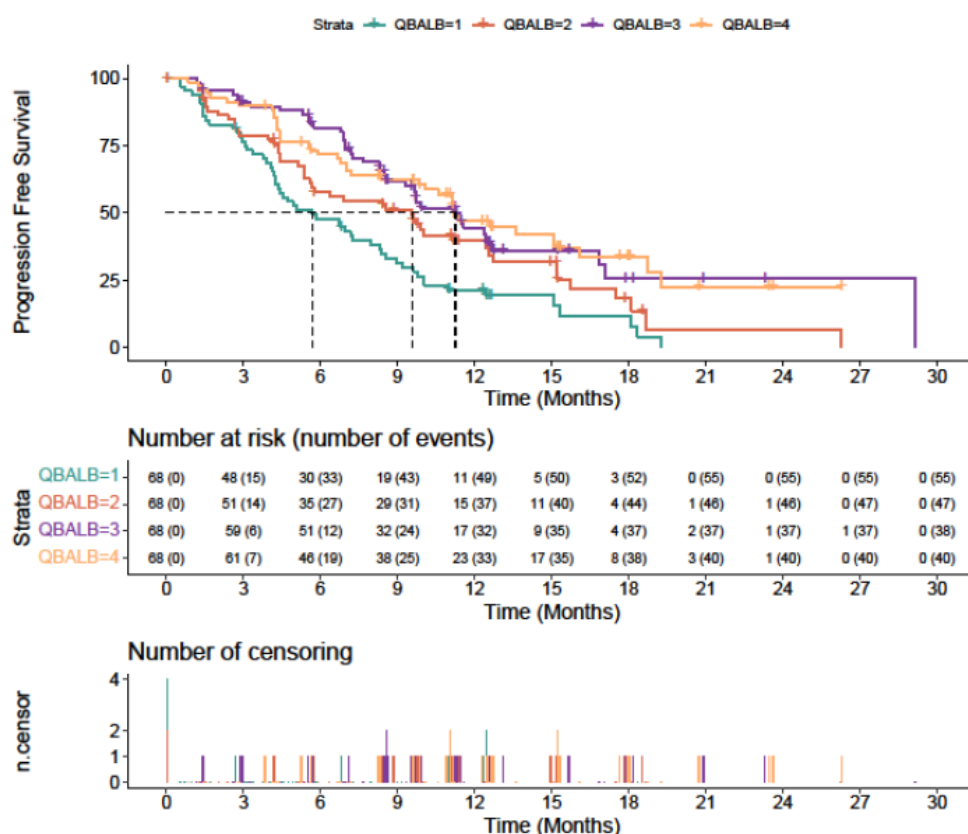
**Table 17 GS-US-592-6238: PFS Median Survival Times in Quartiles of  $C_{min,SS,SG}$**

| $C_{min,SS,SG}$ Quartile (N) | Median (Range) ng/mL | Median Survival Time (90% CI) Months |
|------------------------------|----------------------|--------------------------------------|
| 1 (68)                       | 1800 (544, 2281)     | 5.4 (4.2, 8.3)                       |
| 2 (68)                       | 2661 (2318, 3090)    | 9.7 (7.0, 11.6)                      |
| 3 (68)                       | 3405 (3099, 3932)    | 9.6 (7.0, 17.5)                      |
| 4 (68)                       | 4497 (3942, 9615)    | 12.6 (11.3, 18.1)                    |

PFS = progression-free survival

Serum albumin (ALB) was identified as a significant covariate on the hazard function affecting PFS events.

**Figure 18 GS-US-592-6238: Kaplan-Meier Curves of PFS Stratified by Quartiles of Baseline Albumin**



PFS = progression-free survival; QBALB = quartiles of baseline albumin

The vertical dashed lines indicate the median survival time (corresponding to a survival probability of 0.5) associated with each quartile.

**Table 18 GS-US-592-6238: Parameter Estimates of Final Parametric TTE Model for PFS**

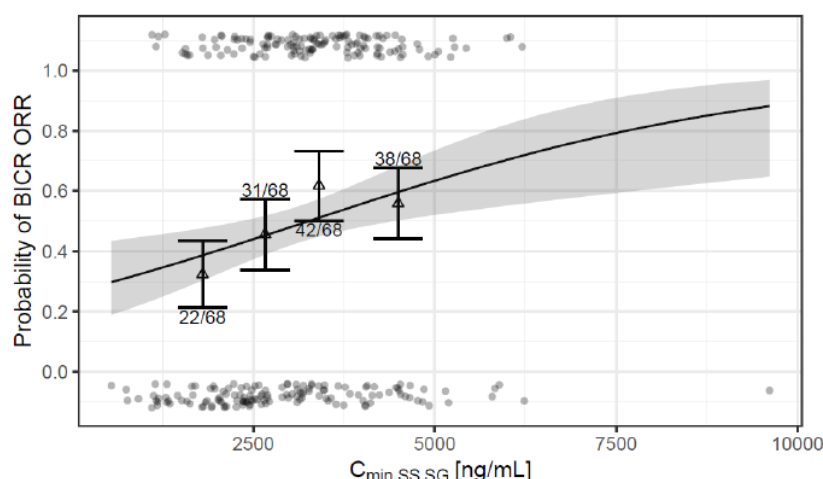
| Structural Parameters |            |                                                        | Estimate  | RSE (%) |
|-----------------------|------------|--------------------------------------------------------|-----------|---------|
| MU                    | $\theta_1$ | Hazard scaling parameter                               | -1.99016  | 11.6    |
| SIG                   | $\theta_2$ | Hazard shape parameter                                 | 1.37874   | 6.07    |
| EC50 (ng/mL)          | $\theta_3$ | SG concentration producing half-maximum effect         | 2434.43   | 27.1    |
| Emax                  | $\theta_4$ | Emax (logit)                                           | 0.939573  | 89.6    |
| GAM                   | $\theta_5$ | Gamma                                                  | 4.03375   | 73.7    |
| BALB on MU            | $\theta_6$ | Baseline albumin covariate effect on scaling parameter | 0.0188689 | 35.9    |

BALB = individual baseline albumin level for each participant; PFS = progression-free survival; RSE = relative standard error; TTE = time-to-event

- *Exposure-ORR*

Exposure-response analysis for ORR endpoint based on BICR was conducted using a parametric logistic regression model and were evaluated across four quartiles of steady-state  $C_{min}$  of SG and BICR Objective Response.

**Figure 19 GS-US-592-6238: Logistic Regression of  $C_{min,SS,SG}$  and BICR Objective Response**



BICR = blinded independent central review; ORR = objective response rate  
Solid line is the median prediction and the shaded region is the 95% CI. Triangles and error bars represent the observed rate of objective response per exposure quartile and 95% CI, plotted at the median exposure of the quartile. Points are individual participants, with 0 representing no event and 1 representing event plotted at the individual exposure metric.

**Table 19 GS-US-592-6238: Summary of Final Covariate BICR ORR Logistic Regression Model**

| Parameter                                                    | Odds Ratio (95% CI) |
|--------------------------------------------------------------|---------------------|
| Steady-state $C_{min}$ SG for every 25% increase in exposure | 1.28 (1.12-1.48)    |

BICR = blinded independent central review; ORR = objective response rate; SG = sacituzumab govitecan

#### Exposure-response (E-R) analysis for safety

Exposure-safety relationships were evaluated in participants with various advanced epithelial cancers or advanced or metastatic breast cancers who received a starting dose of SG 8 mg/kg (16 participants from studies IMMU-132-01 and IMMU-132-05), 10 mg/kg (1044 participants from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238), or 12 mg/kg (3 participants from study IMMU-132-01) on Days 1 and 8 of a 21-day cycle.

The exposure-safety analysis dataset included a total of 1063 participants (98.2% in the SG 10-mg/kg starting dose group) from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238 who had PopPK parameter estimates to enable estimation of exposure metrics related to SG dosing and had data for the respective safety endpoints.

Rare events (< 5%) of the selected AEs were not analyzed in the exposure-safety analysis. For the following safety endpoints, a parametric logistic regression model was used to assess the relationship between SG exposure and safety outcome, as well as explore known prognostic factors (covariates): adverse event of special interest (AESI) neutropenia (any grade/Grade 3 or higher), neutropenia only (preferred term [PT] = neutropenia; any grade/Grade 3 or higher), febrile neutropenia (any grade/Grade 3 or higher), infections (any grade/Grade 3 or higher), vomiting (any grade), diarrhoea (any grade/Grade 3 or higher), AESI hypersensitivity (any grade), and nausea (any grade).

In addition, a semiparametric Cox proportional hazards model was used to assess the relationship for time to AEs leading to dose reductions and time to AEs leading to dose delays versus SG exposure, as well as explore prognostic factors (covariates).

**Table 20 Summary of Safety and Tolerability Endpoints**

| Safety/Tolerability Endpoints | Preferred Term/Definition                                                                      | Description                                                                                                                                                                                 |
|-------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vomiting                      | Vomiting                                                                                       | Categorical variables describing the incidence of any grade, Grade 3 or higher, and Grade 4 safety variable for each participant within the treatment period                                |
| Diarrhea                      | Diarrhoea                                                                                      |                                                                                                                                                                                             |
| AESI Hypersensitivity         | Hypersensitivity SMQ (narrow) and anaphylactic reaction SMQ (broad and narrow)                 |                                                                                                                                                                                             |
| Nausea                        | Nausea                                                                                         |                                                                                                                                                                                             |
| AESI Neutropenia              | Neutropenia, neutrophil count decreased, and febrile neutropenia                               |                                                                                                                                                                                             |
| Infections                    | SOC: Infections and infestations (Serious infections occurring after any grade neutropenia AE) |                                                                                                                                                                                             |
| Dose reductions               | NA                                                                                             | Time-to-event variable; defined as the time to first dose reduction event (in participants with reported AEs leading to dose reductions) during the treatment period or right censored      |
| Dose delays                   | NA                                                                                             | Time-to-event variable; defined as the time to first dose interruption event (in participants with reported AEs leading to dose interruption) during the treatment period or right censored |

AE = adverse event; AESI = adverse event of special interest; NA = not applicable; SOC = system organ class; SMQ = Standardised MedDRA Query  
Definitions for AESIs are provided in the m2.7.4, Table 15.

A statistically significant relationship between  $C_{max}$ ,  $D1_{SG}$  and any grade/grade 3 or higher neutropenia, febrile neutropenia and diarrhoea has been observed. A statistically significant relationship between  $C_{max}$ ,  $D1_{SG}$  and any grade nausea has been observed.

No statistically significant relationship was observed between SG exposure and any grade or Grade 3 or higher infections and infestations, vomiting. No statistically significant relationship was observed between SG exposure and any grade hypersensitivity. A statistically significant relationship between  $C_{max}$ ,  $D1_{SG}$  and the time to AEs leading to dose reduction has been observed.

### 2.3.5. Discussion on clinical pharmacology

The clinical pharmacology package of sacituzumab govitecan so far comprised study GS-US-592-6238 and three completed clinical studies (study IMMU-132-01, study IMMU-132-05, and study IMMU-132-09) contributing to the characterization of PK and immunogenicity of SG, and one ongoing study (study IMMU-132-06) contributed data to the immunogenicity package as well.

In the pivotal study GS-US-592-6238 for the current application for extension of the indication of sacituzumab govitecan (SG, Trodelvy), the recommended dose of SG is 10 mg/kg administered intravenously (IV) once weekly on Days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity.

The pharmacokinetics of SG for the proposed dosing regimen of 10 mg/kg administered intravenously (IV) once weekly on Days 1 and 8 of continuous 21-day treatment cycles had already been characterized in previous applications (e.g. initial MAA application in TNBC).

In the pivotal study GS-US-592-6238, sparse PK sampling was collected. The PK of total antibody, SG and free SN-38 was characterized in participants with solid tumours using an integrated PopPK model. The integrated PopPK model was also used to evaluate the effect of various intrinsic and extrinsic factors on the exposure of total antibody, SG, and free SN-38. Data from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238 were used to develop the model.

### **Bioanalytical methods**

The bioanalytical methods submitted for the determination of total SN-38, free SN-38/SN-38G and total antibody (hRS7-IgG and HRS7-SN38) in human serum, were found overall acceptable for their intended purpose.

### **Pharmacokinetics**

In the pivotal study GS-US-592-6238 pre-( $C_{\text{trough}}$ ) and post-dose ( $C_{\text{max}}$ ) concentrations were collected. The mean  $C_{\text{max}}$  for total antibody, total SN-38, and free SN-38 ranged from approximately 226,000 to 342,000 ng/mL, 4470 to 4930 ng/mL, and 85.6 to 129 ng/mL, respectively and were similar compared to the concentrations reported in previous studies.

The data from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238 were used to develop an integrated PopPK model to characterize the PK of total antibody, free SN-38, and conjugated SN-38 in participants with solid tumours.

The absorption, distribution, metabolism, and excretion of SG, total antibody and free SN-38, total SN-38, SN-38G, was well-characterised and described in the initial TNBC application and have been updated based on the results of the integrated PopPK model.

### **Integrated popPK model**

A population PK analysis was conducted based on data from studies GS-US-592-6238, IMMU-132-01, IMMU-132-05, IMMU-132-09, to characterize the disposition of Sacituzumab Govitecan. PK of total antibody, and conjugated and free SN-38, were described by a two-compartment model for each of the species, with linear clearance for free SN-38 and linear and nonlinear clearance for total antibody and conjugated SN-38. Of note, all studies showed a very pronounced percentage of BLQ samples for free SN-38. Data handling resulted in 8415 samples that were included in the final data set for model development – 5438 quantifiable observations and 2977 BLQ samples (35%). These BLQ observations were flagged in the popPK analysis dataset and a likelihood-based approach (M3) was implemented and is agreed. The current population analysis applied an integrated model structure with the measured PK data of three analytes: TAb, free SN-38 and total SN-38 including additional data from the phase 3 study GS-US-592-6238 (ASCENT-03) in first-line patients with unresectable locally advanced or metastatic TNBC. Previous model-based description of these analytes were based on separate popPK models. Along with this change in model structure, two strong assumptions regarding the PK of SG have been considered. First, the PK of SG were now derived based on model-estimated kinetics of conjugated SN-38 and potential change in drug-to-antibody ratio (DAR) over time. In contrast, for the purpose of the previous popPK analysis, SG concentrations were calculated based on an assumed DAR of 8 and the molecular weights for free SN-38 and the loaded hRS7 antibody of 392 Da and 161 kDa, respectively. Second, conjugated SN-38 and TAb are assumed to share the same PK parameters of clearances and volume of distributions since kinetics are expected to be driven by the monoclonal antibody. Both assumptions are deemed overall plausible, however they impact the concentration of SG, that is solely based on model-based simulations, with no confirmatory data available. The MAH provided a comparison of former and current predictions of SG PK and the cSG-time-course. The provided justifications for changes in  $t_{1/2}$  and AUC as well as for the implementation of DAR (which was shown to be the main driver in the mention exposure metrics) are deemed reasonable.

### **PopPK model parameters and model performance**

The integrated model is characterized by several covariates on PK parameters for each of the analytes that were observed to be correlated which is expected also due to the integrated new structure.

One pivotal parameter  $K_{dec}$  could be estimated acceptably well, however, covariate selection and inter-individual variability (IIV) parameters (10 parameters in total), that show moderate to high shrinkage (up to 78.3% for  $K_m$ ) with partially fixed variance parameters indicate some model deficiencies. Allometric scaling factors were estimated on CL, Q and  $V_c, V_p$  to 0.428 and 0.523 are below the expected ones for a monoclonal antibody. This may be attributed to interference with the other covariates that were identified statistically relevant and on the assumed lumping of tab and cSN38 PK behaviour.

Body weight is the most influential covariate on the PK of the total antibody, Free SN-38, and SG AUC and  $C_{max1}$ , almost exceeding the reference range at both the lower (49 kg) and higher (104 kg) body weight range. This became relevant for conducted exposure-response-analyses, also showing the trends of gain of benefit but also increase in safety endpoint with exposure. In addition, UGT1A1 genotype is indicated to have a potentially clinically relevant effect on Free SN-38 exposure (AUC and  $C_{max1}$ ), which is discussed in the exposure-response analyses section.

Prediction-corrected VPC of free SN-38 indicated a slight underprediction of p95 later than 150 hrs after dose and slight overprediction in the period before. Pronounced BLQ percentage after 150 hrs after dose (data and simulations) are observed. The pcVPCs of tab and total SN-38 are deemed acceptable. A slight underprediction of the median tab up to 10000 hrs after first dose could be identified. VPCs of total antibody at 10 mg/kg stratified by study indicate no consistent trends, however, prediction-corrected VPC of total antibody vs time after dose indicated underprediction of median and p5. VPC of total (free and conjugated) SN-38 at 10 mg/kg by study indicate well performance for the previously included studies, whereas for the clinical study relevant for this indication, the model has issues in describing the first 100 hrs after dose. The same trend is indicated for free SN-38 at 10 mg/kg, that might also interfere with the slight under-prediction of free SN-38 BLQ percentage in this study.

The model-derived exposure (mean  $C_{max}$  and mean AUC of SG and free SN-38) during cycle 1 was higher in the integrated popPK model compared to the serum pharmacokinetics of sacituzumab govitecan and SN-38 evaluated in the ASCENT study (population of mTNBC patients who received sacituzumab govitecan as a single agent at a dose of 10 mg/kg body weight) and previously reported in the SmPC. Especially AUC is more than twice as high for SG. In addition, the predicted half-life for SG was higher than previously reported. The reasons for these differences, the quite high predicted  $AUC_{(0-168h)}$  and  $t_{1/2}$  for SG, needed to be further clarified by the MAH. In this context, a comparison between the previous pop-PK model and the current pop-PK model for all three analytes and a summary table with the descriptive PK parameters: mean  $C_{max}$ , mean  $C_{trough}$ , and mean  $AUC_{(0-168h)}$  for the four different studies, which are included in the integrated pop-PK model (studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238), and for the three analytes (total antibody, total SN-38, and free SN-38) were provided by the MAH and in general showed reasonable similarity.

Section 5.2 of the SmPC has been updated based on the results of the integrated PopPK-model.

### **Immunogenicity**

**In study GS-US-592-6238**, the immunogenicity samples for ADA incidence assessments were evaluable for 247 participants. 3 of these participants (1.2%) had treatment-emergent ADAs to SG. All 3 participants with treatment-emergent ADAs were classified as having persistent ADA responses and were also NAb positive. The incidence of ADA to SG was low in study GS-US-592-6238 and was similar to the immunogenicity results previously reported for SG.

**Across studies**, immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 1157 and 1058 participants, respectively, across studies IMMU-132-01, IMMU-132-05, IMMU-132-06 (Cohorts 1 and 2), IMMU-132-09, and GS-US-592-6238.

The currently presented data indicates a low prevalence and incidence of ADA across the studied patient populations. The incidence of treatment-emergent ADA to SG was low (N=13 [1.2%]). Neutralizing antibodies were rare (N=10 [0.9%]). The maximum reportable ADA titer observed across the studies ranged from 10 to 90.

However, a potential trend has been observed, that the ADA status might have an impact on the exposure of free SN-38, SG and total antibody. Due to the low occurrence of ADAs, the **impact of positive ADAs on the PK** is therefore currently uncertain.

Based on the individual study efficacy results presented, no clear impact of ADA on efficacy was identified, whereas analyses of progression-free survival, overall survival, and objective response rate presented by study and ADA status showed a numerically higher efficacy in the ADA– group when compared with the ADA+ group across studies. However, the prevalence of participants who were ADA+ ( $\leq 5$  participants who were ADA+ in each study) is low and the results should therefore be interpreted with caution. Nevertheless, a trend has been observed and thus a potential impact on the efficacy can not currently be excluded.

Moreover, no clear **impact of ADAs on safety** have been identified at present. The occurrence of any TEAE appears similar between participants with or without ADAs to SG across individual studies and pooled populations. However, in the pooled all treated SG population, the incidence ( $\geq 10\%$  difference) of the following treatment-emergent AEs: TEAE with Grade 3 or higher, serious TEAE, and all deaths, were higher in participants who were tested positive for ADAs compared to participants tested negative for ADAs. Such differences in the occurrence of treatment-emergent AEs between ADA positive and ADA negative participants was especially observed in study GS-US-592-6238 SG (10 mg/kg). Nevertheless, it needs to be considered that the number of participants who were tested positive for ADAs was very low in study GS-US-592-62 (N=3) and in the pooled all treated SG population (N=13). Therefore, the results should be interpreted with caution.

**Overall**, the currently limited data of ADA-positive patients available limits the ability to conclusively determine whether positive ADAs have an impact on pharmacokinetics, efficacy, and safety. Therefore, no final conclusion can be drawn at present and the impact of positive ADAs on the PK, efficacy and safety of SG is currently unknown and needs to be further evaluated during the ongoing clinical studies and the clinical development of SG.

### **Exposure-response analyses**

Exposure-response analyses were conducted to evaluate the relationships between SG-related exposure and its efficacy endpoints (as described by PFS and ORR) and safety endpoints (as described by AESI Neutropenia, Neutropenia Only, Febrile Neutropenia, Infections and Infestations, Vomiting, Diarrhea, Hypersensitivity, Nausea, AEs leading to dose reductions, AEs leading to dose interruptions). Exposures of tAb, SG and free SN-38 increased with increasing body weight under body weight-based dosing. The effect of body weight was statistically significant. Individual empirical Bayes estimates (EBE) of PK parameters from this popPK model were used to calculate the exposure metrics of tAb, SG and free SN-38, which were tested in the presented E-R analyses.

### **Exposure-Efficacy-Relationship**

Exposure-response (E-R) for efficacy analyses were conducted using data from a total of 272 participants with metastatic TNBC from study GS-US-592-6238.

The evaluated efficacy endpoints included PFS and ORR and the exposure-response relationships were analyzed using binomial logistic regression models for ORR and parametric time-to-event (TTE) models for PFS. Investigated PK metrics are indicated to be highly correlated.

**Kaplan-Meier plot for PFS** stratified by popPK predicted  $C_{min,SS,SG}$  quartiles revealed statistically significant relationships between  $C_{min,SS,SG}$  and PFS. The median survival times across quartiles of  $C_{min,SS,SG}$  showed that  $C_{min,SS,SG}$  levels in Q1 are associated with a higher risk of PFS events and that higher exposure (higher exposure quartiles) is associated with longer median survival times.

In addition to  $C_{min,SS,SG}$ , baseline albumin was identified as a statistically significant predictor of PFS. The Kaplan-Meier plot for PFS stratified by popPK predicted baseline albumin quartiles showed that baseline albumin levels in Q1 are associated with a higher risk of disease progression or death (lower risks of PFS events) whereas baseline albumin levels greater than Q1 are associated with lower risk of disease progression or death (lower risks of PFS events). However, there was no clear trend within quartiles 3 and 4 of baseline albumin patients. It was noted that although the final PFS TTE model only picked albumin as the significant predictor, other factors, especially those unbalanced and disease related ones between Q1 and Q2-4 may still have had some effect and contributed to the PFS difference. In addition, exposure-efficacy analyses are limited since exposure is only based on one dose level.

Using a **logistic regression model**, statistically significant relationships were identified between  $C_{min,SS,SG}$  and independent **ORR** and PK exposure metrics within the range of SG dose of 10 mg/kg. For every 25% increase in  $C_{min,SS,SG}$ , the odds are 1.29-fold higher.

Overall, the exposure-response analyses for efficacy demonstrated that a PFS and ORR benefit of SG appears to be dependent on exposure, with increasing benefit with increase in exposure. There were imbalances in patient characteristics across the quartiles of exposure. As also suggested by popPK, Q1 patients had lower body weight, and also higher baseline tumour size, higher lactate dehydrogenase (LDH) and more patients with mild hepatic impairment.

#### Exposure-Safety-Relationship

Exposure-response (E-R) for safety analyses were conducted using data from a total of 1063 participants with solid tumours who received SG in studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238. Individual SG, free SN-38 and total antibody exposure metrics for the participants in the analysis population were derived based on a population PK model for these studies.

Using a logistic regression model, statistically significant E-R relationships between  $C_{max,D1,SG}$  and AESI Neutropenia, Neutropenia Only, Febrile Neutropenia and Diarrhoea were identified.

In addition, statistically significant E-R relationships were identified between  $C_{min,C1,SG}$  and Any Grade Nausea.

Kaplan-Meier estimates of  $C_{max,D1,SG}$  quartiles and Time to AEs Leading to Dose Reductions showed a E-R-relationships between  $C_{max,D1,SG}$  and Time to AEs leading to dose reductions. The probability of AEs leading to dose reduction increased with higher quartiles (increasing exposure).

In general, a higher risk (odds ratio >1) of associated neutropenia related AEs and non-neutropenia related AEs as diarrhoea and Time to AEs leading to dose reductions was identified for every 25% increase in  $C_{max,D1,SG}$ .

Overall, the exposure-response analyses with regards to safety indicated also a dependency on exposure with higher probability of event or Odds Ratio with increase in exposure ( $C_{max,SG}$ ).

Moreover, a higher risk (odds ratio >1) of associated Grade 3 or higher AESI Neutropenia, Grade 3 or higher Neutropenia Only and Any Grade Febrile Neutropenia as well as time to AEs leading to dose reductions was identified for the UGT1A1 genotype \*1/\*28 and \*28/\*28 in comparison to \*1/\*1 genotype evaluated. This is also indicated in the popPK model (forest plots).

However, special warnings and precautions for use in patients with reduced UGT1A1 activity and information regarding interaction with UGT1A1 inhibitors and UGT1A1 inducers are already included in section 4.4, 4.5 and 4.8 of the SmPC.

Special warnings and precautions for use regarding the ADRs neutropenia and diarrhoea are also included in sections 4.2 and 4.4. of the SmPC.

2.3.6. Conclusions on clinical pharmacology

In general, pharmacokinetics and pharmacodynamics of sacituzumab govitecan have been sufficiently characterized. Results from the pivotal study GS-US-592-6238, supporting this application for extension of indication, appear overall consistent with the analyses provided in previous applications.

2.4. Clinical efficacy

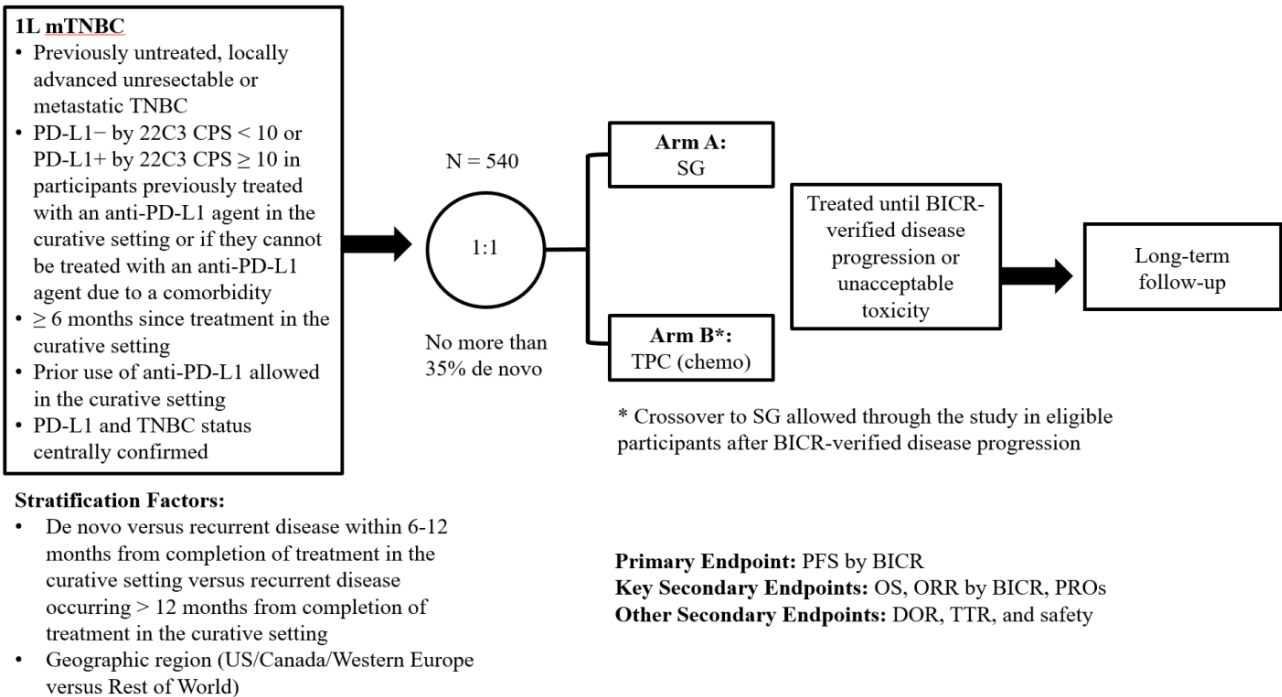
2.4.1. Dose response study

The dosing regimen of SG in study ASCENT-03 (10 mg/kg IV D1 and D8, Q3W) is the same as already approved for the treatment of patients with unresectable or metastatic TNBC and HR+, HER2- breast cancer after at least two prior systemic therapies. The SG dose of 10 mg/kg was selected based on results from study IMMU-132-01, a phase 1/2 dose escalation and expansion phase study in metastatic epithelial cancers.

2.4.2. Main study

**ASCENT-03 (GS-US-592-6238): A randomized, open-label, phase 3 study of sacituzumab govitecan versus treatment of physician’s choice in patients with previously untreated, locally advanced, inoperable or metastatic triple-negative breast cancer whose tumours do not express PD-L1 or in patients previously treated with anti-PD-(L)1 agents in the early setting whose tumours do express PD-L1**

Figure 20 ASCENT-03 Study Schema



1L = first-line treatment; BICR = blinded independent central review; chemo = chemotherapy; CPS = combined positive score; DOR = duration of response; mTNBC = metastatic triple-negative breast cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PRO = patient-reported outcome; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; TTR = time to response; US = United States

## Methods

Participants who were randomized to the control group (TPC chemotherapy) were eligible to receive SG through the study in the **crossover** phase upon disease progression verified by BICR and upon meeting eligibility criteria.

Tumour assessments were obtained by computed tomography (CT) or magnetic resonance imaging (MRI) scans every 6 weeks for the first year, then every 12 weeks thereafter.

All participants were followed for survival until death, loss to follow-up, or withdrawal of consent, whichever occurred first.

## Study participants

### Main inclusion criteria:

- 1) 18 years of age or older, able to understand and give written informed consent.
- 2) Patients with locally advanced, inoperable, or metastatic TNBC who have not received previous systemic therapy for advanced disease and whose tumors are PD-L1 negative at screening. Alternatively, patients whose tumours are PD-L1 positive at screening will be eligible if they received an anti-programmed death (ligand) 1 (anti-PD-[L]1) agent (i.e. checkpoint inhibitor) in the adjuvant or neoadjuvant setting or if they cannot be treated with an anti-PD-(L)1 agent due to a comorbidity.
  - a) Patients must have completed treatment for stage I-III breast cancer, if indicated, and  $\geq 6$  months must have elapsed between completion of treatment with curative intent (e.g. date of primary breast cancer surgery or date of last (neo)adjuvant chemotherapy administration [including anti-PD-(L)1 treatment], whichever occurred last) and first documented local or distant disease recurrence. Dates of postoperative radiotherapy are not included in this calculation.
    - i) Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane or gemcitabine/carboplatin) if  $\geq 12$  months have elapsed between the completion of treatment with curative intent (e.g. date of primary breast tumour surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence. (*Note: included with protocol amendment 1*)
    - ii) Patients enrolled should have received prior anthracycline in the (neo)adjuvant setting or be considered not eligible for anthracyclines as assessed by the treating physician. (*Note: included with protocol amendment 1*).
  - b) Patients presenting with de novo metastatic TNBC are eligible for this study. Note: They were capped at approximately 35% of all enrolled participants.
  - c) TNBC status and tumour PD-L1 CPS will be confirmed centrally on a recent or archival tumor specimen.  
Patients must have histologically or cytologically documented TNBC, according to current ASCO/CAP criteria, defined as negative for ER, progesterone receptor, and HER2 (Allison et al.

2020, Wolff et al. 2018). Patients initially diagnosed with hormone receptor-positive or HER2-positive breast cancer must have central confirmation of TNBC in a tumour biopsy obtained from a local recurrence or distant metastasis prior to entry. Tumour combined positive score (CPS) < 10 using the PD-L1 IHC 22C3 assay will be required for eligibility. Alternatively, patients with tumour CPS  $\geq 10$  will be eligible if they received an anti-PD-(L)1 agent (i.e. checkpoint inhibitor) in the adjuvant or neoadjuvant setting or if they cannot be treated with an anti-PD-(L)1 agent due to a comorbidity.

- d) Patients must have measurable disease by CT or MRI as per RECIST Version 1.1 criteria as evaluated locally. Tumour lesions situated in a previously irradiated area are considered measurable if unequivocal progression has been documented in such lesions since radiation.
- 3) Have provided representative formalin-fixed paraffin-embedded (FFPE) tumour specimen in blocks (preferred) or have at least 20 to 25 freshly sectioned unstained slides from fresh biopsy tissue (preferred) or archival tissue block for central testing of ER, progesterone receptor, HER2, and PD-L1 and additional biomarker testing.
- 4) ECOG performance status score of 0 or 1.
- 5) Life expectancy  $\geq 3$  months.
- 6) Recovered from major surgery for  $\geq 2$  weeks.
- 7) Adequate hematologic counts without transfusional or growth factor support within 2 weeks of study treatment initiation (hemoglobin  $\geq 9$  g/dL, ANC  $\geq 1500/\text{mm}^3$ , and platelets  $\geq 100,000/\mu\text{L}$ ).
- 8) Adequate hepatic function (bilirubin  $\leq 1.5 \times \text{ULN}$ , AST and ALT  $\leq 2.5 \times \text{ULN}$  or  $\leq 5 \times \text{ULN}$  if known liver metastases, and serum albumin  $> 3$  g/dL).
- 9) Creatinine clearance  $\geq 30$  mL/min as assessed by the Cockcroft-Gault equation.
- 10) International Normalized Ratio (INR)/PT and PTT or aPTT  $\leq 1.5 \text{ ULN}$  unless patient is currently receiving therapeutic anticoagulant therapy.
- 11) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.
- 12) Patients with HIV must be on antiretroviral therapy (ART) and have a well-controlled HIV infection/disease.

Main exclusion criteria:

- Patients may not have received systemic anticancer treatment (with the exception of endocrine therapy) within the previous 6 months or radiation therapy within 2 weeks prior to enrolment. Patients must have recovered (i.e. > Grade 2 is considered not recovered) from AEs due to a previously administered agent at the time of study entry.
- Have previously received topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor.
- Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate (with the exception of those treated with chemotherapy) provided they have stable CNS disease (defined as radiographic stability demonstrated with a minimum of 2 posttreatment brain imaging assessments; one performed during screening) for at least 4 weeks prior to enrolment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases, and have also

been clinically stable for at least 2 weeks while taking  $\leq 10$  mg/day of prednisone or its equivalent. All patients with carcinomatous meningitis are excluded regardless of clinical stability.

- Met any of the following criteria for cardiac disease:
  - a) Myocardial infarction or unstable angina pectoris within 6 months of enrolment.
  - b) History of serious ventricular arrhythmia, high-grade atrioventricular block, or other cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.
  - c) New York Heart Association Class III or greater congestive heart failure or known left ventricular ejection fraction of  $< 40\%$ .
- Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or GI perforation within 6 months of enrollment.
- Have active serious infection requiring antibiotics.
- Have active HBV or HCV
- Has received a live vaccine within 30 days prior to randomization.

## Treatments

**Sacituzumab govitecan** (SG): 10 mg/kg intravenously (IV) on Days 1 and 8 of 21-day cycles.

The treatment of physician's choice chemotherapy (**TPC**) was selected prior to randomization from 1 of the 3 allowed regimens:

- Paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8, and 15 of 28-day cycles; or
- nab-Paclitaxel 100 mg/m<sup>2</sup> IV on Days 1, 8, and 15 of 28-day cycles; or
- Gemcitabine 1000 mg/m<sup>2</sup> IV plus carboplatin AUC 2 IV on Days 1 and 8 of 21-day cycles.

### Duration of treatment

Participants received study drug until blinded independent central review (BICR)-verified disease progression, unacceptable toxicity, withdrawal of consent, initiation of other anticancer therapy (including any investigational agent), or death.

Treatment beyond BICR-verified disease progression per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) was permitted if there was evidence of clinical benefit per the investigator and the patient was tolerating the study drug, if agreed upon by the investigator and the sponsor medical monitor.

## Objectives and endpoints

**Table 21 Objectives and endpoints**

| Primary Objective                                                                                            | Primary Endpoint                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• To compare PFS as assessed by BICR between SG versus TPC</li> </ul> | <ul style="list-style-type: none"> <li>• PFS is defined as the time from the date of randomization until the date of objective progressive disease (PD), as assessed by BICR per RECIST v1.1, or death (whichever comes first).</li> </ul> |
| Secondary Objectives                                                                                         | Secondary Endpoints                                                                                                                                                                                                                        |

| <ul style="list-style-type: none"> <li>To compare OS between the 2 groups</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>OS is defined as the time from the date of randomization until death due to any cause.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>To compare ORR as assessed by BICR between the 2 groups</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>ORR is defined as the proportion of participants who achieve a complete response (CR) or partial response (PR) that is confirmed at least 4 weeks after initial documentation of response as assessed by BICR per RECIST v1.1.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>To compare DOR as assessed by BICR between the 2 groups</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>DOR is defined as the time from the first documentation of CR or PR to the earlier of the first documentation of definitive PD or death from any cause (whichever comes first) as assessed by BICR per RECIST v1.1.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>To compare TTR as assessed by BICR between the 2 groups</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>TTR is defined as the time from the date of randomization until the first documentation of CR or PR as assessed by BICR per RECIST v1.1.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>To compare safety and tolerability between the 2 groups</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>Incidence of treatment-emergent AEs and clinical laboratory abnormalities.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>To compare mean change from baseline in the physical functioning domain and TTD in fatigue as measured by the EORTC QLQ-C30 between the 2 groups</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Mean change from baseline in the physical functioning domain of the EORTC QLQ-C30 at Week 25.</li> <li>TTD of fatigue domain of the EORTC QLQ-C30 is defined as the time between the date of randomization and the date of assessment at which a participant experienced a deterioration (i.e. <math>\geq 10</math> points worsening from baseline in the fatigue domain) or death.</li> </ul>                                                                                                                                                                                                                                                                        |
| Exploratory Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Exploratory Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>To assess tumor expression of Trop-2 as a potential biomarker of response to SG</li> <li>To explore blood and tumor biomarkers that may be associated with response to SG</li> <li>To explore the relationship of AEs to uridine diphosphate glucuronosyltransferase A1A (<i>UGT1A1</i>) status</li> <li>To characterize the pharmacokinetics and immunogenicity of SG</li> <li>To compare additional QOL outcomes as measured by EQ-5D-5L, the European Organisation for Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire (EORTC QLQ-BR23), EORTC QLQ-C30, Patient Global Impression of Change/Patient Global Impression of Severity (PGIC/PGIS), and Functional Assessment of Cancer Therapy-General item GP5 (FACT-GP5) between the 2 arms</li> </ul> | <ul style="list-style-type: none"> <li>Correlation of clinical outcome (PFS, OS, ORR, and DOR) with baseline tumor Trop-2 expression</li> <li>Correlation of clinical outcome (PFS, OS, ORR, and DOR) with tumor, tumor microenvironment, and blood biomarkers at baseline and post-SG treatment</li> <li>Clearance of circulating tumor DNA upon SG treatment</li> <li>Correlation of AEs to <i>UGT1A1</i> status</li> <li>Correlation of pharmacokinetics and immunogenicity of SG</li> <li>Additional QOL endpoints include mean change from baseline, TTD (in addition to the subscales specified as secondary endpoints), time to improvement, proportion improved, and proportion worsened.</li> </ul> |

No estimands were defined.

## Sample size

Approximately 540 patients were planned to be randomised in a 1:1 ratio to receive either SG or TPC over a planned non-uniform accrual period of 20 months.

The primary analysis of PFS was planned to be conducted when approximately 352 PFS events as assessed by BICR have occurred. With 352 events, the study provided more than 95% power to demonstrate superiority in PFS of SG relative to TPC at a 1-sided alpha of 2.5%, assuming proportional hazards with a true HR of 0.65, median PFS time for the TPC arm of 5.6 months, and a 30% annual dropout rate. The target number of events was expected to occur approximately 27.6 months after the first patient was randomised.

For the final analysis of the secondary endpoint OS, 391 events were needed to detect an average HR of 0.75 with 80% power at a 1-sided significance level of 2.5% using a log-rank test, given 2 efficacy interim analyses at 70% and 85% information fraction, respectively. Assuming a median OS time for the TPC arm of 17.5 months, with a total sample size of 540 patients, and a 5% annual dropout rate, it was estimated that the final OS analysis would occur at approximately 56 months after the first patient was randomised.

## **Randomisation**

Randomisation occurred centrally using an interactive voice response system/integrated web response system (IWRS). Patients were randomised in a 1:1 ratio to SG or physician's choice of chemotherapy starting on Day 1.

Randomisation was stratified by:

- De novo versus recurrent disease within 6 to 12 months from completion of treatment in the curative setting versus recurrent disease occurring > 12 months from completion of treatment in the curative setting.
- Geographic region (US/Canada/Western Europe versus rest of the world).

Curative treatment interval was defined as systemic (neo)adjuvant breast cancer therapy or surgery (whichever occurred last) and first local or distant recurrence. Adjuvant radiotherapy was not included in the 6-month interval.

## **Blinding (masking)**

This was an open-label study. The investigators and patients were not blinded to treatment assignment. For the sponsor study management team, until the in-house study unblinding, the access to the treatment assignment was limited and controlled, depending on the functional or study roles. The details of the controlled access setup were described in a data access restriction plan (DAP).

According to the DAP, restricted members of the Gilead Study Management Team (Clinical Development and Study Biostatistician) were not permitted to aggregate efficacy data by assigned treatment group until study unblinding at the time of data finalization for the PFS primary analysis. Additionally, no aggregated analysis with treatment-related information for primary or key secondary efficacy endpoints or efficacy surrogate endpoints by assigned treatment group was allowed until data finalization for the PFS primary analysis, except for safety monitoring purposes (e.g. for the Data Monitoring Committee [DMC] or Patient Safety to monitor safety signals).

Tumour response was measured by an independent centralised and blinded group of radiology experts who assessed tumour response using RECIST version 1.1 criteria.

## Statistical methods

### Analysis Population

ITT analysis set: The ITT analysis set included all randomised patients according to the treatment arm to which the patient was randomised to. The ITT Analysis set was the primary analysis set for efficacy analyses, demographic characteristics, baseline assessments, and quality of life assessments.

Safety analysis set: The safety analysis set included all patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received. This analysis set was the primary analysis set for all safety analyses.

PK analysis set: The PK analysis set included all randomised patients who received at least 1 dose of SG per the protocol and had at least 1 measurable post treatment serum concentration of SG.

Immunogenicity analysis set: The Immunogenicity analysis set included all randomised patients who received at least 1 dose of SG and had at least 1 evaluable non missing anti-SG antibody test result.

### Efficacy Analysis

#### PFS assessed by BICR

PFS was defined as the time from the date of randomisation until the date of first documentation of objective progressive disease, as assessed by BICR per RECIST Version 1.1, or death from any cause (whichever comes first). The primary analysis of PFS comparing SG versus TPC was performed using the log-rank test stratified by randomisation factors in the ITT analysis set. The hazard ratio with the corresponding 2-sided 95% CIs estimated using a Cox proportional hazard regression model stratified by randomisation stratification factors were planned. PFS was planned to be summarised by treatment arm using Kaplan-Meier estimates, including median and the proportion of event-free patients at benchmark time points such as 3, 6, 12 and 18 months. Kaplan-Meier plots were planned to be provided.

The following sensitivity analyses were planned:

- PFS assessed by investigator
- PFS using different censoring rules.

Censoring rules for the primary and sensitivity analyses are provided in the below table.

**Table 22 Censoring rules for the primary and sensitivity analyses**

| Case                                                                                                                   | Date of Event/Censoring                                                                      |                                                        |                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                        | Primary Analysis (PA)                                                                        | Sensitivity analysis 1 (SA1)                           | Sensitivity analysis 2 (SA2)                                                                                                |
| <b>No baseline tumor assessments or no adequate response assessment after randomization</b>                            |                                                                                              |                                                        |                                                                                                                             |
| Did not die                                                                                                            | Censored at Randomization date                                                               | Censored at Randomization date                         | Censored at Randomization date                                                                                              |
| Died prior to second scheduled assessment without initiation of new anti-cancer therapy                                | Event at Death date                                                                          | Event at Death date                                    | Event at Death date                                                                                                         |
| Died after 2 consecutive missing assessments without initiation of new anti-cancer therapy                             | Censored at Randomization date                                                               | Event at Death Date                                    | Censored at Randomization date                                                                                              |
| Died after initiation of new anti-cancer therapy                                                                       | Censored at Randomization date                                                               | Event at Death Date                                    | Event at date of discontinuation of treatment, if any, or start date of new anti-cancer treatment whichever occurs earlier  |
| <b>Continued scheduled response assessments until objective PD or death</b>                                            |                                                                                              |                                                        |                                                                                                                             |
| PD or death before $\geq 2$ consecutive missing assessments and before initiation of new anti-cancer treatment, if any | Event at Death date or PD date, whichever occurs first                                       | Event at Death date or PD date, whichever occurs first | Event at Death date or PD date, whichever occurs first                                                                      |
| PD or death immediately after $\geq 2$ consecutive missing assessments                                                 | Censored at Date of last adequate tumor assessment before missed assessments                 | Event at Death date or PD date, whichever occurs first | Censored at Date of last adequate tumor assessment before missed assessments                                                |
| Initiated new anti-cancer treatment prior to PD or death                                                               | Censored at Date of last adequate tumor assessment before starting new anti-cancer treatment | Event at Death date or PD date, whichever occurs first | Event at Date of discontinuation of treatment, if any, or start date of new anti-cancer treatment whichever occurs earlier. |
| <b>Continued scheduled response assessments without objective PD or death</b>                                          |                                                                                              |                                                        |                                                                                                                             |
| Treatment discontinuation or initiated new anti-cancer treatment                                                       | Censored at Date of last adequate tumor assessment before starting new anti-cancer treatment | Censored at Date of last adequate tumor assessment     | Event at Treatment discontinuation date or start date of new anti-cancer therapy, whichever occurs earlier.                 |
| Ongoing in study treatment                                                                                             | Censored at Date of last adequate tumor assessment                                           | Censored at Date of last adequate tumor assessment     | Censored at Date of last adequate tumor assessment                                                                          |

## OS

OS was defined as the time from the date of randomisation until death due to any cause. For participants who were not known to have died at the time of the analysis, OS data was censored at the last date that they were known to be alive. In the event that the participant was lost to follow-up or withdrew consent from the study, the survival status may have been obtained from publicly available resources under applicable local laws.

The analysis of OS was planned to be performed using a similar methodology as for the primary analysis of PFS.

To account for the effect of crossover on OS, methods such as the rank preserving structural failure time model, two-stage method, or inverse probability censoring weighting method were planned.

## ORR assessed by BICR

ORR was defined as the proportion of participants who achieved complete response or partial response that was confirmed at least 4 weeks after initial documentation of response as assessed by BICR per RECIST Version 1.1. Tumour response assessments after the date of participants receiving new anticancer therapy were excluded from the analysis. Participants, who did not have sufficient baseline or on-study tumour status information that was not adequate for response status assessment or received new anticancer therapy prior to achieving CR or PR, were considered as non-responders.

ORR assessed by BICR was planned to be analysed and compared between treatment arms in the ITT analysis set using the Cochran Mantel-Haenszel test stratified by the stratification factors used in the randomisation. The 2-sided 95% CIs for each treatment arm was planned to be calculated using the Clopper-Pearson exact method.

The following sensitivity analyses were planned:

- ORR assessed by investigator.

Concordance/discordance of best overall response as assessed by BICR and investigator was planned to be summarised in a frequency table.

#### Quality of Life Analysis

Mean change from baseline in physical functioning domain as measured by EORTC QLQ-C30 was planned to be analysed using linear mixed model for repeated measures (MMRM) longitudinal analysis based on the ITT analysis set.

The time to deterioration (TTD) of fatigue domain of the EORTC QLQ-C30, measured as the time between the date of randomisation and the date of assessment at which a patient experienced a deterioration (i.e.  $\geq 10$  points worsening from baseline in the fatigue domain) or death, was planned to be assessed using the Kaplan-Meier method for the ITT analysis set. The TTD distribution of the two treatment arms was planned to be compared using the log-rank test, stratified by the randomisation stratification factors. The hazard ratio with the corresponding 2-sided 95% CIs estimated using a Cox proportional hazard regression model stratified by randomisation stratification factors were planned.

#### Other secondary endpoints

DOR assessed by BICR and investigator were planned to be analysed using Kaplan-Meier methodology including estimates of median and 95% CIs.

Time to response (TTR) assessed by BICR and investigator were planned to be summarised using descriptive statistics by treatment arm for responders.

#### **Multiplicity**

The overall type I error rate for this study was controlled at a 1-sided alpha of 2.5%.

The primary endpoint analysis of PFS assessed by BICR served as the gatekeeper for the secondary endpoint analyses: OS, ORR and analysis for QoL (TTD in fatigue and change from baseline in physical functioning), which were planned to be tested sequentially when the above hypotheses in the hierarchy were statistically significant. For OS, the 1-sided alpha of 0.0005% was used to account for the descriptive noncomparative analysis at the time of PFS analysis, and 1-sided alpha of 2.495% for the comparative analysis in the formal test. If both, PFS and OS were tested significantly, 1-sided alpha of 2.5% was used to test ORR and QoL endpoints.

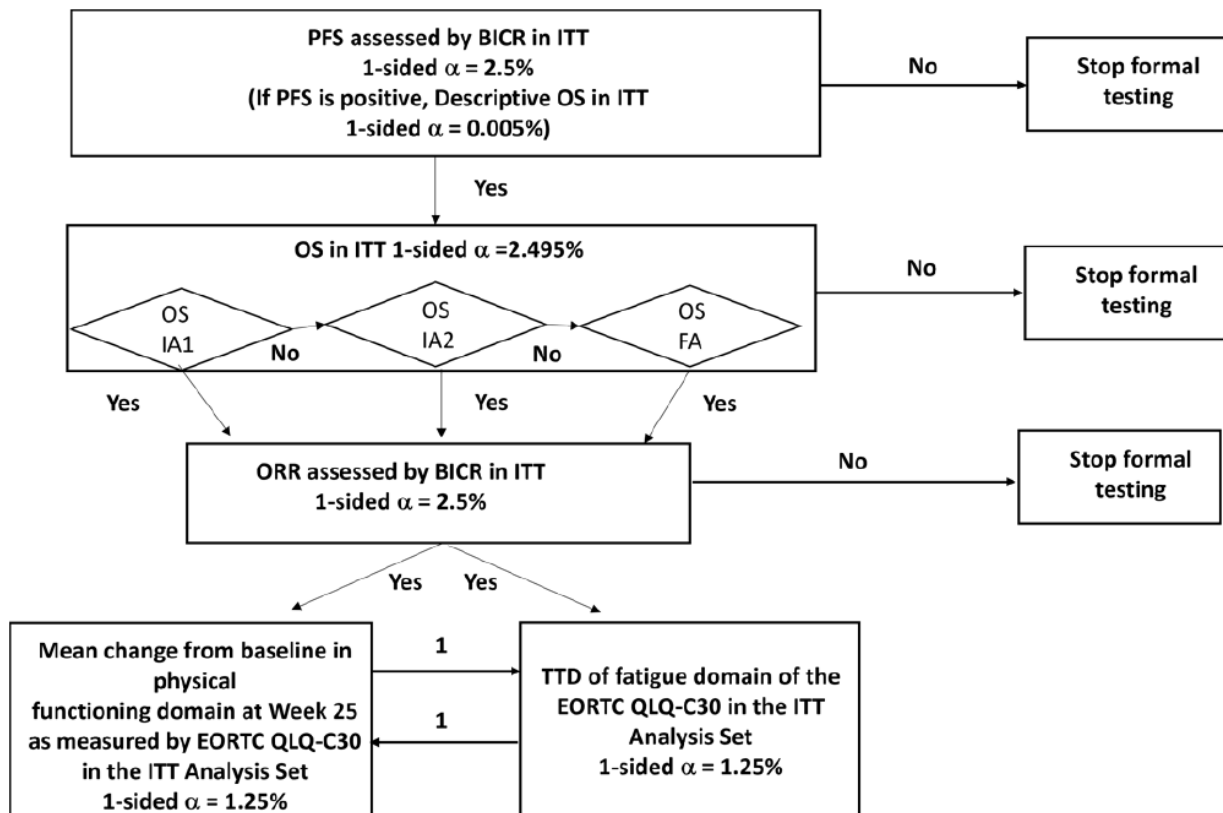
The QoL endpoints TTD in fatigue and change from baseline in physical functioning at Week 25 were planned to be tested when the above endpoints in the hierarchy were all statistically significant. The total 1-sided alpha of 2.5% was split between the 2 tests evenly, initially. If the test of TTD in fatigue was significant at a 1-sided alpha of 1.23%, then this 1-sided alpha were to be passed to the test of change from baseline in physical functioning at Week 25 resulting in a 1-sided alpha of 2.5%. Similarly, if the test of change from baseline in physical functioning at Week 25 was significant at a 1-sided alpha of 1.25%, then TTD in fatigue was tested at a 1-sided alpha of 2.5%.

The ORR and QoL were planned to be analysed and tested in the same dataset that is used for OS analysis.

The hierarchical testing procedure is described in the figure below.

**Figure 21 Hierarchical Testing Procedures**

### Hierarchical Testing Procedures



### Interim Analyses

The study planned for 3 interim analyses (IA) and 1 final analysis.

At the first analysis, which was the primary analysis for PFS, PFS was planned to be tested when approximately 352 PFS events would have occurred using a 1-sided alpha level of 2.5% after approximately 27.6 months after the first patient was randomised. At the same time, a descriptive, noncomparative analysis of OS was planned to be performed using a 1-sided alpha of 0.005% without formal hypothesis testing. It was expected to observe 218 OS events (56% information fraction of the total 391 OS events) at IA1.

At the second analysis, which was the first interim analysis for OS (IA1), OS was planned to be tested when approximately 274 (70% information fraction) deaths would have been observed at approximately 34 months after the first patient was randomised.

At the third analysis, which was the second interim analysis for OS (IA2), OS was planned to be tested when approximately 332 (85% information fraction) deaths would have been observed at approximately 43 months after the first patient was randomised.

At the final analysis, OS was planned to be tested when approximately 391 deaths would have been observed at approximately 56 months after the first patient was randomised.

The first analysis was planned to serve as the final analysis for PFS. No interim analysis of PFS was planned.

To account for the interim analyses of OS, a nominal 1-sided alpha of 0.005% was spent at the first analysis for a noncomparative and descriptive analysis of OS, while the Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach was used to adjust the remaining alpha of 2.495% for IA1, IA2 for OS and the final analysis, resulting in nominal alpha of 0.74%, 1.28% and 2.01% at IA2, IA3 and the final analysis, respectively.

Details on the expected number of events and 1-sided alpha levels at analysis are provided in the table below.

**Table 23 Expected number of events at interim and final analyses**

| Description                                                                | Expected Events<br>n (Information Fraction) | Expected Timing of Analysis<br>(Months From Randomization) | Stopping Boundary<br>(1-Sided Alpha)                              |
|----------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------|
| Primary PFS analysis (final)                                               | ~352 PFS events                             | 27.6                                                       | HR $\leq$ 0.811<br>( $P \leq$ 0.025)                              |
| OS analysis concurrent at<br>primary PFS analysis<br>(descriptive summary) | ~218 deaths (56%)                           |                                                            | No formal testing,<br>1-sided $\alpha = 0.00005$<br>will be spent |
| OS 1st interim analysis                                                    | ~274 deaths (70%)                           | 34                                                         | HR $\leq$ 0.745<br>( $P \leq$ 0.0074)                             |
| OS 2nd interim analysis                                                    | ~332 deaths (85%)                           | 43                                                         | HR $\leq$ 0.783<br>( $P \leq$ 0.0128)                             |
| OS final analysis                                                          | ~391 deaths                                 | 56                                                         | HR $\leq$ 0.813<br>( $P \leq$ 0.0201)                             |

HR = hazard ratio; OS = overall survival; PFS = progression-free survival

## Results

### Participant flow

**Figure 22 Participant Flow at the time of OS IA1 – DCO 27 Oct 25**

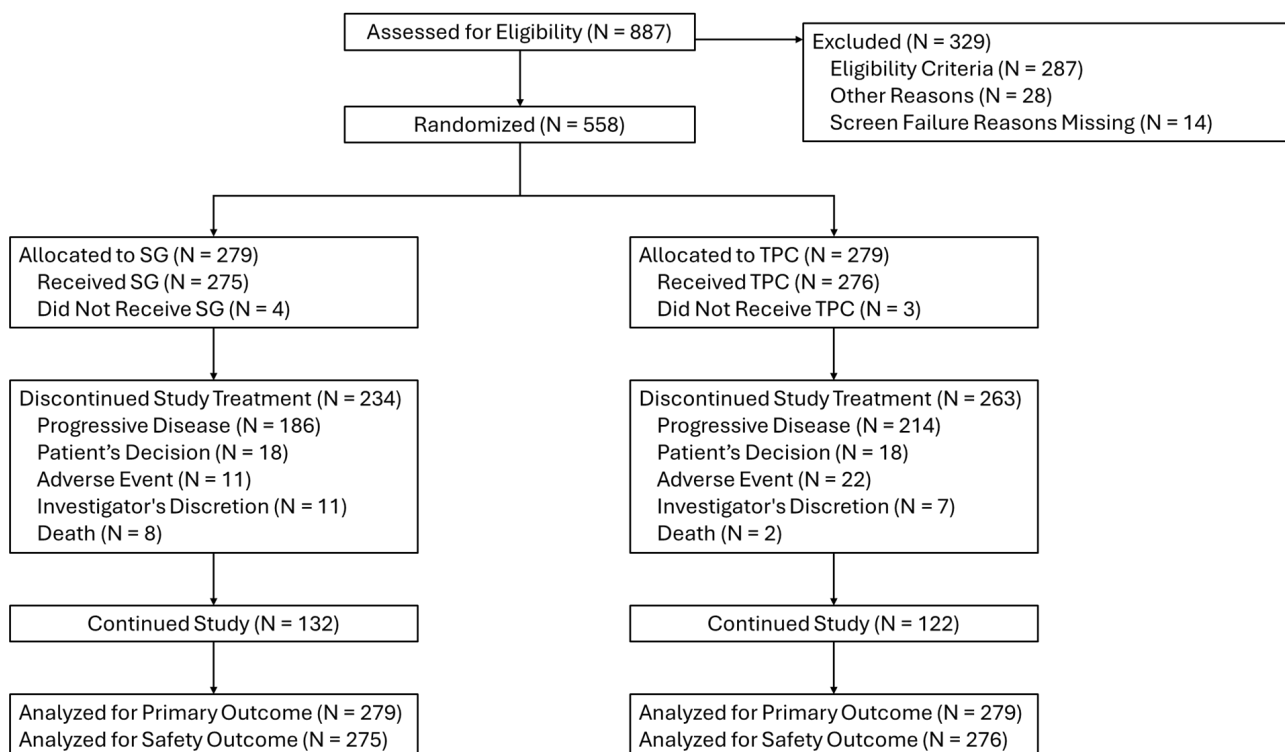


**Table 24 Disposition of Participants (All Screened Participants) at OS IA1 – DCO 27 Oct 2025**

|                                                          | SG          | TPC         | Total       |
|----------------------------------------------------------|-------------|-------------|-------------|
| Screened                                                 |             |             | 887         |
| Intent to Treat Analysis Set (ITT)                       | 279         | 279         | 558         |
| Randomized but not Treated                               | 4           | 3           | 7           |
| Safety Analysis Set                                      | 275         | 276         | 551         |
| Study Treatment Completion Status (Randomized Phase)     |             |             |             |
| Continuing Study Treatment                               | 45 (16.1%)  | 16 (5.7%)   | 61 (10.9%)  |
| Discontinued Study Treatment                             | 234 (83.9%) | 263 (94.3%) | 497 (89.1%) |
| Adverse Event                                            | 11 (3.9%)   | 22 (7.9%)   | 33 (5.9%)   |
| Pregnancy                                                | 0           | 0           | 0           |
| Investigator's Discretion                                | 11 (3.9%)   | 7 (2.5%)    | 18 (3.2%)   |
| Non-Compliance with Study Drug                           | 0           | 0           | 0           |
| Subject Decision                                         | 18 (6.5%)   | 18 (6.5%)   | 36 (6.5%)   |
| Study Terminated by Sponsor                              | 0           | 0           | 0           |
| Progressive Disease                                      | 186 (66.7%) | 214 (76.7%) | 400 (71.7%) |
| Lost to Follow-Up                                        | 0           | 0           | 0           |
| Death                                                    | 8 (2.9%)    | 2 (0.7%)    | 10 (1.8%)   |
| Received Study Treatment in Crossover Phase <sup>a</sup> |             | 125 (44.8%) |             |
| Study Completion Status                                  |             |             |             |
| Continuing Study                                         | 132 (47.3%) | 122 (43.7%) | 254 (45.5%) |
| Discontinued Study                                       | 147 (52.7%) | 157 (56.3%) | 304 (54.5%) |
| Death                                                    | 133 (47.7%) | 139 (49.8%) | 272 (48.7%) |
| Withdrew Consent                                         | 14 (5.0%)   | 18 (6.5%)   | 32 (5.7%)   |
| Lost to Follow-Up                                        | 0           | 0           | 0           |
| Study Terminated by Sponsor                              | 0           | 0           | 0           |

Denominator of percentages is the number of participants in each treatment group in the ITT Analysis Set.

Randomized Phase excludes crossover phase when participants in the TPC group started to receive SG.

a SG is provided through the study in the crossover phase to eligible participants after BICR-verified disease progression.

#### Treatment in the control arm

Among 276 participants in the TPC group who received study treatment, 55.8% (154 participants) received a taxane (paclitaxel or nab-paclitaxel) and 44.2% (122 participants) received gemcitabine with carboplatin).

#### **Subsequent treatment**

Of the 196 participants in the TPC group who received second line anticancer therapy, 154 participants (55.2%) received SG. Of these, 125 received SG through the crossover phase of the study, and the remainder received commercial SG in the second-line setting.

**Table 25 Subsequent Anti-Cancer Therapy in Second Line (ITT) (DCO 27 Oct 2025)**

|                                                                        | SG<br>(N=279) | TPC<br>(N=279) | Total<br>(N=558) |
|------------------------------------------------------------------------|---------------|----------------|------------------|
| Participants with Subsequent Anti-Cancer Therapy in Second Line, n (%) | 159 ( 57.0%)  | 196 ( 70.3%)   | 355 ( 63.6%)     |
| Taxanes                                                                | 49 ( 17.6%)   | 5 ( 1.8%)      | 54 ( 9.7%)       |
| Platinum                                                               | 51 ( 18.3%)   | 4 ( 1.4%)      | 55 ( 9.9%)       |
| Anthracyclines                                                         | 17 ( 6.1%)    | 4 ( 1.4%)      | 21 ( 3.8%)       |
| PARP inhibitors                                                        | 3 ( 1.1%)     | 2 ( 0.7%)      | 5 ( 0.9%)        |
| Anti-PD-1/PD-L1 agents                                                 | 6 ( 2.2%)     | 2 ( 0.7%)      | 8 ( 1.4%)        |
| ADC                                                                    | 17 ( 6.1%)    | 162 ( 58.1%)   | 179 ( 32.1%)     |
| Trastuzumab Deruxtecan                                                 | 16 ( 5.7%)    | 8 ( 2.9%)      | 24 ( 4.3%)       |
| Sacituzumab Govitecan                                                  | 1 ( 0.4%)     | 154 ( 55.2%)   | 155 ( 27.8%)     |
| Other                                                                  | 99 ( 35.5%)   | 27 ( 9.7%)     | 126 ( 22.6%)     |

### Duration of follow-up

At the time of the primary PFS analysis (DCO 02 April 2025), the median duration of OS follow-up was 13.31 months (range: 0.07, 29.21) in the SG group and 13.14 months (range: 0.03, 27.86) in the TPC group; total: 13.2 (0.03 to 29.21) months.

At the time of OS IA1 (DCO 27 October 2025), the median duration of OS follow-up was 17.74 (0.07 to 36.04) months in the SG group and 17.64 (0.03 to 34.69) months in the TPC group; total: 17.72 (0.03 to 36.04) months.

## **Recruitment**

The first participant was randomized on 27 October 2022 (on 20 July 2022 the first patient was screened) and the last participant was enrolled on 29 July 2024. The trial is ongoing; 02 April 2025 was the data cut-off date (DCO) for the primary PFS analysis, 27 October 2025 was the DCO for OS IA1.

Participants were enrolled in 229 study centres across 30 countries:

- Africa (n=13): South Africa 13
- Asia Pacific (n=140): Australia 11, China 17, Hong Kong 3, Japan 43, Malaysia 18, South Korea 37, Taiwan 11
- Europe (n=219): Austria 4, Belgium 7, Czech Republic 9, Israel 16, France 22, Germany 15, Hungary 8, Italy 36, NL 6, Poland 8, Romania 10, Slovakia 3, Spain 39, Switzerland 1, Turkey 31, UK 4
- Latin America (n=142): Argentina 22, Brazil 52, Chile 27, Mexico 41
- North America (n=44): Canada 9, US 35.

## **Conduct of the study**

### **Protocol amendments**

**Original protocol** dated 27 October 2021

Excerpt from statistical considerations:

The primary analysis of the PFS primary end point as assessed by BICR was to be conducted in the ITT Analysis Set when approximately 227 PFS events have occurred across the treatment arms and will be

tested at the 1-sided significance level of 2.5%. The primary analysis was projected to occur at approximately 20 months after the first patient is randomized.

OS analyses: A descriptive, noncomparative analysis of OS was to be performed at the time of the PFS final analysis. To be conservative, a nominal 1-sided alpha of 0.005% will be spent even without formal hypothesis testing. The descriptive OS summary was to include Kaplan-Meier estimates of median OS by treatment arms and hazard ratio between treatment arms. It is estimated that 114 OS events (~29% information fraction of the total 391 OS events) will occur at this time of analysis.

The study planned to have 2 interim efficacy analyses of the secondary end point, OS, performed when approximately a total of 254 (65% information fraction) and 332 (85% information) death events have occurred, respectively. The interim analyses were projected to occur approximately 32 months and 44 months after the first patient is randomized, respectively.

The final analysis of the key secondary end point of OS was to be conducted in the ITT Analysis Set when approximately 391 death events occurred across the treatment arms (391/540 events with 72% maturity), which was projected to occur at approximately 57 months after the first patient was randomized.

**Amendment 1** dated 31 January 2022 (before randomisation of first patient)

The primary reason for this amendment was to address the feedback received from the CHMP regarding study GS-US-592-6238 (EMA SA November 2021), see summary of main changes:

- “Time to deterioration of global health status/quality of life (QOL), pain, and fatigue” replaced with “Mean change from baseline in the physical functioning”.
- Stratification by geographic region updated from ‘US/Canada vs rest of world’ to ‘US/Canada/Western Europe vs rest of world’ to more accurately reflect the different treatment practices and outcomes between different regions and the contributions of each region to the study plan.
- Updated inclusion criterion 2) to add that patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy if  $\geq 12$  months have elapsed between the completion of treatment with curative intent and disease recurrence.
- Updated inclusion criterion 2) to add that patients enrolled should have received prior anthracycline in the (neo)adjuvant setting or be considered not eligible for anthracyclines as assessed by the treating physician.
- Update of the primary analysis: PFS analysis will be conducted in the first 400 randomized patients (PFS Analysis Set) instead of the ITT population in order to increase the data maturity and follow-up time at the time of PFS analysis. The primary analysis will be conducted when approximately 227 PFS events have occurred across the treatment arms in the PFS Analysis Set; it is projected to occur at approximately 22 months after the first patient is randomized, which is about 6 months after the last patient in the PFS Analysis Set is randomized. This analysis of the primary end point will serve as the final analysis for this end point.
- Added sensitivity analyses for PFS based on different censoring rules.

**Amendment 2** dated 30 August 2023 (189 participants have been randomised)

Summary of main changes:

- The primary end point analysis was revised, including:
  - Changed the number of PFS events (from 227 to 280)

- Changed from PFS Analysis Set to ITT Analysis Set

To follow the ITT principle, the primary PFS analysis was to be performed in the ITT analysis set. The number of PFS events was updated to 280 in order to achieve 95% power at a 1-sided significance level of 2.5% using a log-rank test.

- The number of OS events in the descriptive summary at the time of PFS analysis was revised. Descriptive summary of OS will be provided at the time of primary PFS analysis in the ITT analysis set. The corresponding number of OS events at the time of PFS analysis in the ITT Analysis Set was updated accordingly.
- Specified the Week 25 timepoint for physical functioning domain of the EORTC QLQ-C30 in the secondary end points.
- Added comparison of time to deterioration (TTD) in fatigue as measured by the EORTC QLQ-C30 between the 2 arms.
- Inclusion criteria were revised to include:
  - Patients with tumour CPS  $\geq 10$  or PD-L1 positive at screening will be eligible if they cannot receive treatment with an anti-PD-(L)1 agent due to a comorbidity.

Patients with PD-L1 positive mTNBC who have comorbidities precluding treatment with anti-PD-(L)1 agents have limited treatment options. The amended criterion allows for patients with mTNBC who are not eligible to be treated with anti-PD-(L)1 agents in the first-line metastatic setting to be enrolled.
- The de novo cap for the mTNBC population was changed from 25% to 35%, and clarification was added for consistency with the Study Design Overview.  
Thirty-five percent de novo representation is more reflective of recent real-world data reports.
- Language has been added for instances of treatment beyond the initial BICR-assessed PD per RECIST Version 1.1 to allow patients to continue receiving treatment if there is evidence of clinical benefit.
- Added bone scan when clinically indicated as a new study procedure.

**Amendment 3** dated 14 May 2024 (499 out of 558 participants have been randomised)

Key changes:

- The primary end point analysis was revised, including:
  - Changed the number of PFS events (from 280 to 352)
- The first OS interim analysis timing has correspondingly been adjusted

Rationale for change: Based on the study design in protocol amendment 2 (30 August 2023), 280 progression-free survival (PFS) events were required for the planned PFS primary analysis, corresponding to limited data maturity of 52% with respect to the total population, and only 2.4 months of follow-up after the last patient is enrolled. Based on the assumed median PFS in both arms and given that this is the only and final PFS analysis, a significant number of patients may still be on treatment at the time of the PFS primary analysis with inadequate follow-up time to observe PFS events. In this protocol amendment, the data maturity rate has been increased to 65% (352 of 540 events) to ensure that the PFS analysis is not planned too early and allows for adequate follow-up to observe PFS events in the fully enrolled population, consistent with health authority advice. The first overall survival (OS) interim analysis timing has correspondingly been adjusted to ensure sufficient time between the PFS primary analysis and the first OS interim

analysis. The text was also clarified to explain the scenarios in which PFS and OS may be performed at the same time.

- Revised to perform patient-reported outcomes (PRO) analysis on the Intent-to-Treat (ITT) Analysis Set, consistent with health authority advice.
- Text added to clarify that when complete response (CR) is achieved, a bone scan is only required if bone lesions were present at baseline.

**Amendment 4** dated 18 November 2024 (last patient enrolled 29 July 2024)

Rationale for key changes:

- Strengthen the guidance on the use of G-CSF for the management of neutropenia (in line with SG investigator brochure (IB) update to Edition 14, dated 22 October 2024, and EU EMEA/H/C/005182/II/0037 variation application, dated 24 October 2024, to revise the product information to include updated G-CSF primary prophylaxis mitigation language).
  - Fatal infections in the setting of neutropenia have been observed in clinical trials with TRODELVY, primarily in the first two cycles of treatment.
  - Primary prophylaxis with G-CSF is recommended starting in the first cycle of treatment in patients at increased risk of febrile neutropenia, e.g. older patients (in particular aged 65 years and older), patients with previous neutropenia, poor performance status, organ dysfunction (including renal, liver or cardiovascular dysfunction), or multiple comorbid conditions. Monitor absolute neutrophil count during treatment.
  - Dose modification may be required due to neutropenia or febrile neutropenia. Treat neutropenia with G-CSF and consider prophylaxis in subsequent cycles as clinically indicated.
  - Risk factors for febrile neutropenia per the American Society of Clinical Oncology were included to identify patients who may benefit from primary prophylaxis with granulocyte colony-stimulating factor
- Addition of statement in section 8 that details of any deviations from the original statistical analysis planned will be provided in the SAP

**Statistical Analysis Plan Version 1.0** dated 01 April 2025 (all patients randomized)

The SAP Version 1.0 is based on the Protocol Amendment 4 dated 18 November 2024 and was finalized after all patients have been randomized, one day prior to data cut-off for the PFS primary analysis.

To account for the effect of crossover on OS, methods such as the rank preserving structural failure time model, two-stage method, or inverse probability censoring weighting method were planned but not provided yet.

**Table 26 Summary of changes in planned efficacy analysis (Assessor's table)**

|                                                                             | Original protocol    | Amendment 1                          | Amendment 2          | Amendment 3                        |
|-----------------------------------------------------------------------------|----------------------|--------------------------------------|----------------------|------------------------------------|
| Date of initiation<br>(N already randomised at the time of implementation*) | 27 Oct 2021<br>(N/A) | 31 Jan 2022<br>0                     | 30 Aug 2023<br>(189) | 14 May 2024<br>(499 <sup>a</sup> ) |
| <b>Primary PFS analysis</b>                                                 | ITT (n=540)          | <b>PFS analysis set <sup>b</sup></b> | ITT (n=540)          | ITT (n=540)                        |
| Expected events                                                             | 227                  | 227 (in first 400)                   | 280                  | 352                                |
| Maturity                                                                    | 42%                  | 57%                                  | 52%                  | 65%                                |

|                                                                                 |                             |                         |                           |                           |
|---------------------------------------------------------------------------------|-----------------------------|-------------------------|---------------------------|---------------------------|
| Expected timing <sup>d</sup><br>Stopping boundary <sup>e</sup>                  | 20 months<br>NR             | 22 months<br>HR ≤ 0.771 | 22.4 months<br>HR ≤ 0.791 | 27.6 months<br>HR ≤ 0.811 |
| <b>Descriptive OS analysis<sup>c</sup></b><br>Expected events (IF)              | 114 (29%)                   | 141 (36%)               | 146 (37%)                 | 218 (56%)                 |
| <b>OS IA1</b><br>Expected events n (IF)<br>Expected timing <sup>d</sup>         | 254 (65%)<br>32 months      | 254 (65%)<br>32 months  | 254 (65%)<br>32 months    | 274 (70%)<br>34 months    |
| <b>OS IA2</b><br>Expected events n(IF)<br>Expected timing <sup>d</sup>          | 332 (85%)<br>44 months      | 332 (85%)<br>44 months  | 332 (85%)<br>44 months    | 332 (85%)<br>43 months    |
| <b>OS final</b><br>Expected events n (maturity)<br>Expected timing <sup>d</sup> | 391 (/540=72%)<br>57 months | 391<br>57 months        | 391<br>57 months          | 391<br>56 months          |

\* based on Listing 16.2.1.2.1

<sup>a</sup> last patient enrolled 29 July 2024

<sup>b</sup> PFS Analysis Set: the primary PFS analysis will be conducted in the first 400 randomized patients

<sup>c</sup> Descriptive OS analysis concurrent with primary PFS analysis, no formal testing

<sup>d</sup> expected timing of analysis (months from randomization)

<sup>e</sup> Stopping Boundary for primary PFS analysis (1-Sided Alpha)

IF: Information fraction, NR: not reported

## Protocol deviations

An important protocol deviation was defined as a protocol deviation that might significantly impact completeness, accuracy, and/or reliability of study data or that may significantly affect a participant's rights, safety, or well-being.

**Table 27 Important Protocol Deviations (ITT) – DCO 02 April 2025**

|                                                           | SG<br>(N = 279) | TPC<br>(N = 279) | Total<br>(N = 558) |
|-----------------------------------------------------------|-----------------|------------------|--------------------|
| Participants with at least 1 Important Protocol Deviation | 150 (53.8%)     | 106 (38.0%)      | 256 (45.9%)        |
| Other treatment compliance issue                          | 89 (31.9%)      | 26 (9.3%)        | 115 (20.6%)        |
| Eligibility criteria                                      | 33 (11.8%)      | 33 (11.8%)       | 66 (11.8%)         |
| Missing data                                              | 39 (14.0%)      | 26 (9.3%)        | 65 (11.6%)         |
| Informed consent                                          | 26 (9.3%)       | 20 (7.2%)        | 46 (8.2%)          |
| Other                                                     | 18 (6.5%)       | 19 (6.8%)        | 37 (6.6%)          |
| Off schedule procedure                                    | 15 (5.4%)       | 12 (4.3%)        | 27 (4.8%)          |
| Wrong treatment or incorrect dose                         | 6 (2.2%)        | 4 (1.4%)         | 10 (1.8%)          |

Further clarifications regarding reported categories of important protocol deviations (IPD):

- Other Treatment Compliance Issue

"Other Treatment Compliance Issues" were reported with higher incidence in the SG group (31.9%) versus the TPC group (9.3%). In the SG group, this was primarily due to nonobservance to the absolute neutrophil count requirements as outlined in the protocol (N=51 with SG, N=0 with TPC), and additional training was conducted by the sponsor. These cases predominantly included SG administration at Grade 2 ANC levels prior to Day 1 dosing across various cycles. The second largest

subcategory contributing to this imbalance was related to faster infusion time than specified per protocol or instances where infusion times were not recorded (N=28 with SG, N=2 with TPC).

- Eligibility criteria

The study was analyzed using intent to treat principles, and no participants were excluded even if they were subsequently found to have not met eligibility criteria, provided it was deemed safe to continue by the treating Investigator.

- Missing Data

The IPDs categorized as “Missing Data” were associated with laboratory and tumour assessments that were not performed during the study or were conducted outside the protocol specified assessment window. IPDs did not result in censoring of PFS.

- Informed Consent

Important protocol deviations regarding informed consent primarily involved administrative errors. There were no instances in which informed consent was not obtained from a participant in the clinical study.

- Other

Occurrence of important deviations in the “Other” category were primarily due to stratification errors and delayed reporting of SAEs.

- Off Schedule Procedure

Deviations were related to tumour assessments completed outside of the protocol prespecified window. IPDs did not result in PFS censoring.

- Wrong Treatment or Incorrect Dose

Deviations were related to the dosing errors of study treatment. The majority of these dosing errors were due to the dose not being recalculated after patient body weight changes. No participants received the wrong study treatment.

## Baseline data

**Table 28 Demographic and Baseline Characteristics**

|                | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|----------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| Age (years)    |                                            |                                             |                                  |                                                                        |
| N              | 275                                        | 276                                         | 963                              | 1999                                                                   |
| Mean (StD)     | 56 (11.9)                                  | 55 (13.3)                                   | 55 (11.5)                        | 61 (11.7)                                                              |
| Median         | 56                                         | 55                                          | 55                               | 61                                                                     |
| Min, max       | 28, 84                                     | 23, 86                                      | 27, 86                           | 27, 90                                                                 |
| Age group      |                                            |                                             |                                  |                                                                        |
| < 50 years     | 89 (32.4%)                                 | 99 (35.9%)                                  | 301 (31.3%)                      | 372 (18.6%)                                                            |
| 50 to 64 years | 123 (44.7%)                                | 99 (35.9%)                                  | 447 (46.4%)                      | 837 (41.9%)                                                            |
| 65 to 74 years | 43 (15.6%)                                 | 58 (21.0%)                                  | 167 (17.3%)                      | 558 (27.9%)                                                            |
| ≥ 75 years     | 20 (7.3%)                                  | 20 (7.2%)                                   | 48 (5.0%)                        | 232 (11.6%)                                                            |
| < 65 years     | 212 (77.1%)                                | 198 (71.7%)                                 | 748 (77.7%)                      | 1209 (60.5%)                                                           |

|                                              | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|----------------------------------------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| ≥ 65 years                                   | 63 (22.9%)                                 | 78 (28.3%)                                  | 215 (22.3%)                      | 790 (39.5%)                                                            |
| Sex                                          |                                            |                                             |                                  |                                                                        |
| Male                                         | 1 (0.4%)                                   | 2 (0.7%)                                    | 5 (0.5%)                         | 708 (35.4%)                                                            |
| Female                                       | 274 (99.6%)                                | 274 (99.3%)                                 | 958 (99.5%)                      | 1291 (64.6%)                                                           |
| Race                                         |                                            |                                             |                                  |                                                                        |
| American Indian or Alaska Native             | 9 (3.3%)                                   | 16 (5.8%)                                   | 9 (0.9%)                         | 9 (0.5%)                                                               |
| Asian                                        | 66 (24.0%)                                 | 65 (23.6%)                                  | 92 (9.6%)                        | 212 (10.6%)                                                            |
| Black or African American                    | 9 (3.3%)                                   | 7 (2.5%)                                    | 50 (5.2%)                        | 70 (3.5%)                                                              |
| Native Hawaiian or Other Pacific Islander    | 0                                          | 0                                           | 0                                | 0                                                                      |
| White                                        | 175 (63.6%)                                | 175 (63.4%)                                 | 692 (71.9%)                      | 1427 (71.4%)                                                           |
| Other                                        | 11 (4.0%)                                  | 10 (3.6%)                                   | 47 (4.9%)                        | 68 (3.4%)                                                              |
| Not Permitted                                | 5 (1.8%)                                   | 3 (1.1%)                                    | 73 (7.6%)                        | 213 (10.7%)                                                            |
| Ethnicity                                    |                                            |                                             |                                  |                                                                        |
| Hispanic or Latino                           | 71 (25.8%)                                 | 76 (27.5%)                                  | 106 (11.0%)                      | 150 (7.5%)                                                             |
| Not Hispanic or Latino                       | 201 (73.1%)                                | 198 (71.7%)                                 | 796 (82.7%)                      | 1686 (84.3%)                                                           |
| Not Permitted                                | 3 (1.1%)                                   | 2 (0.7%)                                    | 33 (3.4%)                        | 121 (6.1%)                                                             |
| Unknown                                      | 0                                          | 0                                           | 26 (2.7%)                        | 40 (2.0%)                                                              |
| Missing                                      | 0                                          | 0                                           | 2 (0.2%)                         | 2 (0.1%)                                                               |
| Region                                       |                                            |                                             |                                  |                                                                        |
| North America                                | 42 (15.3%)                                 | 41 (14.9%)                                  | 484 (50.3%)                      | 907 (45.4%)                                                            |
| Europe                                       | 95 (34.5%)                                 | 105 (38.0%)                                 | 341 (35.4%)                      | 810 (40.5%)                                                            |
| Asia/Pacific                                 | 83 (30.2%)                                 | 73 (26.4%)                                  | 83 (8.6%)                        | 220 (11.0%)                                                            |
| South America                                | 48 (17.5%)                                 | 51 (18.5%)                                  | 48 (5.0%)                        | 55 (2.8%)                                                              |
| South Africa                                 | 7 (2.5%)                                   | 6 (2.2%)                                    | 7 (0.7%)                         | 7 (0.4%)                                                               |
| Baseline weight (kg)                         |                                            |                                             |                                  |                                                                        |
| N                                            | 275                                        | 276                                         | 962                              | 1998                                                                   |
| Mean (StD)                                   | 69.5 (15.98)                               | 68.7 (14.29)                                | 70.4 (16.83)                     | 72.3 (16.87)                                                           |
| Median                                       | 67.9                                       | 68.0                                        | 67.4                             | 70.2                                                                   |
| Min, max                                     | 38.1, 131.4                                | 42.0, 113.0                                 | 37.2, 160.1                      | 32.0, 190.0                                                            |
| Baseline BMI (kg/m <sup>2</sup> )            |                                            |                                             |                                  |                                                                        |
| N                                            | 275                                        | 276                                         | 947                              | 1968                                                                   |
| Mean (StD)                                   | 27.0 (5.72)                                | 26.7 (5.20)                                 | 26.7 (6.14)                      | 26.1 (5.58)                                                            |
| Median                                       | 26.2                                       | 25.7                                        | 25.6                             | 25.2                                                                   |
| Min, max                                     | 14.1, 54.8                                 | 16.8, 44.1                                  | 14.1, 61.0                       | 11.6, 61.0                                                             |
| Baseline body surface area (m <sup>2</sup> ) |                                            |                                             |                                  |                                                                        |
| N                                            | 275                                        | 276                                         | 947                              | 1968                                                                   |
| Mean (StD)                                   | 1.7 (0.20)                                 | 1.7 (0.18)                                  | 1.7 (0.19)                       | 1.8 (0.22)                                                             |
| Median                                       | 1.7                                        | 1.7                                         | 1.7                              | 1.8                                                                    |
| Min, max                                     | 1.3, 2.3                                   | 1.4, 2.2                                    | 1.3, 2.5                         | 1.1, 3.0                                                               |
| UGT1A1 status                                |                                            |                                             |                                  |                                                                        |
| *1/*1                                        | 111 (40.4%)                                | 127 (46.0%)                                 | 396 (41.1%)                      | 723 (36.2%)                                                            |
| *1/*28                                       | 103 (37.5%)                                | 89 (32.2%)                                  | 375 (38.9%)                      | 701 (35.1%)                                                            |

|                  | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|------------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| *1/*36           | 1 (0.4%)                                   | 0                                           | 3 (0.3%)                         | 6 (0.3%)                                                               |
| *1/*37           | 0                                          | 1 (0.4%)                                    | 3 (0.3%)                         | 4 (0.2%)                                                               |
| *1/*6            | 13 (4.7%)                                  | 11 (4.0%)                                   | 13 (1.3%)                        | 19 (1.0%)                                                              |
| *27/*28          | 1 (0.4%)                                   | 1 (0.4%)                                    | 1 (0.1%)                         | 1 (< 0.1%)                                                             |
| *28/*28          | 23 (8.4%)                                  | 27 (9.8%)                                   | 94 (9.8%)                        | 184 (9.2%)                                                             |
| *28/*36          | 1 (0.4%)                                   | 1 (0.4%)                                    | 3 (0.3%)                         | 4 (0.2%)                                                               |
| *28/*37          | 2 (0.7%)                                   | 0                                           | 4 (0.4%)                         | 4 (0.2%)                                                               |
| *36/*36          | 0                                          | 0                                           | 1 (0.1%)                         | 2 (0.1%)                                                               |
| *6/*28           | 2 (0.7%)                                   | 5 (1.8%)                                    | 2 (0.2%)                         | 2 (0.1%)                                                               |
| *6/*6            | 2 (0.7%)                                   | 3 (1.1%)                                    | 2 (0.2%)                         | 4 (0.2%)                                                               |
| Missing/not done | 16 (5.8%)                                  | 11 (4.0%)                                   | 66 (6.9%)                        | 345 (17.3%)                                                            |

**Table 29 Baseline disease characteristics (continued)**

|                                      | <b>SG<br/>(N = 279)</b> | <b>TPC<br/>(N = 279)</b> | <b>Total<br/>(N = 558)</b> |
|--------------------------------------|-------------------------|--------------------------|----------------------------|
| Baseline ECOG Score                  |                         |                          |                            |
| 0                                    | 183 (65.6%)             | 187 (67.0%)              | 370 (66.3%)                |
| 1                                    | 96 (34.4%)              | 92 (33.0%)               | 188 (33.7%)                |
| Menopausal Status (Females Only)     |                         |                          |                            |
| Pre-menopausal                       | 58 (20.9%)              | 78 (28.2%)               | 136 (24.5%)                |
| Post-menopausal                      | 220 (79.1%)             | 199 (71.8%)              | 419 (75.5%)                |
| BRCA1/2 Mutation Status <sup>a</sup> |                         |                          |                            |
| Mutant                               | 17 (6.1%)               | 12 (4.3%)                | 29 (5.2%)                  |
| Wild Type                            | 70 (25.1%)              | 82 (29.4%)               | 152 (27.2%)                |
| Unknown                              | 192 (68.8%)             | 185 (66.3%)              | 377 (67.6%)                |

|                                          |             |              |             |
|------------------------------------------|-------------|--------------|-------------|
| PD-L1 CPS                                |             |              |             |
| <1                                       | 102 (36.6%) | 98 (35.1%)   | 200 (35.8%) |
| 1 to <10                                 | 175 (62.7%) | 180 (64.5%)  | 355 (63.6%) |
| ≥10                                      | 1 (0.4%)    | 1 (0.4%)     | 2 (0.4%)    |
| Missing                                  | 1 (0.4%)    | 0            | 1 (0.2%)    |
| Estrogen Receptor Status                 |             |              |             |
| Negative (< 1%)                          | 277 (99.3%) | 279 (100.0%) | 556 (99.6%) |
| Positive (≥ 1%)                          | 1 (0.4%)    | 0            | 1 (0.2%)    |
| Missing                                  | 1 (0.4%)    | 0            | 1 (0.2%)    |
| Progesterone Receptor Status             |             |              |             |
| Negative (< 1%)                          | 278 (99.6%) | 279 (100.0%) | 557 (99.8%) |
| Positive (≥ 1%)                          | 0           | 0            | 0           |
| Missing                                  | 1 (0.4%)    | 0            | 1 (0.2%)    |
| HER2 Status                              |             |              |             |
| Negative                                 | 277 (99.3%) | 279 (100.0%) | 556 (99.6%) |
| Positive                                 | 1 (0.4%)    | 0            | 1 (0.2%)    |
| Missing                                  | 1 (0.4%)    | 0            | 1 (0.2%)    |
| Prior Radiotherapy                       |             |              |             |
| Yes                                      | 166 (59.5%) | 159 (57.0%)  | 325 (58.2%) |
| No                                       | 113 (40.5%) | 120 (43.0%)  | 233 (41.8%) |
| On Study Radiotherapy                    |             |              |             |
| Yes                                      | 25 (9.0%)   | 33 (11.8%)   | 58 (10.4%)  |
| No                                       | 254 (91.0%) | 246 (88.2%)  | 500 (89.6%) |
| Pre-selected TPC Prior to Randomization  |             |              |             |
| Taxane                                   | 154 (55.2%) | 155 (55.6%)  | 309 (55.4%) |
| Gemcitabine/Carboplatin                  | 125 (44.8%) | 124 (44.4%)  | 249 (44.6%) |
| Breast Cancer Stage at Initial Diagnosis |             |              |             |
| Stage I                                  | 36 (12.9%)  | 30 (10.8%)   | 66 (11.8%)  |
| Stage II                                 | 92 (33.0%)  | 96 (34.4%)   | 188 (33.7%) |
| Stage III                                | 72 (25.8%)  | 72 (25.8%)   | 144 (25.8%) |
| Stage IV                                 | 78 (28.0%)  | 80 (28.7%)   | 158 (28.3%) |
| Missing                                  | 1 (0.4%)    | 1 (0.4%)     | 2 (0.4%)    |

| Subtype of Cancer at Initial Diagnosis                                                                 |             |             |             |
|--------------------------------------------------------------------------------------------------------|-------------|-------------|-------------|
| HR-/HER2- (TNBC)                                                                                       | 234 (83.9%) | 230 (82.4%) | 464 (83.2%) |
| HR-/HER2+                                                                                              | 3 (1.1%)    | 2 (0.7%)    | 5 (0.9%)    |
| HR+/HER2+                                                                                              | 5 (1.8%)    | 4 (1.4%)    | 9 (1.6%)    |
| HR+/HER2-                                                                                              | 36 (12.9%)  | 40 (14.3%)  | 76 (13.6%)  |
| Missing                                                                                                | 1 (0.4%)    | 3 (1.1%)    | 4 (0.7%)    |
| Disease Status at Screening                                                                            |             |             |             |
| Metastatic                                                                                             | 274 (98.2%) | 272 (97.5%) | 546 (97.8%) |
| Locally advanced and Inoperable                                                                        | 5 (1.8%)    | 7 (2.5%)    | 12 (2.2%)   |
| Site of Metastasis at Screening                                                                        |             |             |             |
| Lung                                                                                                   | 166 (59.5%) | 170 (60.9%) | 336 (60.2%) |
| Brain                                                                                                  | 15 (5.4%)   | 14 (5.0%)   | 29 (5.2%)   |
| Liver                                                                                                  | 81 (29.0%)  | 72 (25.8%)  | 153 (27.4%) |
| Bone                                                                                                   | 95 (34.1%)  | 87 (31.2%)  | 182 (32.6%) |
| Lymph Node                                                                                             | 179 (64.2%) | 180 (64.5%) | 359 (64.3%) |
| Other                                                                                                  | 98 (35.1%)  | 84 (30.1%)  | 182 (32.6%) |
| Time from Locally Advanced and Inoperable or Metastatic Disease to Randomization (months) <sup>b</sup> |             |             |             |
| N                                                                                                      | 277         | 279         | 556         |
| Mean (StD)                                                                                             | 2.4 (2.32)  | 2.6 (2.40)  | 2.5 (2.36)  |
| Median                                                                                                 | 1.9         | 1.9         | 1.9         |
| Q1, Q3                                                                                                 | 1.4, 2.6    | 1.3, 2.9    | 1.3, 2.8    |
| Min, Max                                                                                               | 0.4, 26.7   | 0.1, 18.9   | 0.1, 26.7   |

UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

a Mutant denotes participant is either BRCA1 or BRCA2 mutant, or both mutant. Wild type denotes participant is both

BRCA1 and BRCA2 wild type. Unknown denotes participant is BRCA1 unknown and BRCA2 wild type or unknown, or participant is BRCA1 wild type or unknown and BRCA2 unknown.

b Time from locally advanced and inoperable or metastatic disease to randomization in months is defined as the number of days divided by 30.4375 from the date of confirmed disease to the date of randomization.

**Table 30 Enrolment by randomization stratum**

| Randomization Stratum                   | SG<br>(N=279) | TPC<br>(N=279) | Total<br>(N=558) |
|-----------------------------------------|---------------|----------------|------------------|
| <b>IWRS</b>                             |               |                |                  |
| <b>Disease Stratification</b>           |               |                |                  |
| De novo                                 | 87 ( 31.2%)   | 88 ( 31.5%)    | 175 ( 31.4%)     |
| Recurrent disease within 6 to 12 months | 58 ( 20.8%)   | 57 ( 20.4%)    | 115 ( 20.6%)     |
| Recurrent disease occurring > 12 months | 134 ( 48.0%)  | 134 ( 48.0%)   | 268 ( 48.0%)     |
| <b>Geographic Region</b>                |               |                |                  |
| US/Canada/Western Europe                | 89 ( 31.9%)   | 89 ( 31.9%)    | 178 ( 31.9%)     |
| Rest of the World                       | 190 ( 68.1%)  | 190 ( 68.1%)   | 380 ( 68.1%)     |

**Table 31 Prior anti-cancer therapy**

|                                                        | SG<br>(N=279) | TPC<br>(N=279) | Total<br>(N=558) |
|--------------------------------------------------------|---------------|----------------|------------------|
| Participants with Any Prior Anti-Cancer Therapy, n (%) | 185 ( 66.3%)  | 192 ( 68.8%)   | 377 ( 67.6%)     |
| Prior Neoadjuvant or Adjuvant Anti-cancer Therapy [a]  |               |                |                  |
| Yes                                                    | 185 ( 66.3%)  | 191 ( 68.5%)   | 376 ( 67.4%)     |
| Taxanes                                                | 162 ( 58.1%)  | 162 ( 58.1%)   | 324 ( 58.1%)     |
| Anthracyclines                                         | 148 ( 53.0%)  | 159 ( 57.0%)   | 307 ( 55.0%)     |
| Platinum                                               | 51 ( 18.3%)   | 49 ( 17.6%)    | 100 ( 17.9%)     |
| Anti-PD-1/PD-L1 agents                                 | 13 ( 4.7%)    | 11 ( 3.9%)     | 24 ( 4.3%)       |
| Capecitabine                                           | 50 ( 17.9%)   | 57 ( 20.4%)    | 107 ( 19.2%)     |
| PARP inhibitors                                        | 1 ( 0.4%)     | 0              | 1 ( 0.2%)        |
| Other                                                  | 164 ( 58.8%)  | 174 ( 62.4%)   | 338 ( 60.6%)     |

## Numbers analysed

**Table 32 Numbers in analysis populations**

|                              | SG           | TPC          | Total        |
|------------------------------|--------------|--------------|--------------|
| Screened                     |              |              | 887          |
| ITT Analysis Set             | 279 (100.0%) | 279 (100.0%) | 558 (100.0%) |
| Safety Analysis Set          | 275 (98.6%)  | 276 (98.9%)  | 551 (98.7%)  |
| Pharmacokinetic Analysis Set | 272 (97.5%)  | 0            | 272 (48.7%)  |
| Immunogenicity Analysis Set  | 264 (94.6%)  | 0            | 264 (47.3%)  |

Screened Population: Participants who have signed an informed consent and participated in the screening procedures at site to assess eligibility.

Intent-to-treat (ITT) Analysis Set includes all participants who were randomized in the study.

Safety Analysis Set includes randomized participants who have received at least one dose of any study drug.

Pharmacokinetic Analysis Set includes randomized participants who received  $\geq 1$  SG dose and have  $\geq 1$  measurable posttreatment SG concentration.

Immunogenicity Analysis Set includes randomized participants who received  $\geq 1$  SG dose and have  $\geq 1$  evaluable non-missing

anti-SG antibody test result.

The denominator of percentages is the number of participants in each treatment group in the ITT Analysis Set.

## Outcomes and estimation

### Primary Efficacy Endpoint

Efficacy data are from the **primary (final) analysis** of PFS for study ASCENT-03 with a data cut-off date of 02 April 2025.

**Table 33 PFS by BICR using RECIST v1.1 (ITT) – DCO 02 April 2025**

|                                                                                    | SG<br>(N = 279) | TPC<br>(N = 279) |
|------------------------------------------------------------------------------------|-----------------|------------------|
| Number (%) of Participants with Events                                             | 161 (57.7%)     | 188 (67.4%)      |
| Disease Progression (PD)                                                           | 143 (51.3%)     | 180 (64.5%)      |
| Death                                                                              | 18 (6.5%)       | 8 (2.9%)         |
| Number (%) of Participants Censored                                                | 118 (42.3%)     | 91 (32.6%)       |
| PD after Starting New Anticancer Therapy                                           | 1 (0.4%)        | 1 (0.4%)         |
| PD right after $\geq 2$ Consecutive Missing and/or Not Evaluable Tumor Assessments | 0               | 3 (1.1%)         |

|                                                                                  | <b>SG<br/>(N = 279)</b>     | <b>TPC<br/>(N = 279)</b> |
|----------------------------------------------------------------------------------|-----------------------------|--------------------------|
| Death after Starting New Anticancer Therapy                                      | 10 (3.6%)                   | 10 (3.6%)                |
| Death right after ≥ 2 Consecutive Missing and/or Not Evaluable Tumor Assessments | 5 (1.8%)                    | 5 (1.8%)                 |
| No PD and No Death without New Anticancer Therapy                                | 70 (25.1%)                  | 44 (15.8%)               |
| No PD and No Death with New Anticancer Therapy                                   | 26 (9.3%)                   | 22 (7.9%)                |
| No Baseline or Postbaseline Evaluable Assessment <sup>a</sup>                    | 6 (2.2%)                    | 6 (2.2%)                 |
| Kaplan-Meier Estimate of PFS (Months) (95% CI) <sup>b</sup>                      |                             |                          |
| <b>Median</b>                                                                    | <b>9.69</b> (8.15, 11.14)   | <b>6.93</b> (5.62, 8.25) |
| Kaplan-Meier Estimate of PFS Rate (95% CI) <sup>c</sup>                          |                             |                          |
| At 3 Months                                                                      | 0.851 (0.802, 0.889)        | 0.786 (0.732, 0.831)     |
| At 6 Months                                                                      | 0.652 (0.590, 0.708)        | 0.532 (0.469, 0.592)     |
| At 9 Months                                                                      | 0.519 (0.454, 0.580)        | 0.352 (0.291, 0.414)     |
| At 12 Months                                                                     | 0.409 (0.343, 0.474)        | 0.243 (0.186, 0.304)     |
| At 18 Months                                                                     | 0.261 (0.191, 0.336)        | 0.127 (0.071, 0.201)     |
| Stratified Log-rank <i>P</i> value of SG vs TPC <sup>d</sup>                     | < 0.0001                    | —                        |
| Stratified <b>Hazard Ratio</b> of SG vs TPC (95% CI) from Cox Model <sup>d</sup> | <b>0.623</b> (0.501, 0.775) |                          |

CI = confidence interval; ITT = intent to treat; IWRS = interactive web response system; PD = progressive disease; PFS = progression-free survival; Q1 = first quartile; Q3 = third quartile; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SG = sacituzumab govitecan; TPC = treatment of physician's choice

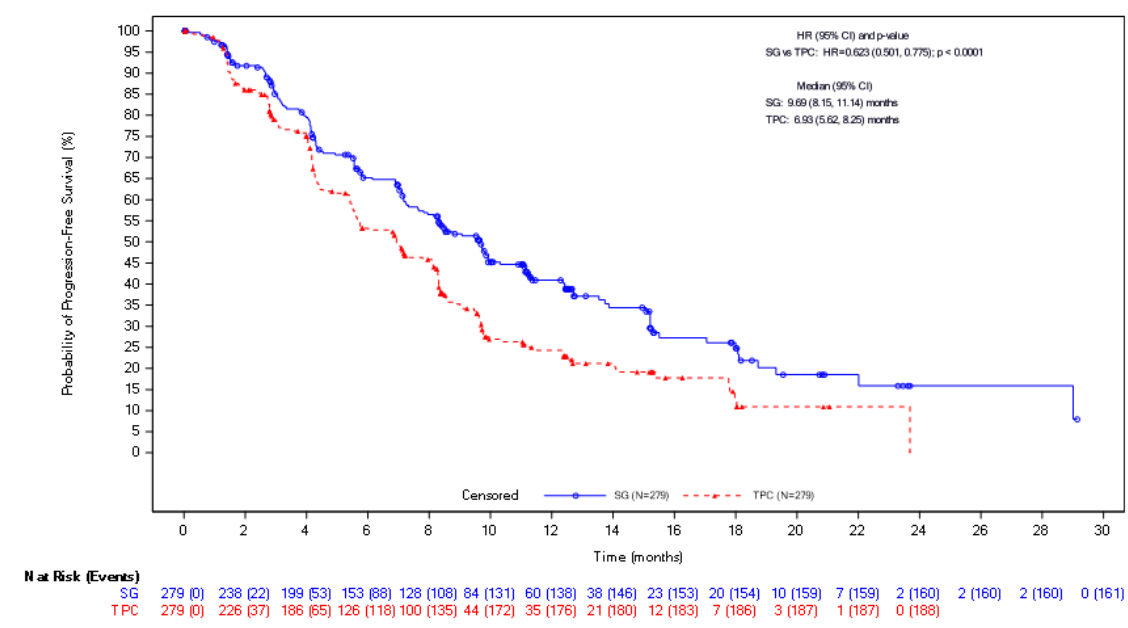
a Censoring due to no baseline or no postbaseline evaluable assessment does not include death event before the 2nd scheduled visit postbaseline.

a PFS (months) = (date of events or censoring - date of randomization + 1)/30.4375. The 95% CI is based on log-log transformation.

b PFS rate is the proportion of participants alive without PD.

c The 2-sided *P* value is from stratified log-rank test and the hazard ratio with 95% CIs calculated using Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).

**Figure 23 KM Plot of PFS by BICR Using RECIST v1.1 (ITT) – DCO 02 April 2025**



**Updated** descriptive PFS analysis at OS IA1

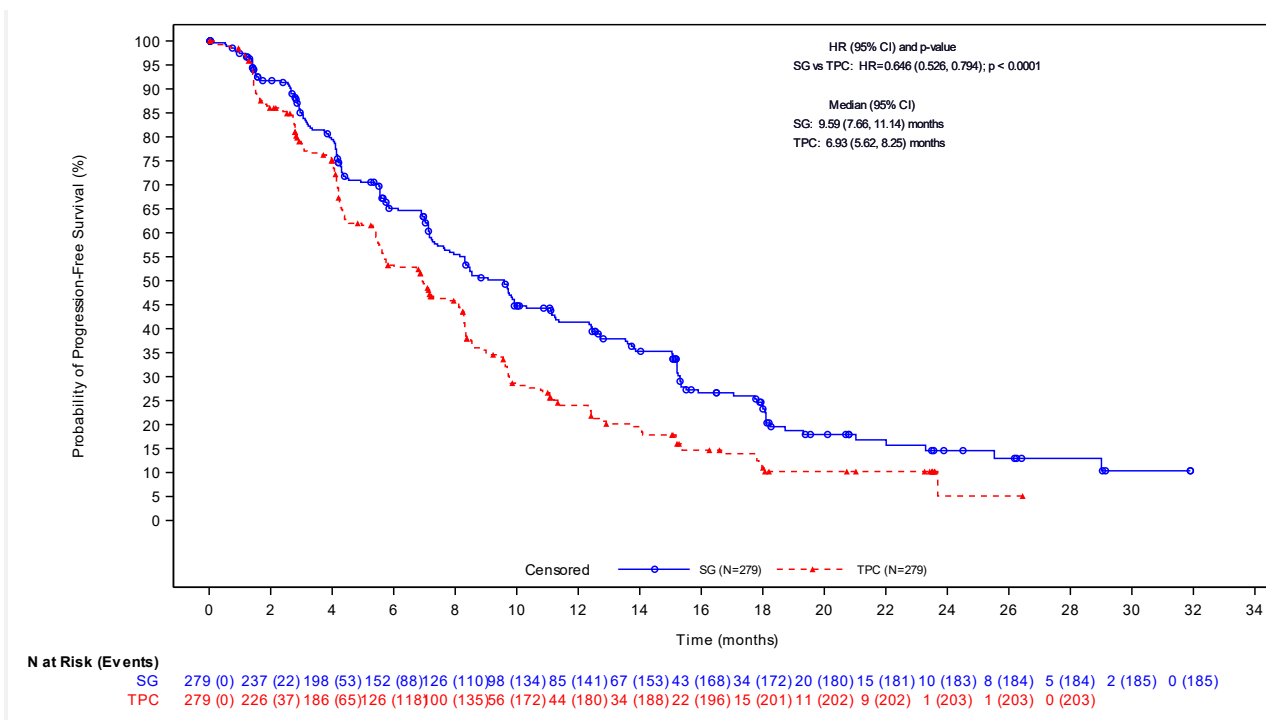
**Table 34 PFS by BICR using RECIST v1.1 at OS IA1 (ITT) – DCO 27 October 2025**

|                                                                                       | <b>SG<br/>(N = 279)</b>   | <b>TPC<br/>(N = 279)</b> |
|---------------------------------------------------------------------------------------|---------------------------|--------------------------|
| Number (%) of Participants with Events                                                | 185 (66.3%)               | 203 (72.8%)              |
| Disease Progression (PD)                                                              | 165 (59.1%)               | 194 (69.5%)              |
| Death                                                                                 | 20 (7.2%)                 | 9 (3.2%)                 |
| Number (%) of Participants Censored                                                   | 94 (33.7%)                | 76 (27.2%)               |
| PD after Starting New Anti-Cancer Therapy                                             | 1 (0.4%)                  | 1 (0.4%)                 |
| PD right after $\geq 2$ Consecutive Missing and/or Not Evaluable Tumor Assessments    | 2 (0.7%)                  | 3 (1.1%)                 |
| Death after Starting New Anti-Cancer Therapy                                          | 24 (8.6%)                 | 16 (5.7%)                |
| Death right after $\geq 2$ Consecutive Missing and/or Not Evaluable Tumor Assessments | 4 (1.4%)                  | 6 (2.2%)                 |
| No PD and No Death without New Anti-Cancer Therapy                                    | 39 (14.0%)                | 25 (9.0%)                |
| No PD and No Death with New Anti-Cancer Therapy                                       | 19 (6.8%)                 | 19 (6.8%)                |
| No Baseline or Postbaseline Evaluable Assessment <sup>a</sup>                         | 5 (1.8%)                  | 6 (2.2%)                 |
| Kaplan-Meier Estimate of PFS (Months) (95% CI) <sup>b</sup>                           |                           |                          |
| <b>Median</b>                                                                         | <b>9.59</b> (7.66, 11.14) | <b>6.93</b> (5.62, 8.25) |
| Kaplan-Meier Estimate of PFS Rate (95% CI) <sup>c</sup>                               |                           |                          |
| At 3 Months                                                                           | 0.850 (0.801, 0.888)      | 0.786 (0.732, 0.831)     |
| At 6 Months                                                                           | 0.651 (0.588, 0.706)      | 0.532 (0.469, 0.592)     |

|                                                                                  | <b>SG<br/>(N = 279)</b>     | <b>TPC<br/>(N = 279)</b> |
|----------------------------------------------------------------------------------|-----------------------------|--------------------------|
| At 9 Months                                                                      | 0.506 (0.441, 0.567)        | 0.355 (0.294, 0.417)     |
| At 12 Months                                                                     | 0.414 (0.350, 0.476)        | 0.240 (0.185, 0.299)     |
| At 18 Months                                                                     | 0.240 (0.182, 0.302)        | 0.110 (0.069, 0.162)     |
| Stratified Log-rank p-value of SG vs TPC <sup>d</sup>                            | <0.0001                     |                          |
| Stratified <b>Hazard Ratio</b> of SG vs TPC (95% CI) from Cox Model <sup>d</sup> | <b>0.646</b> (0.526, 0.794) |                          |

- a Censoring due to no baseline or no postbaseline evaluable assessment does not include death event before the second scheduled visit postbaseline.
- b PFS (months) = (date of events or censoring – date of randomization + 1) / 30.4375. The 95% CI is based on log-log transformation.
- c PFS rate is the proportion of participants alive without PD.
- d The two-sided *P* value is from stratified log-rank test and the hazard ratio with 95% CIs are calculated using Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).

**Figure 24 Plot of PFS by BICR Using RECIST v1.1 at OS IA1 (ITT) – DCO 27 October 2025**



### Secondary Efficacy Endpoints

At the time of the PFS primary analysis (DCO 02 April 2025), descriptive analyses are provided for the key secondary endpoints of OS, ORR, mean change from baseline in the physical functioning domain of the EORTC QLQ-C30 at Week 25, and median TTD in the fatigue domain of the EORTC QLQ C30. Additional secondary endpoints included DOR and TTR.

## Overall Survival

Descriptive analysis of OS at the time of primary analysis for PFS

**Table 35 Overall Survival (ITT) – DCO 02 April 2025**

|                                                                                  | <b>SG<br/>(N = 279)</b>     | <b>TPC<br/>(N = 279)</b> |
|----------------------------------------------------------------------------------|-----------------------------|--------------------------|
| Number (%) of Participants with <b>Events</b> (Death)                            | 103 (36.9%)                 | 103 (36.9%)              |
| Number (%) of Participants Censored                                              | 176 (63.1%)                 | 176 (63.1%)              |
| Ongoing <sup>a</sup>                                                             | 169 (60.6%)                 | 165 (59.1%)              |
| Discontinued Study                                                               | 7 (2.5%)                    | 11 (3.9%)                |
| Kaplan-Meier Estimate of OS (Months) (95% CI) <sup>b</sup>                       |                             |                          |
| <b>Median</b>                                                                    | <b>21.45</b> (17.71, NR)    | <b>20.24</b> (18.23, NR) |
| Stratified <b>Hazard Ratio</b> of SG vs TPC (95% CI) from Cox Model <sup>c</sup> | <b>0.985</b> (0.748, 1.297) |                          |
| Duration of <b>OS Follow-up</b> (Months) <sup>d</sup>                            |                             |                          |
| Median                                                                           | 13.31                       | 13.14                    |

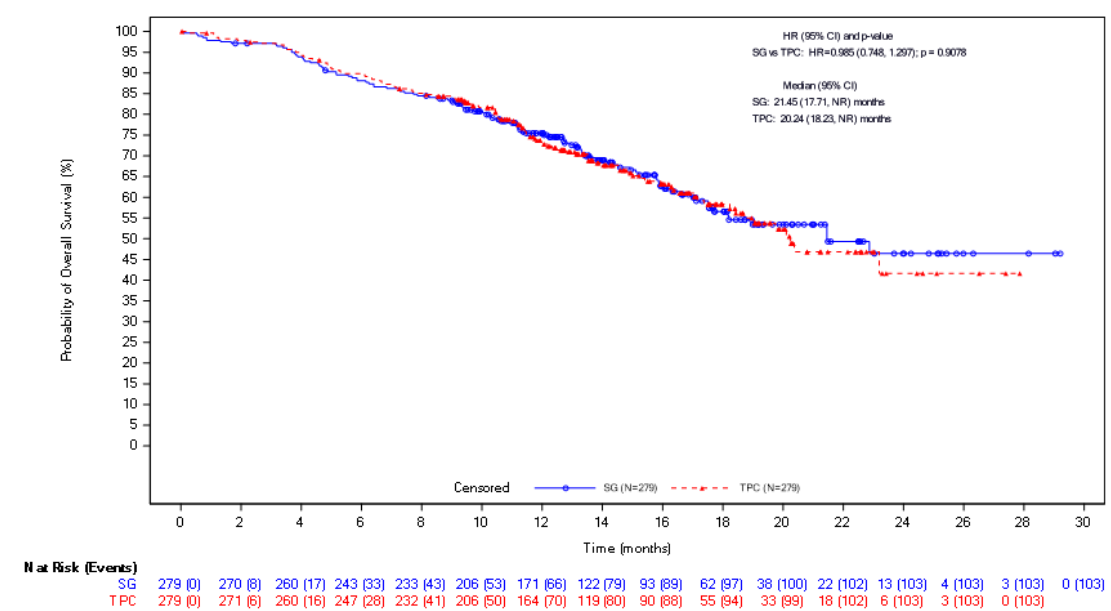
a Ongoing participants are those who have not discontinued participation in the study by the data cutoff date.

b OS (months) = (date of death or censoring - date of randomization + 1) / 30.4375. The 95% CI is based on log-log transformation

c Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).

d Duration of OS follow-up (months) = (date of death or censoring - date of randomization + 1) / 30.4375.

**Figure 25 KM Plot of OS (ITT) – DCO 02 April 2025**



**OS IA1** (First interim analysis of OS) - DCO 27 Oct 2025**Table 36 Overall Survival at OS IA1 – DCO 27 October 2025**

|                                                                                  | <b>SG<br/>(N = 279)</b>     | <b>TPC<br/>(N = 279)</b>    |
|----------------------------------------------------------------------------------|-----------------------------|-----------------------------|
| Number (%) of Participants with Events (Death)                                   | 139 (49.8%)                 | 144 (51.6%)                 |
| Number (%) of Participants Censored                                              | 140 (50.2%)                 | 135 (48.4%)                 |
| Ongoing <sup>a</sup>                                                             | 132 (47.3%)                 | 122 (43.7%)                 |
| Discontinued Study                                                               | 8 (2.9%)                    | 13 (4.7%)                   |
| Kaplan-Meier Estimate of OS (Months) (95% CI) <sup>b</sup>                       |                             |                             |
| <b>Median</b>                                                                    | <b>21.45</b> (18.86, 26.55) | <b>21.26</b> (18.69, 25.17) |
| Kaplan-Meier Estimate of OS Rate (95% CI)                                        |                             |                             |
| At 12 Months                                                                     | 0.754 (0.699, 0.801)        | 0.733 (0.677, 0.782)        |
| At 18 Months                                                                     | 0.594 (0.533, 0.650)        | 0.585 (0.523, 0.641)        |
| At 24 Months                                                                     | 0.452 (0.385, 0.517)        | 0.454 (0.387, 0.519)        |
| At 30 Months                                                                     | 0.405 (0.325, 0.484)        | 0.330 (0.236, 0.427)        |
| Stratified Log-rank <b>p-value</b> of SG vs TPC <sup>c</sup>                     | 0.6860                      |                             |
| Stratified <b>Hazard Ratio</b> of SG vs TPC (95% CI) from Cox Model <sup>d</sup> | <b>0.953</b> (0.755, 1.205) |                             |
| Duration of <b>OS Follow-up</b> (Months) <sup>e</sup>                            |                             |                             |
| Median                                                                           | 17.74                       | 17.64                       |
| Min, Max                                                                         | 0.07, 36.04                 | 0.03, 34.69                 |

Number of OS events is 283 at the time of first OS interim analysis, when two-sided nominal alpha = 0.0168 based on Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach.

a Ongoing participants are those who have not discontinued participation in the study by the data cutoff date.

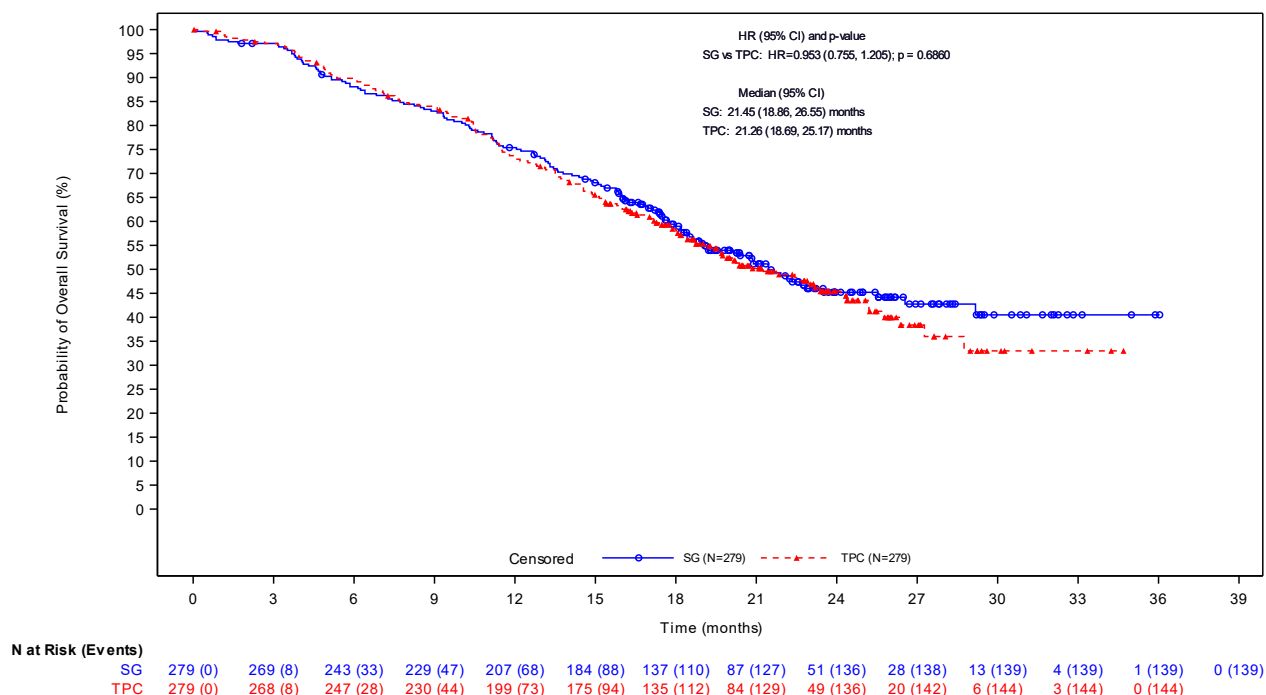
b OS (months) = (date of death or censoring – date of randomization + 1) / 30.4375. The 95% CI is based on log-log transformation.

c The two-sided *P* value is from stratified log-rank test, adjusted for randomization stratification factors (IWRs).

d Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (IWRs).

e Duration of OS follow-up (months) = (date of death or censoring – date of randomization + 1) / 30.4375.

**Figure 26 KM Plot of OS at OS IA1 – DCO 27 October 2025**



## Objective Response Rate

**Table 37 ORR and CBR by BICR using RECIST v1.1 (ITT) - DCO 02 April 2025**

|                                                              | <b>SG<br/>(N = 279)</b>     | <b>TPC<br/>(N = 279)</b>    |
|--------------------------------------------------------------|-----------------------------|-----------------------------|
| Best Overall Response ( <b>BOR</b> )                         |                             |                             |
| Complete Response (CR)                                       | 20 (7.2%)                   | 15 (5.4%)                   |
| Partial Response (PR)                                        | 115 (41.2%)                 | 112 (40.1%)                 |
| Stable Disease (SD)                                          | 113 (40.5%)                 | 101 (36.2%)                 |
| SD ≥ 6 months                                                | 37 (13.3%)                  | 32 (11.5%)                  |
| Progressive Disease (PD)                                     | 14 (5.0%)                   | 36 (12.9%)                  |
| Not Evaluable (NE)                                           | 17 (6.1%)                   | 15 (5.4%)                   |
| Objective Response Rate ( <b>ORR</b> ) (95% CI) <sup>a</sup> | <b>48.4%</b> (42.4%, 54.4%) | <b>45.5%</b> (39.6%, 51.6%) |
| Responders (CR+PR)                                           | 135 (48.4%)                 | 127 (45.5%)                 |
| Non-responders (SD+PD+NE)                                    | 144 (51.6%)                 | 152 (54.5%)                 |
| Stratified <b>Odds Ratio</b> for ORR of SG vs TPC (95% CI)   | <b>1.122</b> (0.804, 1.566) |                             |
| Clinical Benefit Rate ( <b>CBR</b> ) (95% CI) <sup>b</sup>   | 61.6% (55.7%, 67.4%)        | 57.0% (51.0%, 62.9%)        |
| Responders (CR + PR + SD ≥ 6 months)                         | 172 (61.6%)                 | 159 (57.0%)                 |
| Non-responders (SD < 6 months + PD + NE)                     | 107 (38.4%)                 | 120 (43.0%)                 |
| Stratified Odds Ratio for CBR of SG vs TPC (95% CI)          | 1.215 (0.866, 1.705)        |                             |

<sup>a</sup> ORR is the proportion of participants who achieved best overall response of CR/PR. The 95% CI is based on Clopper-Pearson method.

<sup>b</sup> CBR is defined as the proportion of participants who achieved best overall response of CR/PR or durable SD with duration ≥ 6 months. The 95% CI is based on Clopper-Pearson method.

BOR is derived based on overall response per BICR at each tumor assessment according to RECIST v1.1. Response of CR/PR is confirmed at least 4 weeks after initial documentation of response, SD requires at least 35 days on

study since randomization to be classified as SD. Participants without any evaluable post-baseline tumor assessment are included in Not Evaluable.

**Table 38 ORR and CBR by BICR using RECIST v1.1 at OS IA1 - DCO 27 October 2025**

| <b>Efficacy Endpoints</b>                                | <b>SG<br/>(N = 279)</b> | <b>TPC<br/>(N = 279)</b> |
|----------------------------------------------------------|-------------------------|--------------------------|
| <b>Objective Response Rate per BICR</b>                  |                         |                          |
| ORR (%) (95% CI) <sup>e</sup>                            | 48.4% (42.4%, 54.4%)    | 45.9% (39.9%, 51.9%)     |
| Stratified Odds Ratio for ORR of SG vs TPC (95% CI)      | 1.106 (0.793, 1.543)    |                          |
| <b>Clinical Benefit Rate (CBR)</b> (95% CI) <sup>f</sup> | 61.3% (55.3%, 67.0%)    | 57.0% (51.0%, 62.9%)     |
| Stratified Odds Ratio for CBR of SG vs TPC (95% CI)      | 1.197 (0.853, 1.679)    |                          |

### Duration of response

**Table 39 DOR and Time to Response by BICR Using RECIST v1.1 in Participants with Confirmed CR or PR (DCO 02 April 2025)**

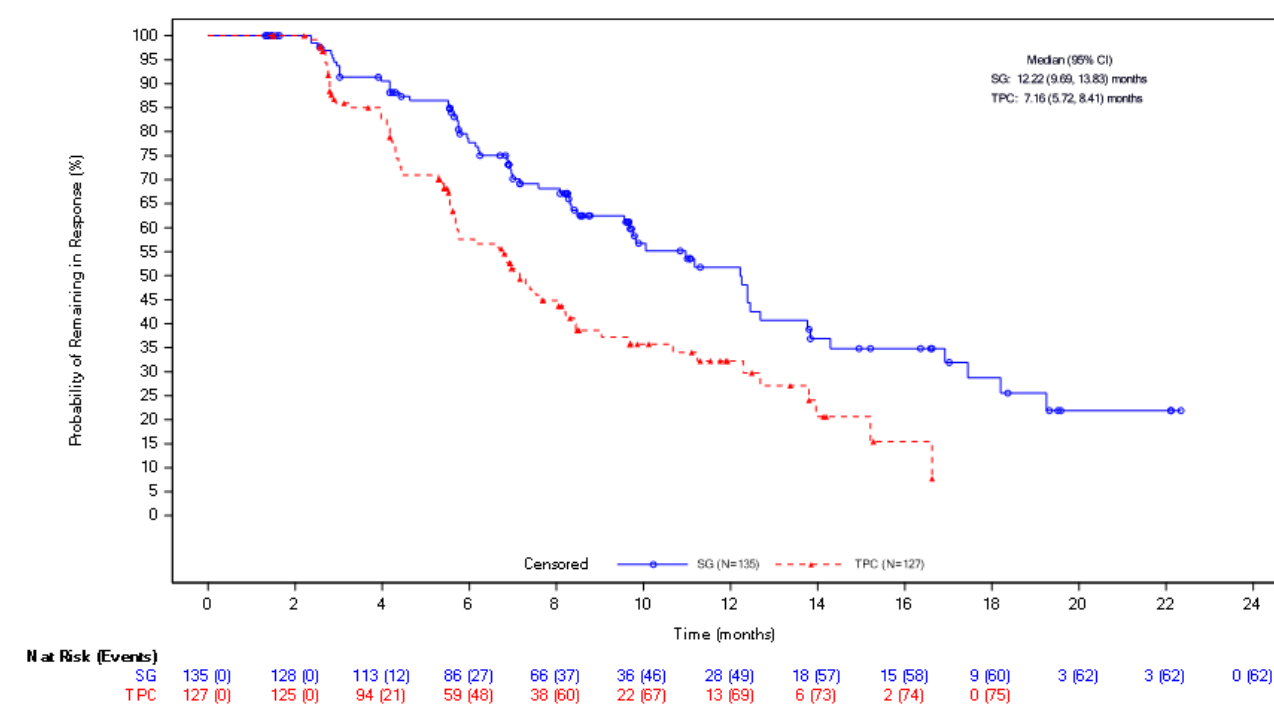
|                                                                    | <b>SG<br/>(N = 135)</b>    | <b>TPC<br/>(N = 127)</b> |
|--------------------------------------------------------------------|----------------------------|--------------------------|
| Number (%) of Participants with Events                             | 62 (45.9%)                 | 75 (59.1%)               |
| Disease Progression (PD)                                           | 60 (44.4%)                 | 74 (58.3%)               |
| Death                                                              | 2 (1.5%)                   | 1 (0.8%)                 |
| Number (%) of Participants Censored                                | 73 (54.1%)                 | 52 (40.9%)               |
| Kaplan-Meier Estimate of <b>DOR</b> (Months) (95% CI) <sup>a</sup> |                            |                          |
| <b>Median</b>                                                      | <b>12.22</b> (9.69, 13.83) | <b>7.16</b> (5.72, 8.41) |
| Kaplan-Meier Estimate of DOR Rate (95% CI)                         |                            |                          |
| At 6 Months                                                        | 0.777 (0.692, 0.842)       | 0.576 (0.478, 0.661)     |
| At 9 Months                                                        | 0.625 (0.526, 0.709)       | 0.386 (0.289, 0.482)     |
| At 12 Months                                                       | 0.518 (0.407, 0.617)       | 0.322 (0.226, 0.422)     |
| <b>Time to Response</b> (Months) <sup>b</sup>                      |                            |                          |
| N                                                                  | 135                        | 127                      |
| Mean (StD)                                                         | 2.6 (2.19)                 | 2.4 (1.32)               |
| Median                                                             | 1.6                        | 1.6                      |

a DOR (months) = [date of event or censoring - date of first confirmed CR or PR + 1] / 30.4375. For participants with confirmed CR or PR by BICR in the ITT Analysis Set.

b Time to response (months) = (date of first confirmed CR or PR - date of randomization + 1) / 30.4375.

Denominator of percentages is the number of participants with confirmed CR or PR by BICR in each treatment group in the ITT Analysis Set.

**Figure 27 KM Plot of DOR by BICR Using RECIST v1.1 in Participants With confirmed CR or PR (ITT)  
(DCO 02 April 2025)**



## PRO (Patient-Reported Outcomes)

Mean change from baseline in the **physical functioning** domain of the EORTC QLQ C30 at Week 25

**Table 40 Summary of Physical Functioning Domain of EORTC QLQ-C30 Scores at Baseline, Week 25, and Change from Baseline at Week 25 (ITT Analysis Set) – Excerpt from Table 8 SCE (DCO 02 April 2025)**

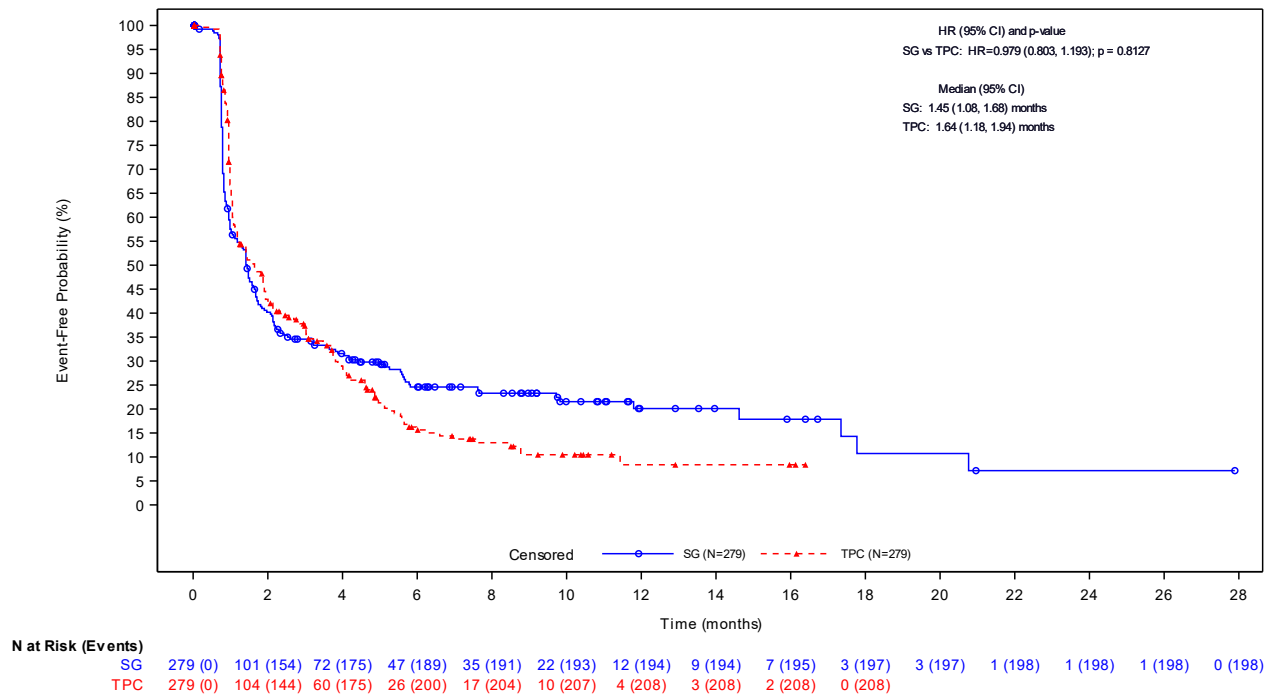
|                                                    | SG<br>(N = 279)   | TPC<br>(N = 279)   |
|----------------------------------------------------|-------------------|--------------------|
| <b>Baseline</b>                                    |                   |                    |
| N                                                  | 274               | 273                |
| Mean (StD)                                         | 79.0 (21.67)      | 80.5 (21.50)       |
| Median                                             | 86.7              | 86.7               |
| <b>Week 25</b>                                     |                   |                    |
| N                                                  | 160               | 136                |
| Mean (StD)                                         | 82.8 (18.11)      | 77.5 (20.75)       |
| Median                                             | 86.7              | 80.0               |
| <b>Change from Baseline at Week 25</b>             |                   |                    |
| N                                                  | 158               | 135                |
| Mean (StD)                                         | 1.1 (18.32)       | -6.2 (16.77)       |
| Median                                             | 0.0               | -6.7               |
| <b>LS-Means (SE)</b>                               | <b>0.3 (1.23)</b> | <b>-6.6 (1.28)</b> |
| 95% CI                                             | -2.10, 2.73       | -9.10, -4.05       |
| LS-Mean of Treatment <b>Difference</b> vs TPC (SE) | <b>6.9 (1.72)</b> |                    |
| 95% CI                                             | 3.50, 10.28       |                    |

LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error; StD = standard deviation;  
Analysis uses an MMRM including data from all visits up to and including Week 25.  
The MMRM model adjusted for the baseline score, treatment group, visit week, randomization stratification factors (IWRS), and the interaction between visit week and treatment group as fixed effects.

Time to Deterioration (TTD) of **fatigue** domain of the EORTC QLQ C30

Deterioration was defined as a  $\geq 10$  points worsening from baseline in the fatigue domain.  
Median TTD in the fatigue domain of the EORTC QLQ-C30 was 1.45 (95% CI: 1.08, 1.68) months in the SG and 1.64 (95% CI: 1.18, 1.94) months in the TPC groups (HR: 0.979; 95% CI: 0.803, 1.193).

Figure 28 KM Plot of TTD of Fatigue Domain of the EORTC QLQ C30 (ITT) (DCO 02 April 2025)



TTD is defined as the time in months (30.4375 days) between randomization date and the date of assessment at which a participant experienced a deterioration ( $\geq 10$  points worsening from baseline in the fatigue domain) or death.

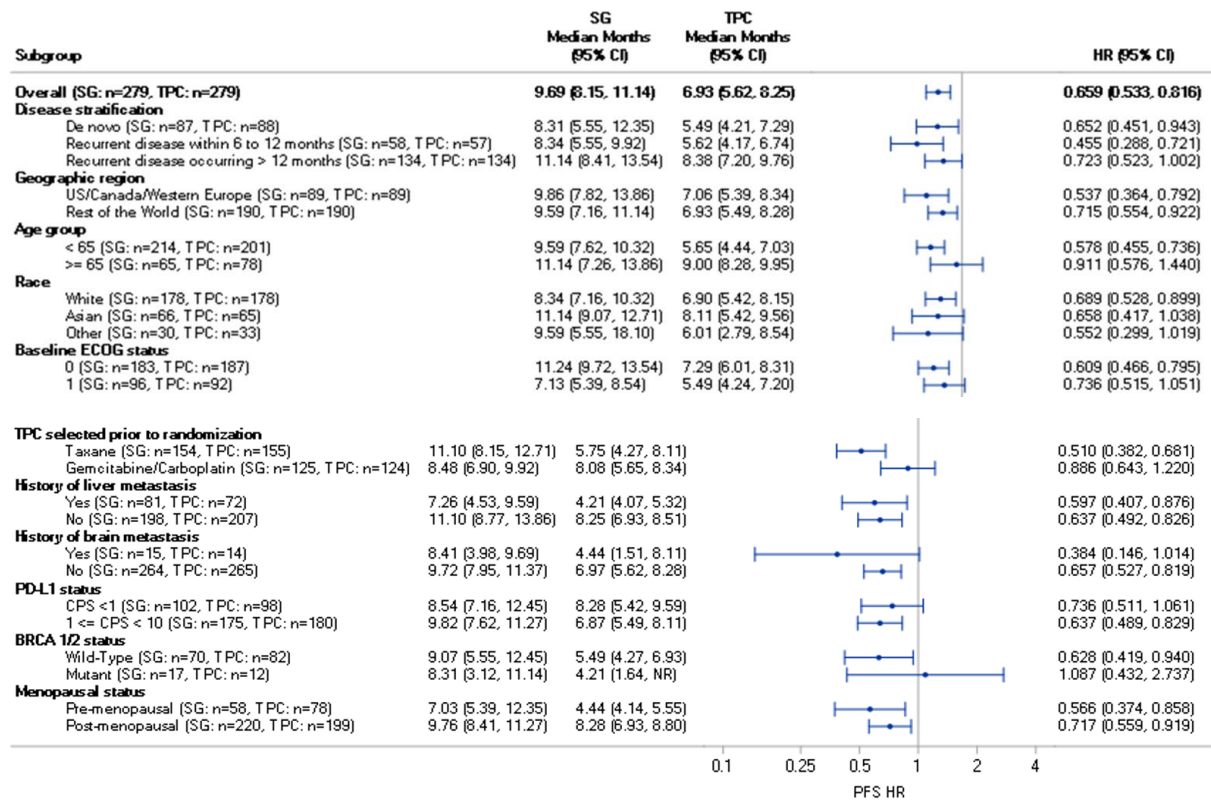
The two-sided *P* value is from stratified log-rank test and the HR with 95% CIs are calculated using Cox proportional hazards model, adjusted for randomization stratification factors collected in IWRS

## Ancillary analyses

### Subgroup Analyses

#### Subgroup Analysis of PFS

**Figure 29 Forest Plot of PFS by BICR for Subgroups at the primary PFS analysis (ITT) (DCO: 02 April 2025)**



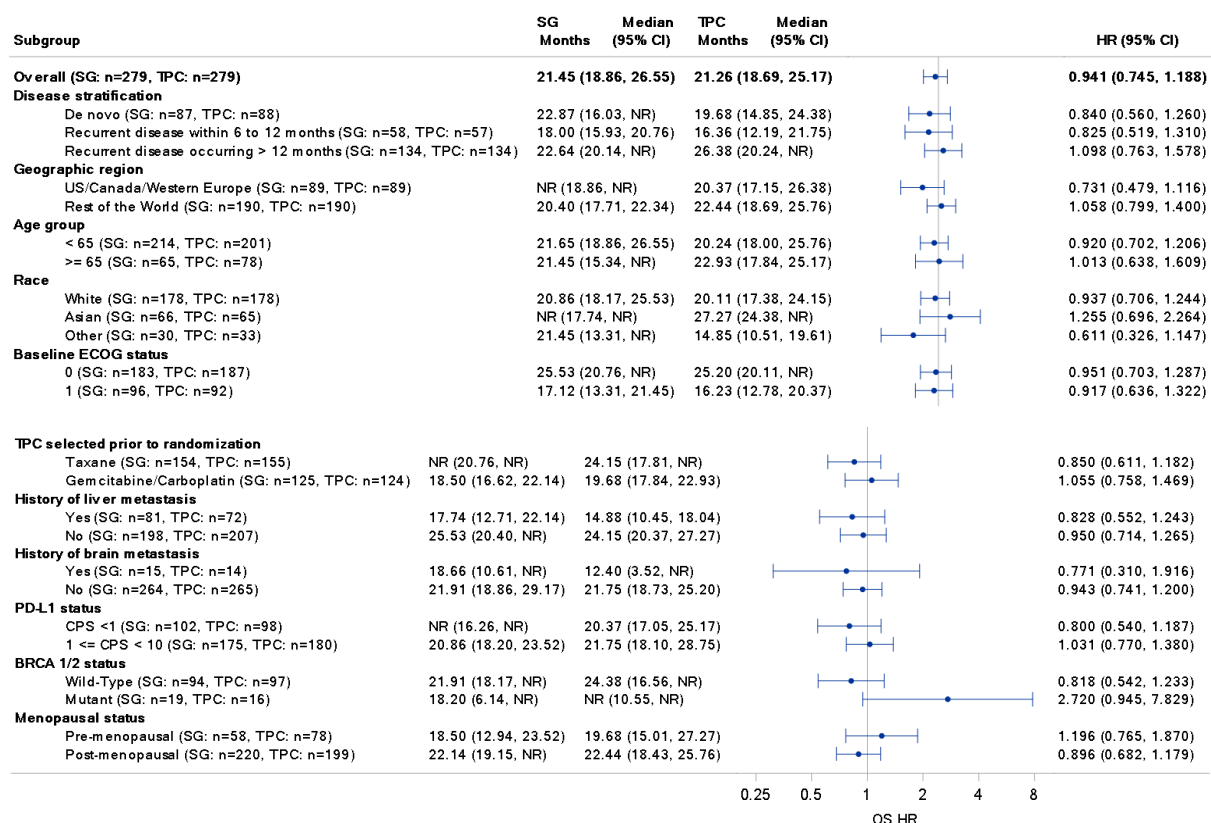
HR and 95% CIs are calculated using the unstratified Cox proportional hazards model without any adjustment. Disease stratification and geographic region are collected from IWRS.

Race subgroup "Other" includes American Indian or Alaska Native, Black, Native Hawaiian or Pacific Islander and Other collected in clinical database.

PD-L1 status subgroup "CPS ≥ 10" is not included in the forest plot due to small sample size.

## Subgroup analysis of overall survival

**Figure 30 Forest Plot of OS for Subgroups at OS IA1 – DCO 27 October 2025**



Median OS is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.

Hazard ratio and 95% CIs are calculated by unstratified Cox proportional hazards model without any adjustment. Efron method is used to handle ties.

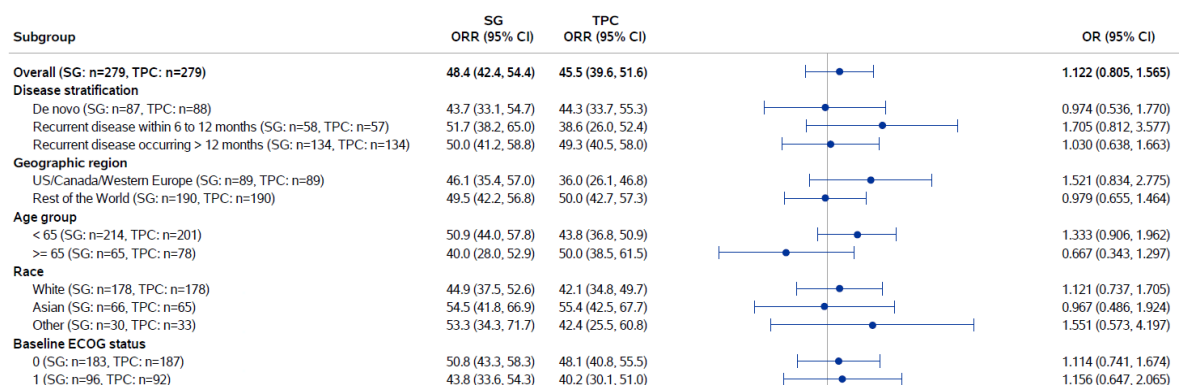
Disease stratification and geographic region are collected from interactive web response system (IWRs).

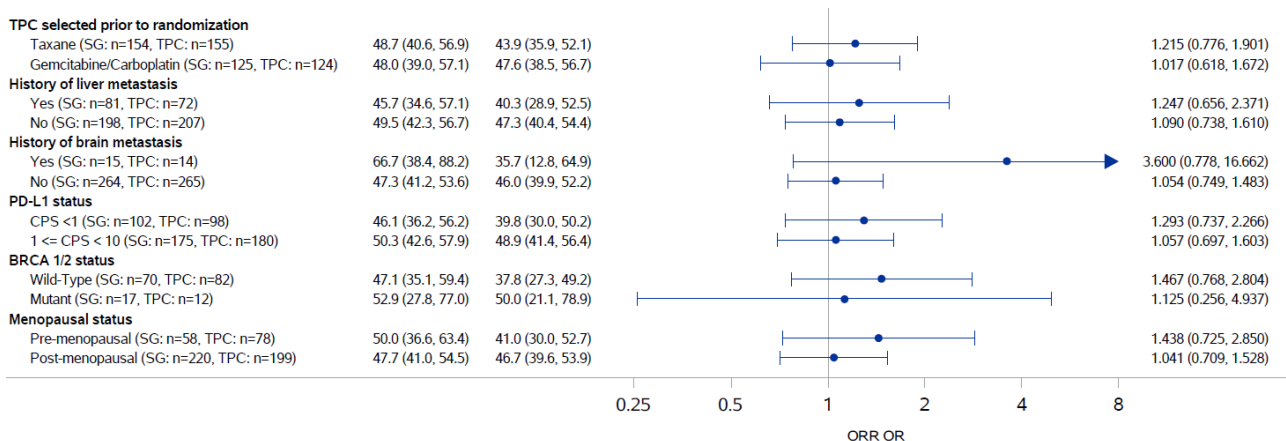
Race subgroup "Other" includes American Indian/Alaska Native, Native Hawaiian/Pacific Islander and other as collected in clinical database.

PD-L1 status subgroup "CPS ≥ 10" is not included in the forest plot due to small sample size.

## Subgroup analyses of ORR

**Figure 31 Forest Plot of ORR by BICR for Subgroups (DCO: 02 April 2025)**



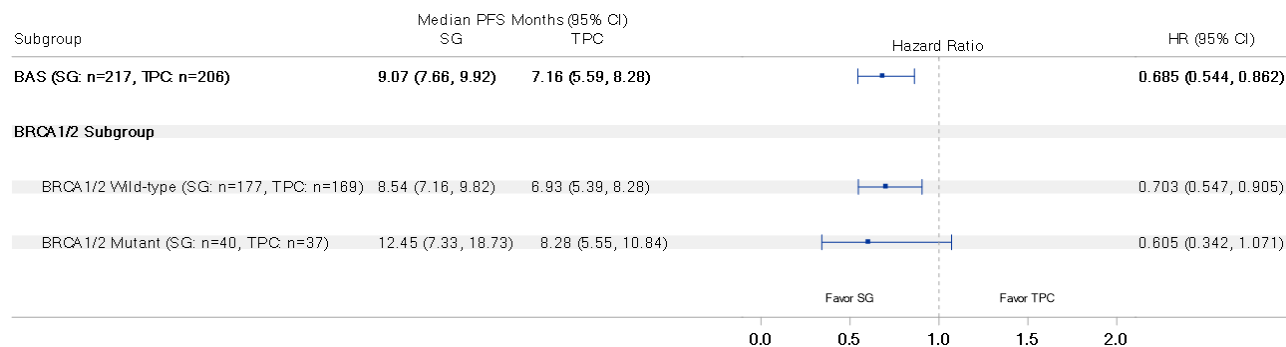


Odds ratio and 95% CI are calculated from unstratified Mantel-Haenszel estimates without any adjustment. Arrow indicates 95% confidence interval for the odds ratio is beyond the range of odds ratio in the forest plot. Disease stratification and geographic region are collected from IWRS (Interactive Web Response System). Race subgroup "Other" includes American Indian or Alaska Native, Black, Native Hawaiian or Pacific Islander and Other collected in clinical database. PD-L1 status subgroup "CPS ≥10" is not included in the forest plot due to small sample size.

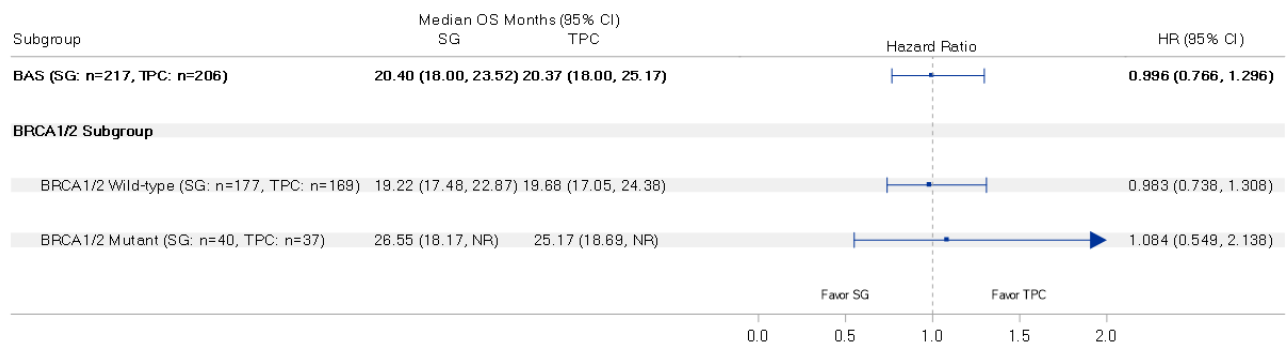
### Efficacy by BRCA central testing at OS IA1

An exploratory objective of the study as per the protocol was to conduct tumour whole exome sequencing (WES) analyses in a central laboratory. These analyses included participants with sufficient formalin-fixed paraffin-embedded (FFPE) tumour material for the WES-based BRCA assessment and the correlation of BRCA1/BRCA2 mutation status with efficacy endpoints. The Biomarker Analysis Set (BAS) comprised 423 participants (SG, n = 217 and TPC, n = 206), of which 18.2% had a BRCA1/2 mutation.

**Figure 32 Forest Plot of PFS by BICR Across BRCA 1 and 2 Subgroups (BAS) – DCO 27 October 2025**



BRCA1/2 status was derived from whole-exome sequencing using tumor samples. Survival time estimated with Kaplan-Meier method. Confidence Interval for median computed using the Brookmeyer-Crowley method. Hazard ratio and CI are derived from an unstratified Cox regression analysis, with treatment as the only predictor.

**Figure 33 Forest Plot of OS by BICR Across BRCA 1 and 2 Subgroups (BAS) – DCO 27 October 2025****Table 41 Summary of ORR by BICR Across BRCA 1 and 2 Subgroups (BAS) – DCO 27 October 2025**

| Outcome                 | BRCA1/2 Wild-type    |                | BRCA1/2 Mutant       |                | BRCA1/2 BAS          |                |
|-------------------------|----------------------|----------------|----------------------|----------------|----------------------|----------------|
|                         | SG (N = 177)         | TPC (N = 169)  | SG (N = 40)          | TPC (N = 37)   | SG (N = 217)         | TPC (N = 206)  |
| Objective Response Rate |                      |                |                      |                |                      |                |
| n (%)                   | 78 (44.1%)           | 73 (43.2%)     | 27 (67.5%)           | 26 (70.3%)     | 105 (48.4%)          | 99 (48.1%)     |
| 95% CI                  | (36.6%, 51.7%)       | (35.6%, 51.0%) | (50.9%, 81.4%)       | (53.0%, 84.1%) | (41.6%, 55.2%)       | (41.1%, 55.1%) |
| Odds Ratio (95% CI)     | 1.036 (0.677, 1.585) |                | 0.879 (0.334, 2.311) |                | 1.013 (0.692, 1.484) |                |

### Efficacy by age groups

Excerpts of forest plots of PFS, OS and ORR for the age cut-offs of 65 and 75 years at OS IA1 (DCO 27 October 25):

*Age group < 65 versus ≥ 65 years*

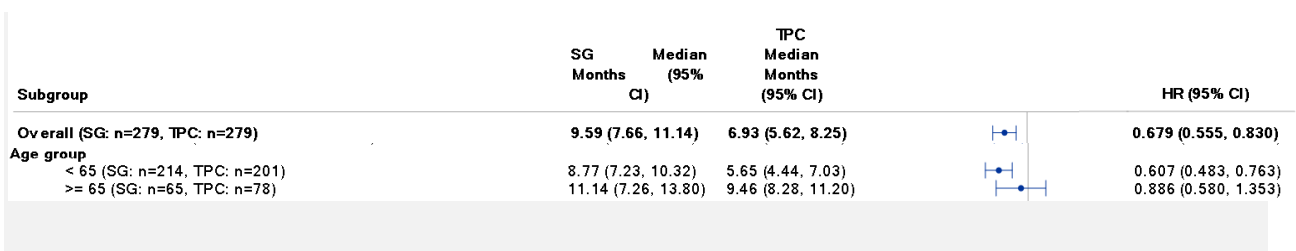
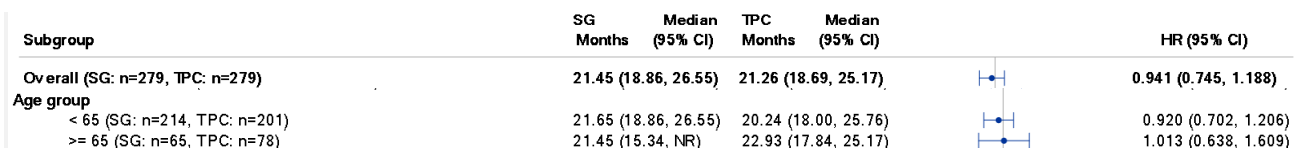
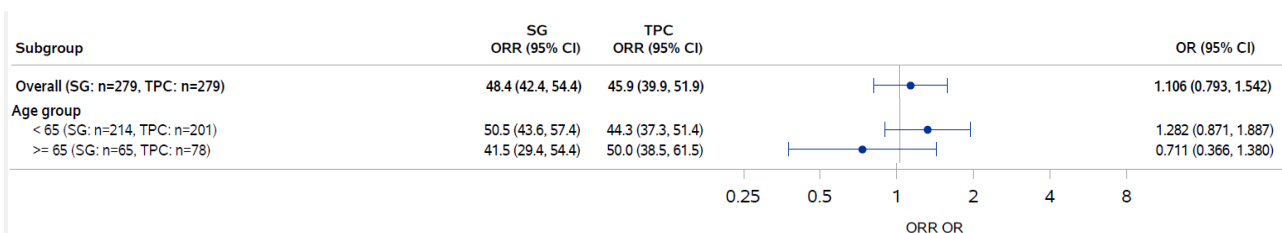
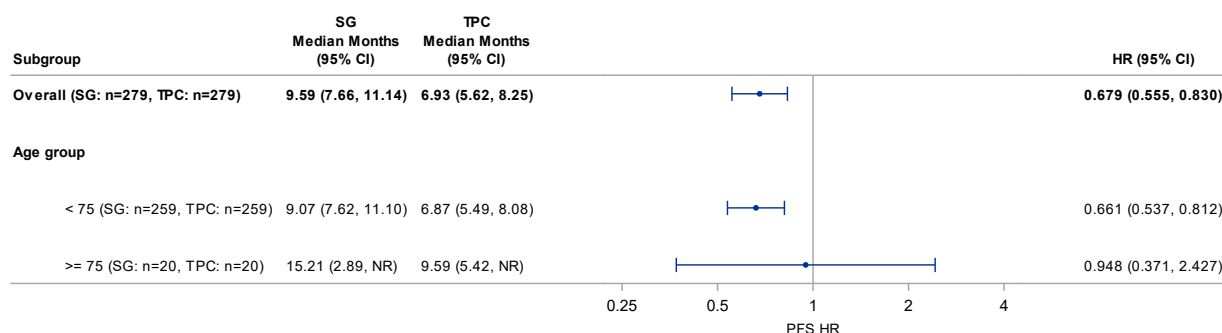
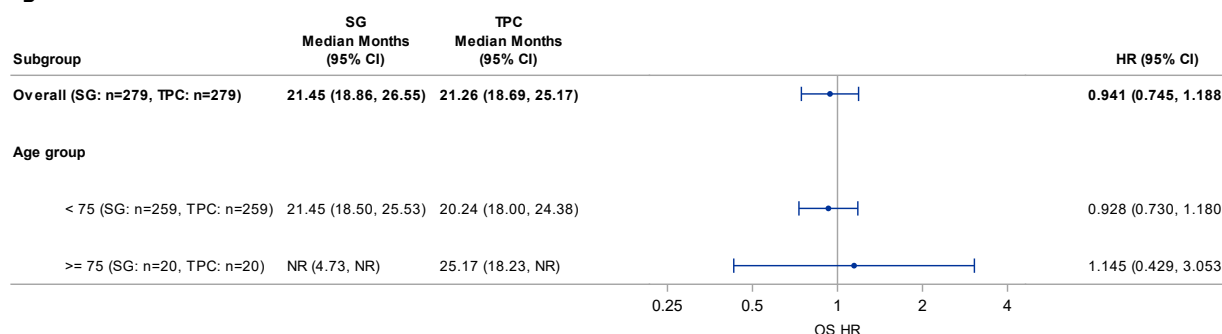
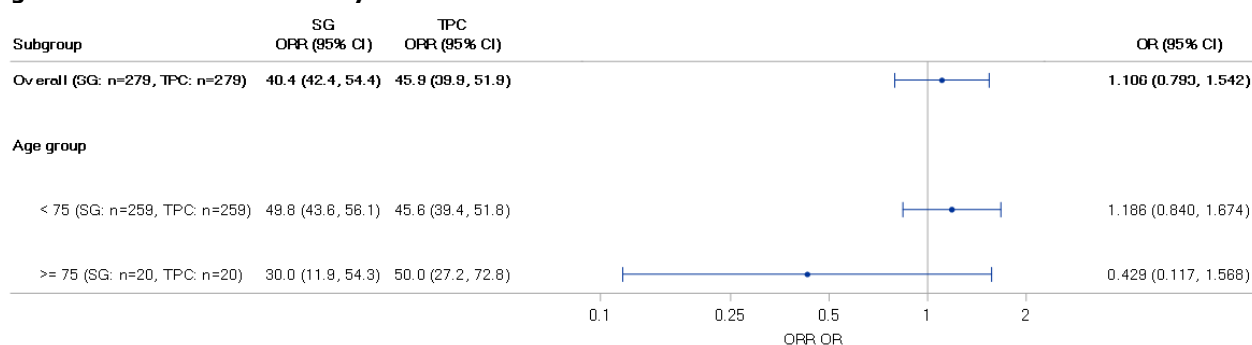
**Figure 34 Forest Plot of PFS by BICR****Figure 35 Forest Plot of OS**

**Figure 36 Forest Plot of ORR by BICR**

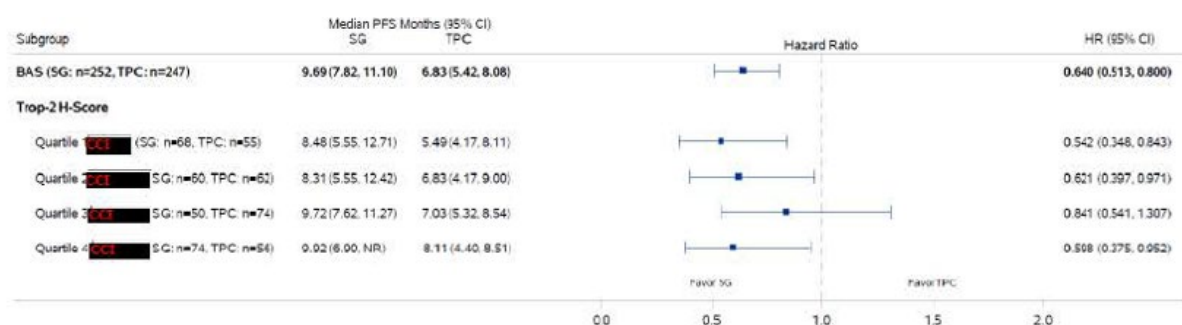
Age group < 75 versus ≥ 75 years

**Figure 37 Forest Plot of PFS by BICR****Figure 38 Forest Plot of OS****Figure 39 Forest Plot of ORR by BICR**

### Efficacy by Trop-2 expression (exploratory analysis)

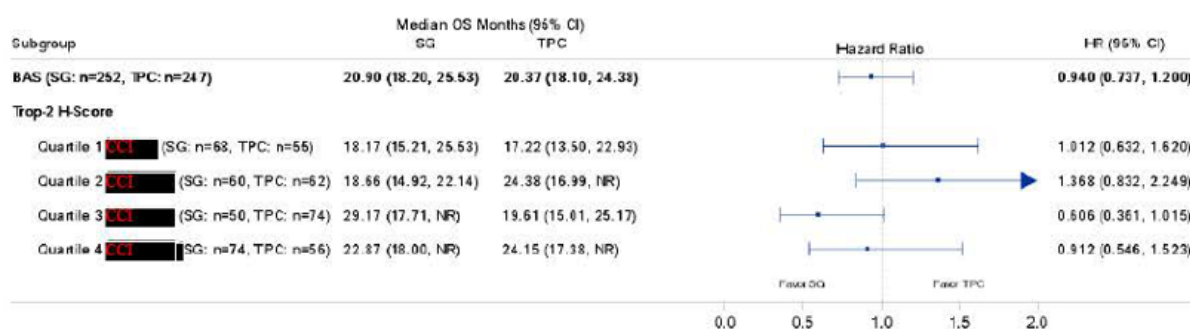
Evaluation of baseline trophoblast cell-surface antigen 2 (Trop-2) expression in fresh or archival tumour tissue as a biomarker for efficacy was an exploratory endpoint. Trop-2 expression in tumour tissue was assessed by immunohistochemistry (IHC) using a fit-for-purpose, validated EPR20043 formulation locked assay (FLA) at Roche Tissue Diagnostics (RTD). Trop-2 data were available from 499 participants (89.4%) in the Intent to Treat (ITT) Analysis Set = Biomarker Analysis Set (BAS).

**Figure 40 Forest Plot of PFS by BICR Across Trop-2 H-score Subgroups (Biomarker Analysis Set) (DCO: 02 April 2025)**



Trop-2 was tested by EPR20043 Formulation Locked Assay  
Survival time estimated with Kaplan-Meier method. Confidence Interval (CI) for median computed using the Brookmeyer-Crowley method.  
Hazard Ratio (HR) and Confidence Interval (CI) are derived from an unstratified Cox regression analysis, with treatment as the only predictor.

**Figure 41 Forest Plot of OS Across Trop-2 H-score Subgroups (Biomarker Analysis Set) (DCO: 27 October 2025)**



Trop-2 was tested by EPR20043 Formulation Locked Assay  
Survival time estimated with Kaplan-Meier method. Confidence Interval (CI) for median computed using the Brookmeyer-Crowley method.  
Hazard Ratio (HR) and Confidence Interval (CI) are derived from an unstratified Cox regression analysis, with treatment as the only predictor.

**Table 42 Summary of ORR by BICR and Investigator by Trop-2 H-Score Quartiles (BAS) (DCO: 02 April 2025)**

| Outcome                      | Quartile 1 [0, 184]     |                 | Quartile 2 [185, 239]   |                 | Quartile 3 [240, 283]   |                 | Quartile 4 [284, 300]   |                 |
|------------------------------|-------------------------|-----------------|-------------------------|-----------------|-------------------------|-----------------|-------------------------|-----------------|
|                              | SG<br>(N = 68)          | TPC<br>(N = 55) | SG<br>(N = 60)          | TPC<br>(N = 62) | SG<br>(N = 50)          | TPC<br>(N = 74) | SG<br>(N = 74)          | TPC<br>(N = 56) |
| <b>ORR (by BICR)</b>         |                         |                 |                         |                 |                         |                 |                         |                 |
| n (%)                        | 27 (39.7%)              | 22 (40.0%)      | 26 (43.3%)              | 28 (45.2%)      | 29 (58.0%)              | 37 (50.0%)      | 38 (51.4%)              | 24 (42.9%)      |
| 95% CI                       | (28.0%, 52.3%)          | (27.0%, 54.1%)  | (30.6%, 56.8%)          | (32.5%, 58.3%)  | (43.2%, 71.8%)          | (38.1%, 61.9%)  | (39.4%, 63.1%)          | (29.7%, 56.8%)  |
| Odds ratio (95% CI)          | 0.988<br>(0.478, 2.041) | —               | 0.929<br>(0.454, 1.898) | —               | 1.381<br>(0.670, 2.846) | —               | 1.407<br>(0.700, 2.830) | —               |
| <b>ORR (by investigator)</b> |                         |                 |                         |                 |                         |                 |                         |                 |
| n (%)                        | 32 (47.1%)              | 18 (32.7%)      | 27 (45.0%)              | 29 (46.8%)      | 23 (46.0%)              | 35 (47.3%)      | 42 (56.8%)              | 23 (41.1%)      |
| 95% CI                       | (34.8%, 59.6%)          | (20.7%, 46.7%)  | (32.1%, 58.4%)          | (34.0%, 59.9%)  | (31.8%, 60.7%)          | (35.6%, 59.3%)  | (44.7%, 68.2%)          | (28.1%, 55.0%)  |
| Odds ratio (95% CI)          | 1.827<br>(0.874, 3.820) | —               | 0.931<br>(0.457, 1.898) | —               | 0.949<br>(0.462, 1.949) | —               | 1.883<br>(0.932, 3.806) | —               |

BAS = Biomarker Analysis Set; BICR = blinded independent central review; CI = confidence interval; CR = complete response; FLA = formulation locked assay;  
ORR = objective response rate; PR = partial response; SG = sacituzumab govitecan; TPC = treatment of physician's choice; Trop-2 = trophoblast cell-surface antigen 2  
Trop-2 tested by EPR20043 FLA.  
Objective response rate is the proportion of participants who achieved a best overall response of CR/PR. The 95% CI is based on the Clopper-Pearson method.  
Odds ratio and 95% CI are derived from an unstratified model.

- **Supplementary analyses**

### Sensitivity Analyses

#### Sensitivity Analyses of PFS

**Table 43 Sensitivity analyses of PFS (Assessor's Table, excerpt from CSR Tables 14, 15.9.1.1.3 – 5; DCO: 02 April 2025)**

| Analysis                                                                                                                                                                                                                              | Summary statistics                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Primary analysis                                                                                                                                                                                                                      | Strat. HR = 0.62 (95% CI: 0.5, 0.78)<br>Median PFS 9.69 (8.2, 11.1) vs 6.93 (5.6, 8.3) months  |
| <b>Sensitivity analyses</b>                                                                                                                                                                                                           |                                                                                                |
| 1. Same as primary analysis except that objective documented PD or death were counted as events regardless of missed study visits or initiation of new anti-cancer therapy                                                            | Strat. HR = 0.63 (95% CI: 0.52, 0.78)<br>Median PFS 9.69 (8.2, 11.1) vs 6.93 (5.6, 8.2) months |
| 2. Same as primary analysis except that discontinuation of treatment or initiation of alternative anticancer treatment, whichever occurred earlier, was considered to be a PD event for participants censored in the primary analysis | Strat. HR = 0.66 (95% CI 0.55 to 0.81)<br>Median PFS 7.62 (6.7, 8.7) vs 5.7 (5.3, 6.8) months  |
| 3. PFS by <b>Investigator Assessment</b>                                                                                                                                                                                              | Strat. HR: 0.640 (95% CI: 0.52, 0.79)<br>Median PFS 9.63 (8.3, 10.6) vs 6.83 (5.6, 7.2) months |

#### Sensitivity analyses of overall survival

At the time of OS IA1, a total of 154 participants (55.2%) in the TPC group received SG in the second-line setting; 125 of these 154 participants received SG during the crossover phase of the study and the remainder received commercial SG in the second-line setting.

To adjust for the effect of crossover on OS, prespecified sensitivity analyses using 3 simplified 2-stage model [TSE], inverse probability of censoring weighting [IPCW], and rank preserving structural failure time model [RPSFT]) were performed, in which the crossover to SG by participants in the TPC group per protocol was considered (**n = 125**).

Using the TSE method, 139 (49.8%) and 82 (29.4%) participants in the SG and TPC groups had OS events after re-censoring survival times for participants in the TPC group and the adjusted OS HR (95% CI) of SG versus TPC was 0.622 (0.442, 0.859).

Using the IPCW method, 139 (49.8%) and 81 (29.0%) participants in the SG and TPC groups had OS events after censoring crossover participants in the TPC group. The adjusted OS HR (95% CI) of SG versus TPC was 0.727 (0.518, 1.048).

Using the RPSFT method, 139 (49.8%) and 141 (50.5%) participants in the SG and TPC groups had OS events after re-censoring survival times for participants in the TPC. The adjusted OS HR (95% CI) of SG versus TPC was 0.908 (0.723, 1.133).

In addition, exploratory analyses were performed to adjust for the treatment switch to second line SG in the TPC group (including participants in the TPC group who received SG provided by the study in the crossover phase and also those who received SG through commercial means in the second line [**n = 154**]) which resulted in similar HR point estimates.

## Sensitivity analyses of ORR

**Table 44 ORR by Investigator Assessment using RECIST v1.1 (ITT) (DCO: 02 April 2025)**

|                                                              | <b>SG<br/>(N = 279)</b> | <b>TPC<br/>(N = 279)</b> |
|--------------------------------------------------------------|-------------------------|--------------------------|
| Best Overall Response ( <b>BOR</b> )                         |                         |                          |
| Complete Response (CR)                                       | 16 (5.7%)               | 13 (4.7%)                |
| Partial Response (PR)                                        | 121 (43.4%)             | 107 (38.4%)              |
| Stable Disease (SD)                                          | 104 (37.3%)             | 103 (36.9%)              |
| SD ≥ 6 months                                                | 47 (16.8%)              | 44 (15.8%)               |
| Progressive Disease (PD)                                     | 21 (7.5%)               | 41 (14.7%)               |
| Not Evaluable (NE)                                           | 17 (6.1%)               | 15 (5.4%)                |
| Objective Response Rate ( <b>ORR</b> ) (95% CI) <sup>a</sup> | 49.1% (43.1%, 55.1%)    | 43.0% (37.1%, 49.0%)     |
| Responders (CR+PR)                                           | 137 (49.1%)             | 120 (43.0%)              |
| Non-responders (SD+PD+NE)                                    | 142 (50.9%)             | 159 (57.0%)              |
| Stratified Odds Ratio for ORR of SG vs TPC (95% CI)          | 1.277 (0.916, 1.781)    |                          |
| Clinical Benefit Rate ( <b>CBR</b> ) (95% CI) <sup>b</sup>   | 65.9% (60.1%, 71.5%)    | 58.8% (52.8%, 64.6%)     |
| Responders (CR + PR + SD ≥ 6 months)                         | 184 (65.9%)             | 164 (58.8%)              |
| Non-responders (SD < 6 months + PD + NE)                     | 95 (34.1%)              | 115 (41.2%)              |
| Stratified Odds Ratio for CBR of SG vs TPC (95% CI)          | 1.358 (0.964, 1.913)    |                          |

**Table 45 Concordance of ORR between BICR and investigator assessment**

| Blinded Independent Central Review |               |               |              |
|------------------------------------|---------------|---------------|--------------|
|                                    | Responder [a] | Non-responder | Total        |
| <b>SG (N = 279)</b>                |               |               |              |
| Investigator Assessment            |               |               |              |
| Responder [a]                      | 112 (40.1%)   | 25 (9.0%)     | 137 (49.1%)  |
| Non-responder                      | 23 (8.2%)     | 119 (42.7%)   | 142 (50.9%)  |
| Total                              | 135 (48.4%)   | 144 (51.6%)   | 279 (100.0%) |
| Overall Concordance [b]            |               |               | 231 (82.8%)  |
| <b>TPC (N = 279)</b>               |               |               |              |
| Investigator Assessment            |               |               |              |
| Responder [a]                      | 105 (37.6%)   | 15 (5.4%)     | 120 (43.0%)  |
| Non-responder                      | 22 (7.9%)     | 137 (49.1%)   | 159 (57.0%)  |
| Total                              | 127 (45.5%)   | 152 (54.5%)   | 279 (100.0%) |
| Overall Concordance [b]            |               |               | 242 (86.7%)  |
| <b>Total (N = 558)</b>             |               |               |              |
| Investigator Assessment            |               |               |              |
| Responder [a]                      | 217 (38.9%)   | 40 (7.2%)     | 257 (46.1%)  |
| Non-responder                      | 45 (8.1%)     | 256 (45.9%)   | 301 (53.9%)  |
| Total                              | 262 (47.0%)   | 296 (53.0%)   | 558 (100.0%) |
| Overall Concordance [b]            |               |               | 473 (84.8%)  |

[a] Responder is defined as participants whose best overall response is CR (complete response) or PR (partial response).

[b] Overall concordance rate is the sum of percentages of participants whose central read matches investigator read in each of the response categories.

Sensitivity analyses of DOR with response assessed by the investigator was 9.69 months (95% CI: 8.41, 13.70) in the SG group versus 7.39 months (95% CI: 5.75, 9.03) in the TPC group.

## Exploratory Efficacy Analyses

### Progression-Free Survival on Next-Line Therapy (PFS2) at OS IA1

PFS2 was defined as the time from randomization to the first documented progression on next-line therapy per investigator assessment or death due to any cause, whichever occurred first.

**Table 46 PFS2 at OS IA1- DCO 27 October 2025**

|                                                                           | <b>SG<br/>(N = 279)</b>     | <b>TPC<br/>(N = 279)</b>    |
|---------------------------------------------------------------------------|-----------------------------|-----------------------------|
| Number (%) of Participants with Events                                    | 172 (61.6%)                 | 190 (68.1%)                 |
| Disease Progression (PD)                                                  | 86 (30.8%)                  | 129 (46.2%)                 |
| Death                                                                     | 86 (30.8%)                  | 61 (21.9%)                  |
| Number (%) of Participants Censored                                       | 107 (38.4%)                 | 89 (31.9%)                  |
| Kaplan-Meier Estimate of PFS2 (Months) (95% CI) <sup>a</sup>              |                             |                             |
| <b>Median</b>                                                             | <b>16.16</b> (14.82, 19.58) | <b>13.83</b> (12.48, 15.84) |
| Kaplan-Meier Estimate of PFS2 Rate (95% CI) <sup>b</sup>                  |                             |                             |
| At 3 Months                                                               | 0.971 (0.943, 0.986)        | 0.967 (0.938, 0.983)        |
| At 6 Months                                                               | 0.859 (0.812, 0.895)        | 0.869 (0.823, 0.903)        |
| At 9 Months                                                               | 0.764 (0.709, 0.810)        | 0.762 (0.706, 0.808)        |
| At 12 Months                                                              | 0.658 (0.598, 0.710)        | 0.586 (0.525, 0.642)        |
| At 18 Months                                                              | 0.466 (0.405, 0.525)        | 0.378 (0.319, 0.437)        |
| Stratified Log-rank p-value of SG vs TPC <sup>c</sup>                     | 0.0181                      |                             |
| Stratified Hazard Ratio of SG vs TPC (95% CI) from Cox Model <sup>c</sup> | 0.778 (0.632, 0.958)        |                             |

PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy based on investigator assessment of PD or death due to any cause, whichever occurs first. Next-line therapy is defined as the first new systemic anticancer therapy (including crossover treatment) initiated after discontinuation of study treatment regardless of end of treatment reason.

a Quantile of PFS2 is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.

b PFS2 rate is the proportion of participants alive without PD at the next line of therapy.

c The two-sided *P* value is from stratified log-rank test and the hazard ratio with 95% CIs are calculated using Cox proportional hazards model, adjusted for randomization stratification factors from interactive web response system (IWRS).

## Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 47 Summary of efficacy for trial GS-US-592-6238 (ASCENT-03)**

|                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                         |                                           |                           |                |                              |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------------------------|---------------------------|----------------|------------------------------|----------------|
| <p><b>Title:</b> A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Patients With Previously Untreated, Locally Advanced, Inoperable or Metastatic Triple-Negative Breast Cancer Whose Tumors Do Not Express PD-L1 or in Patients Previously Treated With Anti-PD-(L)1 Agents in the Early Setting Whose Tumors Do Express PD-L1</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                         |                                           |                           |                |                              |                |
| Study identifier                                                                                                                                                                                                                                                                                                                                                                             | <p>GS-US-592-6238 (ASCENT-03)</p> <p>EU CT No.:2023-504195-14</p> <p>ClinicalTrials.gov Identifier: NCT05382299</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                         |                                           |                           |                |                              |                |
| Design                                                                                                                                                                                                                                                                                                                                                                                       | <p>Study GS-US-592-6238 is an ongoing international, multicenter, open-label, randomized, Phase 3 study designed to compare the efficacy and safety of SG versus TPC in participants with locally advanced unresectable or metastatic triple-negative breast cancer (TNBC) who have not received previous systemic therapy for advanced disease and who are not candidates for programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors. This study enrolled participants with tumors that are PD-L1 negative (defined as having a tumor combined positive score [CPS] &lt; 10 using the PD-L1 immunohistochemistry [IHC] 22C3 pharmDx assay), and participants with tumors that are PD-L1 positive (defined as having a CPS ≥ 10) if they previously received a PD-1 or PD-L1 inhibitor in the neoadjuvant/adjuvant setting or have a comorbidity precluding treatment with a PD-1 or PD-L1 inhibitor. Participants presenting with de novo metastatic TNBC were eligible for this study and were capped at approximately 35% of all enrolled participants.</p> <p>Approximately 540 eligible participants were planned to be randomized in a 1:1 ratio to receive 1 of the following 2 treatments:</p> <ul style="list-style-type: none"> <li>• SG: 10 mg/kg intravenously (IV) on Days 1 and 8 of 21-day cycles</li> <li>• TPC: 21- or 28-day cycles</li> </ul> <p>The TPC was selected prior to randomization from 1 of the 3 allowed regimens: 1) paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8, and 15 of 28-day cycles; 2) nanoparticle albumin-bound (nab)-paclitaxel 100 mg/m<sup>2</sup> IV on Days 1, 8, and 15 of 28-day cycles; or 3) gemcitabine 1000 mg/m<sup>2</sup> IV with carboplatin area under the curve (AUC) 2 IV on Days 1 and 8 of 21-day cycles.</p> <p>Randomization was stratified by the following factors:</p> <ul style="list-style-type: none"> <li>• De novo versus recurrent disease within 6 to 12 months from completion of treatment in the curative setting versus recurrent disease occurring &gt; 12 months from completion of treatment in the curative setting.</li> <li>• Treatment-free interval was defined as the time between completion of systemic neoadjuvant/adjuvant breast cancer therapy or surgery (whichever occurred last) and first local or distant recurrence. Adjuvant radiotherapy was not included in the 6-month interval.</li> <li>• Geographic region (United States/Canada/Western Europe versus rest of world)</li> </ul> <table border="1"> <tr> <td>Duration of main phase:</td><td>20 July 2022 – Present (study is ongoing)</td></tr> <tr> <td>Duration of Run-in phase:</td><td>not applicable</td></tr> <tr> <td>Duration of Extension phase:</td><td>not applicable</td></tr> </table> | Duration of main phase: | 20 July 2022 – Present (study is ongoing) | Duration of Run-in phase: | not applicable | Duration of Extension phase: | not applicable |
| Duration of main phase:                                                                                                                                                                                                                                                                                                                                                                      | 20 July 2022 – Present (study is ongoing)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                         |                                           |                           |                |                              |                |
| Duration of Run-in phase:                                                                                                                                                                                                                                                                                                                                                                    | not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                         |                                           |                           |                |                              |                |
| Duration of Extension phase:                                                                                                                                                                                                                                                                                                                                                                 | not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                         |                                           |                           |                |                              |                |
| Hypothesis                                                                                                                                                                                                                                                                                                                                                                                   | Superiority                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                         |                                           |                           |                |                              |                |

|                           |                                                                                                     |                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatments groups         | Sacituzumab govitecan (SG)                                                                          |                                                                              | <p>10 mg/kg intravenously (IV) on Days 1 and 8 of 21-day cycles</p> <p>Participants were treated until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, initiation of other anticancer therapy (including any investigational agent), or death. Treatment beyond BICR-verified PD per RECIST v1.1 was permitted if there was evidence of clinical benefit per the investigator and the participants was tolerating the study drug, if agreed upon by the investigator and the sponsor medical monitor. Long-term follow-up began at the time of the completion of the end of treatment visit, which occurred within 30 days (+ 7) after the last dose of study drug</p> <p>Number randomized = 279</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                           | <p>Treatment of Physician's choice (TPC)</p> <p>i.e, 1 of the following single-agent treatments</p> |                                                                              | <p>Gemcitabine 1000 mg/m<sup>2</sup> administered as an IV infusion with carboplatin AUC 2 administered as an IV infusion on Days 1 and 8 of 21-day cycles.</p> <p>OR Paclitaxel 90 mg/m<sup>2</sup> administered as an IV infusion on Days 1, 8, and 15 of 28-day cycles.</p> <p>OR nab-Paclitaxel 100 mg/m<sup>2</sup> administered as an IV infusion on Days 1, 8, and 15 of 28-day cycles.</p> <p>Participants were treated until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, initiation of other anticancer therapy (including any investigational agent), or death. Treatment beyond BICR-verified PD per RECIST v1.1 was permitted if there was evidence of clinical benefit per the investigator and the participants was tolerating the study drug, if agreed upon by the investigator and the sponsor medical monitor. Long-term follow-up began at the time of the completion of the end of treatment visit, which occurred within 30 days (+ 7) after the last dose of study drug.</p> <p>Participants who were randomized to the control group (TPC) were eligible to receive SG through the study in the crossover phase upon disease progression verified by BICR and upon meeting eligibility criteria</p> <p>Number randomized = 279</p> |
| Endpoints and definitions | Primary endpoint                                                                                    | Progression Free Survival (PFS) by blinded independent central review (BICR) | <p>Defined as the time from the date of randomization until the date of objective progressive disease (PD), as assessed by BICR per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), or death (whichever comes first).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|                                                 |                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                 | Secondary endpoint                                                                                                                                                                                                                                                                                                                                                                                    | Overall survival (OS)                                                                                   | Defined as the time from the date of randomization until death due to any cause                                                                                                                                                                                                                                                                             |
|                                                 | Secondary endpoint                                                                                                                                                                                                                                                                                                                                                                                    | Objective response rate (ORR)                                                                           | Defined as the proportion of participants who achieve a complete response (CR) or partial response (PR) that is confirmed at least 4 weeks after initial documentation of response as assessed by BICR per RECIST v1.1.                                                                                                                                     |
|                                                 | Secondary endpoint                                                                                                                                                                                                                                                                                                                                                                                    | Duration of response (DOR)                                                                              | Defined as the time from the first documentation of CR or PR to the earlier of the first documentation of definitive PD or death from any cause (whichever comes first) as assessed by BICR per RECIST v1.1.                                                                                                                                                |
|                                                 | Secondary endpoint                                                                                                                                                                                                                                                                                                                                                                                    | Time to response (TTR)                                                                                  | Defined as the time from the date of randomization until the first documentation of CR or PR as assessed by BICR per RECIST v1.1.                                                                                                                                                                                                                           |
|                                                 | Secondary endpoint                                                                                                                                                                                                                                                                                                                                                                                    | Safety and tolerability                                                                                 | Incidence of treatment-emergent adverse events and clinical laboratory abnormalities.                                                                                                                                                                                                                                                                       |
|                                                 | Secondary endpoint                                                                                                                                                                                                                                                                                                                                                                                    | Mean change from baseline in the physical functioning domain and time to deterioration (TTD) in fatigue | Mean change from baseline in the physical functioning domain of the EORTC QLQ-C30 at Week 25.<br>TTD of fatigue domain of the EORTC QLQ-C30 is defined as the time between the date of randomization and the date of assessment at which a participant experienced a deterioration (ie, ≥ 10 points worsening from baseline in the fatigue domain) or death |
| Database lock                                   | 14 May 2025 (clinical cut-off date for primary analysis: 2 April 2025)                                                                                                                                                                                                                                                                                                                                |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                             |
| <b>Results and Analysis</b>                     |                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                             |
| <b>Analysis description</b>                     | <b>Primary Analysis</b>                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                             |
| Analysis population and time point description  | Primary analysis of PFS was based on BICR using RECIST 1.1 for the Intent- to-Treat (ITT) Population.<br><br>ITT Analysis Set includes all participants who were randomized in the study.<br>Participants were treated until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, initiation of other anticancer therapy (including any investigational agent), or death. |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                             |
| Descriptive statistics and estimate variability | Treatment group                                                                                                                                                                                                                                                                                                                                                                                       | SG<br>n=279                                                                                             | TPC<br>n=279                                                                                                                                                                                                                                                                                                                                                |
|                                                 | Number of participants with events                                                                                                                                                                                                                                                                                                                                                                    | n=161 (57.7%)                                                                                           | n=188 (67.4%)                                                                                                                                                                                                                                                                                                                                               |
|                                                 | PFS (median months)                                                                                                                                                                                                                                                                                                                                                                                   | 9.69                                                                                                    | 6.93                                                                                                                                                                                                                                                                                                                                                        |

|                                                 |                                                                                                                     |                                |                    |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------|
|                                                 | 95% Confidence interval (CI)                                                                                        | 8.15, 11.14                    | 5.62, 8.25         |
| Effect estimate per comparison                  | PFS                                                                                                                 | Comparison groups              | SG vs TPC          |
|                                                 |                                                                                                                     | Hazard ratio (relative to TPC) | 0.623              |
|                                                 |                                                                                                                     | Confidence Interval            | 0.501, 0.775       |
|                                                 |                                                                                                                     | P-value                        | <0.0001            |
| Analysis population and time point description  | A descriptive analysis of OS was performed at the time of PFS primary analysis using the ITT Analysis Set           |                                |                    |
| Descriptive statistics and estimate variability | Treatment group                                                                                                     | SG<br>n=279                    | TPC<br>n=279       |
|                                                 | Number of participants with events                                                                                  | 103 (36.9%)                    | 103 (36.9%)        |
|                                                 | OS (median months)                                                                                                  | 21.45                          | 20.24              |
|                                                 | 95% CI                                                                                                              | 17.71, not reached             | 18.23, not reached |
| Effect estimate per comparison                  | OS                                                                                                                  | Comparison groups              | SG vs TPC          |
|                                                 |                                                                                                                     | Hazard ratio (relative to TPC) | 0.985              |
|                                                 |                                                                                                                     | Confidence Interval            | 0.748, 1.297       |
|                                                 |                                                                                                                     | P-value                        | Not tested         |
| Analysis population and time point description  | A descriptive analysis of ORR by BICR was performed at the time of PFS primary analysis using the ITT Analysis Set. |                                |                    |
| Descriptive statistics and estimate variability | Treatment group                                                                                                     | SG<br>n=279                    | TPC<br>n=279       |
|                                                 | ORR (%)                                                                                                             | 48.4                           | 45.5               |
|                                                 | 95% CI                                                                                                              | 42.4, 54.4                     | 39.6, 51.6         |
| Effect estimate per comparison                  | ORR                                                                                                                 | Comparison groups              | SG vs TPC          |
|                                                 |                                                                                                                     | Odds Ratio (relative to TPC)   | 1.122              |
|                                                 |                                                                                                                     | Confidence Interval            | 0.804, 1.566       |
|                                                 |                                                                                                                     | P-value                        | Not tested         |
| Analysis population and time point              | Duration of Response per BICR                                                                                       |                                |                    |
| Descriptive statistics and estimate variability | Treatment group                                                                                                     | SG<br>n=279                    | TPC<br>n=279       |
|                                                 | DOR (median months)                                                                                                 | 12.22                          | 7.16               |

|                                                 |                                                                                                                                                                   |                                        |              |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|--------------|
|                                                 | 95% CI                                                                                                                                                            | 9.69, 13.83                            | 5.72, 8.41   |
| Effect estimate per comparison                  | Not applicable                                                                                                                                                    |                                        |              |
| Analysis population and time point              | Change From Baseline in the Physical Functioning Domain of the EORTC QLQ-C30 at Week 25 performed at the time of PFS primary analysis using the ITT Analysis Set. |                                        |              |
| Descriptive statistics and estimate variability | Treatment group                                                                                                                                                   | SG<br>n=279                            | TPC<br>n=279 |
|                                                 | Baseline mean (Standard Deviation)                                                                                                                                | 79 (21.67)                             | 80.5 (21.5)  |
|                                                 | Change From Baseline at Week 25, LS Mean (Standard Error)                                                                                                         | 0.3 (1.23)                             | -6.6 (1.28)  |
| Effect estimate per comparison                  | Change From Baseline in the Physical Functioning Domain of the EORTC QLQ-C30 at Week 25                                                                           | Comparison groups                      | SG vs TPC    |
|                                                 |                                                                                                                                                                   | LS-Mean of Treatment Difference vs TPC | 6.9          |
|                                                 |                                                                                                                                                                   | Confidence Interval                    | 3.50, 10.28  |
|                                                 |                                                                                                                                                                   | P-value                                | Not tested   |
| Analysis population and time point description  | Time to Deterioration in Fatigue Domain of the EORTC QLQ-C30 (months), performed at the time of PFS primary analysis using the ITT Analysis Set.                  |                                        |              |
| Descriptive statistics and estimate variability | Treatment group                                                                                                                                                   | SG<br>n=279                            | TPC<br>n=279 |
|                                                 | Median TTD                                                                                                                                                        | 1.45                                   | 1.64         |
|                                                 | 95% Confidence interval (CI)                                                                                                                                      | 1.08, 1.68                             | 1.18, 1.94   |
| Effect estimate per comparison                  | TTD                                                                                                                                                               | Comparison groups                      | SG vs TPC    |
|                                                 |                                                                                                                                                                   | Hazards Ratio (relative to TPC)        | 0.979        |
|                                                 |                                                                                                                                                                   | Confidence Interval                    | 0.803, 1.193 |
|                                                 |                                                                                                                                                                   | P-value                                | Not tested   |

## Clinical studies in special populations

**Table 48 Clinical studies in special population**

|                                                                        | Controlled Trials [a]<br>(N = 1630) | Non-Controlled Trials [b]<br>(N = 162) |
|------------------------------------------------------------------------|-------------------------------------|----------------------------------------|
| Baseline Hepatic Function                                              |                                     |                                        |
| Normal (Bilirubin (BILI) ≤ ULN and Aspartate transaminase (AST) ≤ ULN) | 1067<br>(65.5%)                     | 102 (63.0%)                            |
| Mild ((BILI ≤ ULN and AST > ULN) or (ULN < BILI ≤ 1.5 x ULN))          | 549<br>(33.7%)                      | 60 (37.0%)                             |
| Moderate (1.5 x ULN < BILI ≤ 3 x ULN)                                  | 9 (0.6%)                            | 0                                      |

|                                                         | Controlled Trials [a]<br>(N = 1630) | Non-Controlled Trials [b]<br>(N = 162) |
|---------------------------------------------------------|-------------------------------------|----------------------------------------|
| Severe (BILI > 3 x ULN)                                 | 2 (0.1%)                            | 0                                      |
| Missing                                                 | 3 (0.2%)                            | 0                                      |
| Baseline Renal Function                                 |                                     |                                        |
| Normal (Creatinine Clearance ≥ 90 mL/min)               | 953 (58.5%)                         | 96 (59.3%)                             |
| Mild (60 mL/min ≤ Creatinine Clearance < 90 mL/min)     | 555 (34.0%)                         | 48 (29.6%)                             |
| Moderate (30 mL/min ≤ Creatinine Clearance < 60 mL/min) | 118 (7.2%)                          | 17 (10.5%)                             |
| Severe (Creatinine Clearance < 30 mL/min)               | 1 (<0.1%)                           | 1 (0.6%)                               |
| Missing                                                 | 3 (0.2%)                            | 0                                      |
| Age Group                                               |                                     |                                        |
| < 18 years                                              | 0                                   | 0                                      |
| 18 to 64 years                                          | 1246 (76.4%)                        | 131 (80.9%)                            |
| 65 to 74 years                                          | 299 (18.3%)                         | 27 (16.7%)                             |
| 75 to 84 years                                          | 83 (5.1%)                           | 4 (2.5%)                               |
| ≥ 85 years                                              | 2 (0.1%)                            | 0                                      |

Intent-to-treat (ITT) Analysis Set includes all participants who were randomized in the study.

[a] Controlled trials include ITT Analysis Sets from GS-US-592-6238, IMMU-132-05, IMMU-132-09.

[b] Non-Controlled trials include mTNBC and HR+/HER2- mBC participants from IMMU-132-01 treated with SG 10 mg/kg.

Percentages are based on the total number of participants in the corresponding column.

For baseline hepatic function and baseline renal function, baseline value was derived based on the last assessment on or before the date/time of first study drug administration if dosed, or randomization date if not dosed.

Age (in years) was collected on the date of first study drug administration (Day 1) if dosed, or randomization if not dosed.

### 2.4.3. Discussion on clinical efficacy

The MAH submitted ASCENT-03 study results to support an extension of indication for Trodelvy as monotherapy for the treatment of adult patients with unresectable locally advanced or metastatic TNBC who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy.

### Design and conduct of clinical studies

The global, open-label study ASCENT-03 enrolled 558 patients with locally advanced, inoperable, or metastatic TNBC who have not received previous systemic therapy for advanced disease. Patients could have received (neo)adjuvant chemotherapy (including anti-PD-(L)1 treatment) if this was completed ≥ 6 months before disease recurrence. Previous treatment with a topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor was not allowed. Patients should not have been eligible for PD-(L)1 inhibitor therapy.

Patients were randomized (1:1) to receive either sacituzumab govitecan (SG) or treatment of physician's choice chemotherapy (TPC). SG was applied in the approved dosing regimen of 10 mg/kg IV on Days 1 and 8 of 21-day cycles. TPC was selected prior to randomization to be either paclitaxel, nab-paclitaxel or gemcitabine/carboplatin by the investigator. Retreatment with taxane, gemcitabine, or platinum agents were allowed in case of a treatment-free interval of ≥ 12 months. Patients should have received prior anthracycline in the (neo)adjuvant setting or be considered not eligible for anthracyclines as assessed by the treating physician. The choice of chemotherapies and their dosing

regimens is in line with guideline recommendations and corresponds to the control arm of studies in similar settings, e.g. KEYNOTE-355.

Participants in the control group were eligible to receive SG in the crossover phase upon disease progression verified by BICR.

The eligibility criteria are overall considered adequate. TNBC status and tumour PD-L1 expression was confirmed centrally on a recent or archival tumour specimen. Tumour PD-L1 CPS was determined using the PD-L1 IHC 22C3 assay.

Patients were stratified by geographic region (US/Canada/Western Europe versus Rest of World), and de novo disease versus recurrent disease with a treatment-free interval of 6-12 months versus recurrent disease > 12 months from completion of treatment in the curative setting. Stratification factors are considered acceptable.

Baseline demographic and disease characteristics were overall balanced between treatment arms and representative of a 1L TNBC study population. Median age was 55 years \_with 26% of patients 65 years or over. Most participants were White (64%) or Asian (23%) with only 3% being Black\_and most participants had a good performance status (ECOG PS 0 66%, PS 1 34%).

The majority of study participants had metastatic disease at screening, the most common sites of metastasis were the lymph nodes (64%), lung (60%), bone (33%), and liver (27%). Only 29 participants (5.2%) were enrolled with stable brain metastasis. BRCA 1/2 mutation status was known for 76% of participants, out of which 18% of tested study participants had positive BRCA mutations. More than half of the study participants (67.4%) received prior (neo)adjuvant systemic treatments, most commonly taxanes (58.1%), anthracyclines (55%), capecitabine (19.2%) and platinum (17.9%). 4.3% of patients received prior anti-PD-(L)1 agents. Most patients also had prior radiotherapy (58.2%).

Nearly all study participants had metastatic TNBC and only 12 patients (2.2%) were enrolled with locally advanced and inoperable disease. No subgroup results by disease status were provided, but the sample size of patients with unresectable locally advanced disease is considered too small for reliable conclusions. Disease status is unlikely to be an effect modifier and treatment recommendations do not differ between patients with unresectable locally advanced and metastatic disease; therefore, the extrapolation of study results to the small subgroup of patients with unresectable disease is agreed.

The MAH sought an approval for 1L TNBC patients who are "not candidates for PD-(L)1 inhibitor therapy". Under the initial versions of the study protocol, recruitment was open for patients with PD-L1 negative (i.e. CPS <10) tumours, and patients whose tumours were PD-L1 positive (i.e. CPS ≥10) if they have received an anti-PD-(L)1 inhibitor in the neoadjuvant or adjuvant setting. With the implementation of protocol amendment 2 (dated 30 August 2023, when already 310 participants were randomised), patients with PD-L1 positive tumours were also allowed to be included if they could not receive treatment with an anti-PD-(L)1 agent due to a comorbidity.

However, only two patients with PD-L1 positive tumours were finally enrolled, the clinical study population primarily represents a target population with PD-L1 negative tumours.

There are currently no reliable data available to inform on the use of immune checkpoint inhibitors (ICI) for patients with PD-L1 positive tumours who received an ICI in the curative setting. However, the most recent ESMO guidance recommends a rechallenge with ICI in combination with chemotherapy as 1L treatment for patients with PD-L1 positive tumours and recurrence >6 (-12) months after the end of (neo)adjuvant ICI (*ESMO Living guideline updates 2025<sup>10</sup>*). Therefore, only patients with a

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<sup>10</sup> ESMO Living Guideline for Triple-negative metastatic breast cancer; G Curigliano et al., Ann Oncol. 2025

treatment-free interval of  $\leq 6$  months after treatment with curative intent would be clearly not candidates for PD-(L)1 inhibitor therapy. These patients with a more aggressive tumour biology and worse prognosis were not included in study ASCENT-03.

The MAH argued that patients with PD-L1 positive disease who have a comorbidity precluding treatment with ICI or cannot be rechallenged with ICI upon disease recurrence represent a clinically relevant subgroup with an unmet need. Given that these patients are typically treated with chemotherapy, the results from study ASCENT-03 would be applicable since SG demonstrated superior efficacy compared to chemotherapy. It is acknowledged that the treatment effect of SG is not considered to be associated with tumour PD-L1 expression, i.e. PD-L1 expression is unlikely to be an effect modifier. SG has previously demonstrated efficacy in TNBC patients after prior treatment. In view of the unmet medical need, it might be acceptable to extrapolate the study results to patients with PD-L1 positive tumours who are not eligible for ICI, although these patients were not represented in the study population. Despite the remaining uncertainty on the exact effect size, a broader indication including all patients ineligible for PD-(L)1 inhibitor therapy provides an additional option for individual treatment decisions. However, the study population characteristics are clearly reflected in section 5.1 of the SmPC (. A cross-reference to section 5.1 of the SmPC has been already proposed by the MAH in the indication wording in section 4.1 of the SmPC which is agreed on.

For patients with PD-L1 negative mTNBC and germline BRCA mutations, a PARP inhibitor is the preferred 1L treatment option according to clinical guidelines<sup>13</sup>. BRCA1/2 mutation status at baseline was known only for 34.5% of participants. The MAH did not implement the EMA SA recommendations to require gBRCA1/2 testing for all participants and prior PARPi treatment for eligible patients with BRCA1/2 mutant tumours, but referred to global disparities in resources for testing and drug availability. 5.2% of study participants had positive mutations status (n=17 and 12 in the SG and TPC arm, respectively; DCO: 02 April 2025); only 1 participant received prior treatment with a PARPi. The proportion of patients with positive BRCA mutations appeared rather low compared to literature data for TNBC (e.g. 9.3% to 15.4% according to Armstrong<sup>11</sup>).

The primary endpoint for study ASCENT-03 was PFS by BICR per RECIST v1.1; key secondary endpoints were OS, ORR by BICR and quality of life as measured by change from baseline in the physical functioning score and by time to deterioration (TTD) of fatigue from baseline of EORTC QLQ-C30 V3.0. Duration of response (DOR) and time to response (TTR) by BICR were additional secondary endpoints.

The primary endpoint analysis of PFS by BICR served as the gatekeeper for the secondary endpoints: OS, ORR and analyses for QoL, which were planned to be tested sequentially when the above hypotheses in the hierarchy were statistically significant.

The study planned for 3 interim analyses and 1 final analysis. The first analysis was the final analysis for PFS when 352 PFS events were reached including a descriptive analysis of OS (53% information) at the same time. The remaining 2 interim analyses at 70% and 85% of information and final analysis when 391 deaths would be observed were planned to test OS. To account for the interim analyses of OS, Lan-DeMets alpha spending function approximating an O'Brien Fleming approach was used to adjust the type I error.

Several protocol amendments were implemented in this open-label study that affected changes in the primary efficacy analysis. The rationale for the changes (mainly with the aim to ensure a sufficient follow-up time and data maturity) can be followed based on the provided explanations. A study-specific Data Access Restriction Plan implemented measures to ensure data integrity and regulated that key

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<sup>11</sup> Armstrong N et al. A systematic review of the international prevalence of BRCA mutation in breast cancer. Clin Epidemiol 2019

personnel (clinical development and study biostatistician) involved with the interpretation of the data, remained blinded to treatment assignment until the database was locked for the primary analysis. Post-hoc analysis according to the defined analysis of Protocol Amendment 1 and 2 showed consistent results with the primary analysis and indicated that the trial would have met the primary PFS endpoint also with the prior protocol versions.

A high number of important protocol deviation was reported (45.9% across both treatment arms); but after further review it can be agreed that these are not expected to have had a significant impact on the interpretation of the study results overall.

## **Efficacy data and additional analyses**

Efficacy data were provided from the primary (final) analysis of PFS with a data cut-off date of 02 April 2025 and a median duration of follow-up of approximately 13 months. Analyses of secondary endpoints of OS, ORR, DOR and TTR by BICR as well as PRO data are descriptive only; key secondary endpoints were not formally tested at the time of the PFS primary analysis based on the testing hierarchy. In addition, updated efficacy data at the time of OS Interim Analysis 1 with a median duration of OS follow-up of 17.7 months (DCO: 27 October 2025) were provided during the procedure.

Study ASCENT-03 demonstrated a statistically significant PFS improvement with SG versus TPC (HR: 0.623; 95% CI: 0.501, 0.775; 2-sided  $P < 0.0001$ ) at the time of the primary PFS analysis. Median PFS was 9.69 months (95% CI: 8.15, 11.14) in the SG group and 6.93 months (95% CI: 5.62, 8.25) in the TPC group. Results from PFS sensitivity analyses were consistent with the primary analysis.

Updated descriptive PFS data by BICR at the time of OS IA1 showed similar results (PFS HR: 0.65 [95% CI: 0.53, 0.79]).

**OS** data at the time of the primary PFS analysis were immature with 206 deaths (37% maturity rate; 53% IF) and showed similar results in both treatment arms (HR: 0.985; 95% CI: 0.748, 1.297). Updated OS data at OS IA1 based on 283 events (50.7% maturity) remained overall consistent with longer follow-up. Median OS was 21.45 months (95% CI: 18.86, 26.55) in the SG group and 21.26 months (95% CI: 18.69, 25.17) in the TPC group, the OS HR was 0.953 (95% CI: 0.755, 1.205,  $P = 0.6860$ ). The OS KM curves largely overlapped until month 24 when they began to separate in favour of SG. Of note, numbers at risk were limited beyond 24 months.

Results do not show an OS advantage of SG over first-line chemotherapy but they can be considered sufficiently mature to exclude an OS detriment. Interpretation of OS data is hampered by the high cross-over rate; at OS IA1, 154 out of 279 (55.2%) participants in the TPC group received SG in the second line setting, 125 participants (44.8%) received SG through the crossover phase of the study. On the contrary, more patients received chemotherapy in the SG arm compared to the TPC arm at disease progression.

It is acknowledged that the ability to demonstrate an OS improvement is impacted by the study design allowing cross-over. Given the established OS benefit of SG compared with TPC in previously treated metastatic TNBC (based on the ASCENT study), sensitivity analyses to adjust for the effect of crossover on OS were prespecified. Results showed HR point estimates (range: 0.622-0.908) in favour of the SG group. Similarly, exploratory analyses to adjust for the treatment switch to second line SG in the TPC group (including also participants who received SG through commercial means) showed HR point estimates between 0.561 and 0.901. The point estimates vary depending on each method and are accompanied by wide confidence intervals which limits the robustness and interpretation of the results. Furthermore, no adjustment was performed in the SG group for 2L treatment, which may have affected the OS and thus adjusted HR. Given the limitations of the analyses, the results can only be

considered supportive of no detrimental OS of SG but do not support a demonstration of a survival benefit of SG.

The high proportion of patients receiving SG at PD reflects currently the recommended standard of clinical practice. Results of study ASCENT-03 demonstrated an improvement in PFS but they do not support the assumption that patients with TNBC might benefit from an OS improvement when SG is applied as first-line as opposed to later line treatment.

In view of the still high rate of censoring before month 20, the MAH committed to provide results from the final OS analysis post-approval (**REC**).

Results for secondary efficacy endpoints of ORR (48.4% versus 45.5%), time to response (2.6 vs. 2.4 months) and median TTD in the fatigue domain of the EORTC QLQ-C30 (1.5 vs 1.6 months) were similar between the SG group and TPC group. The mean change from baseline in the physical functioning (PF) domain of EORTC QLQ-C30 at Week 25 numerically favoured the SG group over the TPC group (0.3 vs. -6.6); however, the clinical relevance of the difference of 6.9 (95% CI 3.5, 10.3) is questionable, given that the minimal score change for the PF domain is 6.67, i.e. one item in the PF domain changed by one category assuming all other items were answered the same. Furthermore, the observed difference (mainly driven by the decline in the TPC group) may be biased considering also the potential impact of the open-label study design on PRO endpoints. Median DOR was numerically longer with SG compared with TPC (12.2 versus 7.2 months) in line with PFS results.

Exploratory **PFS2** results indicated a trend in favour of SG (HR: 0.778 [95% CI: 0.632, 0.958]; median PFS2 16.16 months [95% CI: 14.82, 19.58] in the SG group versus 13.83 months [95% CI: 12.48, 15.84] in the TPC group).

**Subgroup results** of PFS generally showed a consistent benefit of SG compared to TPC, including disease stratification factors and geographic region.

For some subgroups, such as patients with stable **brain metastasis** (N=29), the sample size was too small to draw reliable conclusions. It is nonetheless reassuring that subgroup analyses of PFS, OS and ORR for patients with brain metastasis showed favourable results for the SG treatment arm.

Systematic response assessment of brain metastasis was not conducted. MRI brain scan was mandatory at screening in all patients and follow-up was required if brain metastasis was known or suspected. But numeric measurements of the brain lesions were not collected, since brain lesions, per protocol, were captured as nontarget lesions at baseline or as new lesions at the time of progression. Reported results of "noncomplete response/nonprogressive disease" or "not evaluable" for patients with known brain metastasis at baseline or the proportion of patients with new brain metastases during or following treatment appear to be balanced between both treatment groups. No firm conclusions can be drawn from these results.

Subgroup results by **age** were provided for the cut-offs of 65 and 75 years at OS IA1 (DCO: 27 October 2025). For patients beyond 65 years (N=143), the PFS HR point estimate was numerically larger compared to younger patients (HR 0.89 [95% CI 0.58, 1.35] vs 0.61 [95% CI 0.48, 0.76]). For the age group of  $\geq 65$ , the OS HR was 1.01 [95% CI 0.64, 1.61] and response rates were lower for SG versus TPC (Odds Ratio: 0.71). In the small subgroup of patients beyond 75 years (N=40), the PFS HR was 0.95 (95% CI 0.37, 2.43), the OS HR was 1.15 (95% CI 0.43, 3.05) and the Odds Ratio for ORR was 0.43 (95% CI 0.12, 1.57). Interpretation of efficacy results in elderly is limited by the small sample size and low event numbers, especially for patients above 75 years. Data are not considered reliably enough to conclude on a detriment as a basis for restricting access to treatment. Nonetheless subgroup results by age overall indicate no clinically meaningful clinical benefit for SG compared to TPC in elderly patients.

Reported subgroup results for patients with **BRCA1/2 mutations** at baseline based on local testing (N=35 at OS IA1) did not support a PFS benefit of SG compared to TPC (PFS HR: 0.93 [95% CI 0.43, 2.02] and indicated a detriment in OS (OS HR: 2.72 [95% CI 0.95, 7.83]), although the small sample size hampered any reliable conclusions.

The MAH provided additional analyses based on retrospective central BRCA assessment: an exploratory objective of the study as per the protocol was to conduct whole exome sequencing analyses in a central laboratory. In participants with sufficient FFPE tumour material, BRCA1/BRCA2 mutation status was determined and was correlated with efficacy endpoints. For the endpoint of PFS by BICR, hazard ratios suggested a benefit of SG over TPC in both participants with BRCA1/2 mutant alleles (HR: 0.61; 95% CI: 0.34, 1.07) and participants with BRCA wild type alleles (HR: 0.70; 95% CI: 0.55, 0.91). OS HRs were overall similar between BRCA 1/2 mutant and wild type patients (OS HR: 1.08 [95% CI: 0.55, 2.14] and 0.98 [95% CI: 0.74, 1.31]).

The value of the analysis of central BRCA test results based on whole exome sequencing is limited by its exploratory and retrospective nature and the non-randomized comparisons in a Biomarker Analysis Set. Nonetheless, testing was conducted in a relevant proportion of study participants (N=423, 76%) and positive BRCA 1/2 mutations were reported in 18.2% of tested patients (N=77). Results indicated that patients with BRCA1/2 mutant or wild type alleles might derive a similar PFS benefit from SG treatment. In addition, OS data did not confirm the detriment that was observed in the analysis of local BRCA test results. Thus, despite the limitations of the dataset, it can be concluded that the treatment effect of SG might not be relevantly impacted by BRCA mutation status and a presentation of subgroup results in section 5.1 of the SmPC is not considered warranted.

Evaluation of baseline **Trop-2 expression** in fresh or archival tumour tissue as a biomarker for efficacy was an exploratory endpoint. Trop-2 expression in tumour tissue was assessed by IHC using a fit-for-purpose, validated EPR20043 formulation locked assay (FLA) at Roche Tissue Diagnostics (RTD). Trop-2 data were available from 499 participants (89.4%) in the ITT Analysis Set. Subgroup analysis of PFS by BICR generally showed overall a consistent benefit for the SG group compared with the TPC group across Trop-2 H-score quartiles. Subgroup results of OS showed a numerical OS benefit in the two upper Trop-2 H-score quartiles (HR point estimates: 0.61 for Q3 and 0.91 for Q4), but not in the two lower Trop-2 H-score quartiles (HR point estimates: 1.01 for Q1 and 1.37 for Q2). A similar trend was observed for ORR by BICR (odds ratio of 1.4 for Q3 and Q4 versus odds ratio of 0.99 for Q1 and 0.93 for Q2).

Trop-2 expression results need to be interpreted with caution since Trop-2 expression status was not a stratification factor and though expression data were analysed in a large proportion, they were not available for all study participants. There are wide confidence intervals for OS HRs that are likely due to small event numbers per quartile. Nonetheless, considering the mode of action of SG as a targeted therapy, an association between Trop-2 expression status and OS outcome would be biologically plausible.

#### **2.4.4. Conclusions on the clinical efficacy**

The ASCENT-03 study demonstrated a statistically significant improvement in PFS for SG compared to first-line chemotherapy in patients with PD-L1 negative TNBC. This improvement can also be considered clinically relevant. However, the study did not show an OS benefit, with an OS maturity rate of 55%. The interpretation of OS data is complicated by the fact that a large proportion of patients (55%) in the control arm received SG after disease progression. Nonetheless, administering SG after the failure of 1L treatment reflects standard clinical practice. The OS results can be considered sufficiently mature to exclude an OS detriment however they suggest that patients with TNBC may not

benefit from an OS improvement when SG is used as first-line treatment compared to later-line treatment.

## 2.5. Clinical safety

### Introduction

Data from 551 participants treated with either SG 10 mg/kg or TPC chemotherapy (paclitaxel 90 mg/m<sup>2</sup>, nab paclitaxel 100 mg/m<sup>2</sup>, or gemcitabine 1000 mg/m<sup>2</sup> with carboplatin AUC 2) in the pivotal phase 3 Study GS-US-592-6238 were integrated in the summary of clinical safety (SCS).

Pooled data from 4 clinical studies (GS-US-592-6238, IMMU-132-01, IMMU-132-05, and IMMU-132-09) in 963 participants with metastatic TNBC or HR+/HER2– metastatic breast cancer (mBC) are used for the analysis of SG monotherapy safety in patients with breast cancer. Pooled data from 7 clinical studies (studies GS US-592-6238, IMMU-132-01, IMMU 132 05, IMMU-132-06 (Cohort 1 and Cohort 2), IMMU-132-09, IMMU-132-13, and GS-US-577-6153) in 1999 participants across different tumour types were used to contextualize the experience of SG monotherapy in first line metastatic TNBC with the overall SG treatment experience.

**Table 49 Studies and Population Groups Included in the Summary of Clinical Safety and Integrated Summary of Safety**

| Study Number   | Data Cutoff Date <sup>a</sup> | Patient Population                                                                                                                                                                     | Population Groups for ISS Analysis       |                                           |                                       |                                                   |
|----------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-------------------------------------------|---------------------------------------|---------------------------------------------------|
|                |                               |                                                                                                                                                                                        | GS-US-592-6238 SG (N = 275) <sup>b</sup> | GS-US-592-6238 TPC (N = 276) <sup>c</sup> | Overall mBC SG (N = 963) <sup>d</sup> | All Treated (Expanded) SG (N = 1999) <sup>e</sup> |
| GS-US-592-6238 | 02 April 2025                 | Participants with locally advanced unresectable or metastatic TNBC who have not received previous therapy for advanced disease and who are not candidates for PD-1 or PD-L1 inhibitors | 275                                      | 276                                       | 275                                   | 275                                               |
| IMMU-132-01    | 02 April 2021; final data     | Participants with epithelial cancer who received SG 10 mg/kg, including participants with mTNBC and HR+/HER2– mBC                                                                      | —                                        | —                                         | mTNBC: 108 HR+/HER2– mBC: 54          | 402 (any tumor type)                              |
| IMMU-132-05    | 25 February 2021; final data  | Participants with mTNBC who received ≥ 2 prior treatments                                                                                                                              | —                                        | —                                         | 258                                   | 258                                               |

| Study Number             | Data Cutoff Date <sup>a</sup> | Patient Population                                                                                                                                                                        | Population Groups for ISS Analysis        |                                            |                                       |                                                   |
|--------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------|---------------------------------------|---------------------------------------------------|
|                          |                               |                                                                                                                                                                                           | GS-US-592-6 238 SG (N = 275) <sup>b</sup> | GS-US-592-6 238 TPC (N = 276) <sup>c</sup> | Overall mBC SG (N = 963) <sup>d</sup> | All Treated (Expanded) SG (N = 1999) <sup>e</sup> |
| IMMU-132-06 <sup>f</sup> | 28 February 2023              | Cohort 1: participants with mUC who progressed after prior platinum-containing and anti-PD-1 or anti-PD-L1-based therapies                                                                | —                                         | —                                          | —                                     | 113                                               |
|                          |                               | Cohort 2: participants with platinum-ineligible mUC who progressed after prior anti-PD-1 or anti-PD-L1-based therapy                                                                      | —                                         | —                                          | —                                     | 38                                                |
| IMMU-132-09              | 15 December 2023; final data  | Participants with HR+/HER2– mBC who failed at least 2 prior chemotherapy regimens                                                                                                         | —                                         | —                                          | 268                                   | 268                                               |
| IMMU-132-13              | 08 March 2024                 | Participants with metastatic or locally advanced unresectable urothelial cancer who have progressed after prior therapy with a platinum-containing regimen and a PD-1 or PD-L1 inhibitor. | —                                         | —                                          | —                                     | 349                                               |

| Study Number   | Data Cutoff Date <sup>a</sup> | Patient Population                                                                                                                                                                                   | Population Groups for ISS Analysis        |                                            |                                       |                                                   |
|----------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------|---------------------------------------|---------------------------------------------------|
|                |                               |                                                                                                                                                                                                      | GS-US-592-6 238 SG (N = 275) <sup>b</sup> | GS-US-592-6 238 TPC (N = 276) <sup>c</sup> | Overall mBC SG (N = 963) <sup>d</sup> | All Treated (Expanded) SG (N = 1999) <sup>e</sup> |
| GS-US-577-6153 | 29 November 2023              | Participants with advanced or metastatic NSCLC who progressed on or after platinum-containing chemotherapy and anti-PD-1 or anti-PD-L1 immunotherapy received either in combination or sequentially. | —                                         | —                                          | —                                     | 296                                               |

AUC = area under the curve; HER2– = human epidermal growth factor receptor 2-negative; HR+ = hormonal receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; mTNBC = metastatic triple-negative breast cancer; mUC = metastatic urothelial cancer; nab = nanoparticle albumin-bound; NSCLC = non-small-cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

f Studies GS-US-592-6238, IMMU-132-06, GS-US-577-6153, and IMMU-132-13 are ongoing and data up to the specified data cutoff dates were included in the integrated safety analysis. Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09 were completed, and data up to final database lock were included in the integrated safety analysis.

g Includes participants treated with SG 10 mg/kg in Study GS-US-592-6238.

h Includes participants treated with TPC (paclitaxel 90 mg/m<sup>2</sup>, nab-paclitaxel 100 mg/m<sup>2</sup>, or gemcitabine 1000 mg/m<sup>2</sup> with carboplatin AUC 2) in Study GS-US-592-6238.

i Includes all participants with mTNBC or HR+/HER2– mBC treated with SG 10 mg/kg in Studies GS-US-592-6238, IMMU-132-01, IMMU-132-05, and IMMU-132-09.

j Includes all participants treated with SG 10 mg/kg regardless of indication from Studies GS-US-592-6238, IMMU-132-01, IMMU-132-05, IMMU-132-06 (Cohorts 1 and Cohort 2), IMMU-132-09, IMMU-132-13, and GS-US-577-6153.

## Patient exposure

**Table 50 Exposure to Study Drug (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                                             | GS-US-592-6238 SG (N = 275) | GS-US-592-6238 TPC (N = 276) | Overall mBC (N = 963) | All Treated (Expanded) SG (10 mg/kg) (N = 1999) |
|-------------------------------------------------------------|-----------------------------|------------------------------|-----------------------|-------------------------------------------------|
| Treatment duration (months) <sup>a</sup>                    |                             |                              |                       |                                                 |
| N                                                           | 275                         | 276                          | 963                   | 1999                                            |
| Mean (StD)                                                  | 8.77 (6.042)                | 6.62 (4.635)                 | 7.10 (6.890)          | 6.03 (6.429)                                    |
| Median                                                      | 8.31                        | 5.78                         | 5.29                  | 4.17                                            |
| Min, max                                                    | 0.03, 28.68                 | 0.03, 24.18                  | 0.03, 62.55           | 0.03, 62.55                                     |
| Cumulative number (%) of participants exposed to study drug |                             |                              |                       |                                                 |
| ≥ 3 months, n (%)                                           | 222 (80.7%)                 | 207 (75.0%)                  | 650 (67.5%)           | 1196 (59.8%)                                    |
| ≥ 6 months, n (%)                                           | 168 (61.1%)                 | 136 (49.3%)                  | 423 (43.9%)           | 740 (37.0%)                                     |
| ≥ 12 months, n (%)                                          | 76 (27.6%)                  | 35 (12.7%)                   | 169 (17.5%)           | 251 (12.6%)                                     |

|                                             | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|---------------------------------------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| ≥ 24 months, n (%)                          | 5 (1.8%)                                   | 1 (0.4%)                                    | 31 (3.2%)                        | 44 (2.2%)                                                              |
| ≥ 36 months, n (%)                          | 0                                          | 0                                           | 6 (0.6%)                         | 12 (0.6%)                                                              |
| Number of participants with dose reductions |                                            |                                             |                                  |                                                                        |
| Any                                         | 100 (36.4%)                                | —                                           | 314 (32.6%)                      | 678 (33.9%)                                                            |
| 1                                           | 85 (30.9%)                                 | —                                           | 244 (25.3%)                      | 529 (26.5%)                                                            |
| 2                                           | 14 (5.1%)                                  | —                                           | 64 (6.6%)                        | 141 (7.1%)                                                             |
| 3                                           | 1 (0.4%)                                   | —                                           | 2 (0.2%)                         | 4 (0.2%)                                                               |
| > 3                                         | 0                                          | —                                           | 4 (0.4%)                         | 4 (0.2%)                                                               |
| Time to first dose reduction (days)         |                                            |                                             |                                  |                                                                        |
| N                                           | 100                                        | —                                           | 314                              | 678                                                                    |
| Mean (StD)                                  | 99 (100.9)                                 | —                                           | 92 (119.0)                       | 77 (116.4)                                                             |
| Median                                      | 58                                         | —                                           | 46                               | 41                                                                     |
| Min, max                                    | 8, 456                                     | —                                           | 1, 925                           | 1, 1647                                                                |
| Relative dose intensity (%) <sup>b</sup>    |                                            |                                             |                                  |                                                                        |
| N                                           | 275                                        | —                                           | 960                              | 1995                                                                   |
| Mean (StD)                                  | 85.5 (14.60)                               | —                                           | 85.9 (14.63)                     | 85.3 (15.78)                                                           |
| Median                                      | 89.6                                       | —                                           | 89.5                             | 89.1                                                                   |
| Min, max                                    | 45.9, 138.6                                | —                                           | 39.0, 138.6                      | 30.4, 138.6                                                            |
| < 70%                                       | 42 (15.3%)                                 | —                                           | 151 (15.7%)                      | 365 (18.3%)                                                            |
| 70% to < 90%                                | 100 (36.4%)                                | —                                           | 338 (35.1%)                      | 665 (33.3%)                                                            |
| 90% to < 110%                               | 130 (47.3%)                                | —                                           | 460 (47.8%)                      | 938 (46.9%)                                                            |
| ≥ 110%                                      | 3 (1.1%)                                   | —                                           | 11 (1.1%)                        | 27 (1.4%)                                                              |

ISS = Integrated Summary of Safety; max = maximum; mBC = metastatic breast cancer; min = minimum; SG = sacituzumab govitecan; StD = standard deviation; TPC = treatment of physician's choice

a Treatment duration (in months) is (date of the last treatment administration – date of the first treatment administration + 1)/30.4375.

b Relative dose intensity (%) is calculated as (total amount of study drug administered/total amount of study drug planned by protocol) \* 100%.

Percentages are based on the total number of participants in the corresponding column

**Table 51 Participant Disposition and Reason for Discontinuation From Treatment (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                    | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<sup>a</sup><br/>(N = 276)</b> | <b>Overall mBC<sup>b</sup><br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<sup>c</sup><br/>(N = 1999)</b> |
|------------------------------------|--------------------------------------------|---------------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------|
| Participants treated               | 275 (100.0%)                               | 276 (100.0%)                                            | 963 (100.0%)                                 | 1999 (100.0%)                                                                      |
| On treatment                       | 75 (27.3%)                                 | 39 (14.1%)                                              | 75 (7.8%)                                    | 124 (6.2%)                                                                         |
| Permanently discontinued treatment | 200 (72.7%)                                | 237 (85.9%)                                             | 888 (92.2%)                                  | 1875 (93.8%)                                                                       |
| Reason of end of treatment         |                                            |                                                         |                                              |                                                                                    |
| Progressive disease                | 161 (58.5%)                                | 195 (70.7%)                                             | 735 (76.3%)                                  | 1441 (72.1%)                                                                       |

|                                                                             |           |           |           |            |
|-----------------------------------------------------------------------------|-----------|-----------|-----------|------------|
| Protocol deviation                                                          | 0         | 0         | 1 (0.1%)  | 1 (< 0.1%) |
| Death                                                                       | 6 (2.2%)  | 2 (0.7%)  | 10 (1.0%) | 31 (1.6%)  |
| Treatment delay > 3 weeks                                                   | 0         | 0         | 6 (0.6%)  | 9 (0.5%)   |
| Treatment delay for any reason > 5 weeks                                    | 0         | 0         | 0         | 15 (0.8%)  |
| Participant decision                                                        | 16 (5.8%) | 13 (4.7%) | 37 (3.8%) | 94 (4.7%)  |
| Adverse event                                                               | 10 (3.6%) | 22 (8.0%) | 47 (4.9%) | 180 (9.0%) |
| Lost to follow-up                                                           | 0         | 0         | 0         | 3 (0.2%)   |
| Investigator's discretion                                                   | 7 (2.5%)  | 5 (1.8%)  | 30 (3.1%) | 45 (2.3%)  |
| Study drug not administered (after randomization)                           | 0         | 0         | 1 (0.1%)  | 1 (< 0.1%) |
| Sponsor's decision                                                          | 0         | 0         | 1 (0.1%)  | 2 (0.1%)   |
| COVID-19                                                                    | 0         | 0         | 0         | 1 (< 0.1%) |
| Failure to resolve a toxicity within 3 weeks of the last dose of study drug | 0         | 0         | 0         | 2 (0.1%)   |
| Non-compliance with study drug                                              | 0         | 0         | 0         | 1 (< 0.1%) |
| Other                                                                       | 0         | 0         | 20 (2.1%) | 48 (2.4%)  |
| Missing                                                                     | 0         | 0         | 0         | 1 (< 0.1%) |

COVID-19 = coronavirus disease 2019; HER2– = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer, nab = nanoparticle albumin-bound; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

a GS-US-592-6238 TPC group includes participants who received paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin in GS-US-592-6238.

b Overall mBC group includes mTNBC and HR+/HER2–mBC participants from IMMU-132-01 treated with SG 10 mg/kg and all participants from IMMU-132-05, IMMU-132-09, and GS-US-592-6238 treated with SG.

c All Treated (Expanded) SG (10 mg/kg) group includes all participants treated with SG 10 mg/kg regardless of tumor type in IMMU-132-01 and all participants treated with SG from IMMU-132-05, IMMU-132-06 Cohorts 1 & 2, IMMU-132-09, IMMU-132-13, GS-US-577-6153, and GS-US-592-6238.

Participants treated with SG in GS-US-592-6238 crossover phase are excluded from Overall mBC and All Treated (Expanded) SG (10 mg/kg) groups.

On treatment participants are those still on treatment (randomized treatment for GS-US-592-6238) by the date of clinical database cut-off.

One participant from Study IMMU-132-01 who received study drug was mistakenly marked as 'study drug not administered after randomization'.

Patient demographics and baseline characteristics were previously presented in section 552.4.2.

## Adverse events

### Adverse event summary

**Table 52 Overall Summary of Adverse Events (Study GS-US-592-6238 ISS Populations [Expanded])**

|                       | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG (10 mg/kg)<br/>(N = 1999)</b> |
|-----------------------|--------------------------------------------|---------------------------------------------|----------------------------------|--------------------------------------------------------------------|
| AEs                   | 273 (99.3%)                                | 269 (97.5%)                                 | 960 (99.7%)                      | 1991 (99.6%)                                                       |
| Grade 3 or higher     | 181 (65.8%)                                | 171 (62.0%)                                 | 687 (71.3%)                      | 1465 (73.3%)                                                       |
| Treatment-related AEs | 271 (98.5%)                                | 258 (93.5%)                                 | 942 (97.8%)                      | 1937 (96.9%)                                                       |
| SAEs                  | 71 (25.8%)                                 | 67 (24.3%)                                  | 266 (27.6%)                      | 763 (38.2%)                                                        |

|                                                      |             |             |                              |                               |
|------------------------------------------------------|-------------|-------------|------------------------------|-------------------------------|
| Treatment-related SAEs                               | 46 (16.7%)  | 37 (13.4%)  | 148 (15.4%)                  | 420 (21.0%)                   |
| AEs leading to death                                 | 7 (2.5%)    | 1 (0.4%)    | 15 (1.6%)                    | 63 (3.2%)                     |
| Treatment-related AEs leading to death               | 6 (2.2%)    | 1 (0.4%)    | 7 (0.7%)                     | 28 (1.4%)                     |
| AEs leading to study drug withdrawal/discontinuation | 10 (3.6%)   | 33 (12.0%)  | 45 (4.7%)                    | 177 (8.9%)                    |
| AEs leading to study drug dose reduction             | 101 (36.7%) | 124 (44.9%) | 249/801 (31.1%) <sup>a</sup> | 532/1597 (33.3%) <sup>a</sup> |
| AEs leading to study drug interruption               | 181 (65.8%) | 171 (62.0%) | 598 (62.1%)                  | 1214 (60.7%)                  |

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse events; TPC = treatment of physician's choice

a AEs leading to study drug dose reduction were not collected in IMMU-132-01; therefore, IMMU-132-01 participants were excluded from the denominators for percentages of TEAEs leading to study drug dose reduction for the last 2 columns.

Percentages are based on the total number of participants in the corresponding column.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and 'Unrelated'. Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe;

4 = Life-Threatening; 5 = Death.

**Table 53 Adverse Events in ≥ 10% of Participants by Preferred Term (Study GS-US-592-6238 ISS Populations [Expanded])**

| <b>Preferred Term</b>                   | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|-----------------------------------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| Number (%) of participants with any AEs | 273 (99.3%)                                | 269 (97.5%)                                 | 960 (99.7%)                      | 1991 (99.6%)                                                           |
| Neutropenia                             | 183 (66.5%)                                | 157 (56.9%)                                 | 648 (67.3%)                      | 1122 (56.1%)                                                           |
| Nausea                                  | 167 (60.7%)                                | 95 (34.4%)                                  | 598 (62.1%)                      | 1139 (57.0%)                                                           |
| Alopecia                                | 151 (54.9%)                                | 75 (27.2%)                                  | 465 (48.3%)                      | 907 (45.4%)                                                            |
| Diarrhoea                               | 148 (53.8%)                                | 55 (19.9%)                                  | 577 (59.9%)                      | 1192 (59.6%)                                                           |
| Fatigue                                 | 130 (47.3%)                                | 129 (46.7%)                                 | 553 (57.4%)                      | 1165 (58.3%)                                                           |
| Anaemia                                 | 107 (38.9%)                                | 138 (50.0%)                                 | 386 (40.1%)                      | 850 (42.5%)                                                            |
| Constipation                            | 104 (37.8%)                                | 68 (24.6%)                                  | 353 (36.7%)                      | 692 (34.6%)                                                            |
| Leukopenia                              | 70 (25.5%)                                 | 70 (25.4%)                                  | 188 (19.5%)                      | 376 (18.8%)                                                            |
| Vomiting                                | 69 (25.1%)                                 | 35 (12.7%)                                  | 301 (31.3%)                      | 593 (29.7%)                                                            |
| Alanine aminotransferase increased      | 56 (20.4%)                                 | 81 (29.3%)                                  | 136 (14.1%)                      | 222 (11.1%)                                                            |
| Cough                                   | 49 (17.8%)                                 | 35 (12.7%)                                  | 179 (18.6%)                      | 320 (16.0%)                                                            |
| Decreased appetite                      | 48 (17.5%)                                 | 27 (9.8%)                                   | 224 (23.3%)                      | 550 (27.5%)                                                            |
| Aspartate aminotransferase increased    | 47 (17.1%)                                 | 69 (25.0%)                                  | 137 (14.2%)                      | 202 (10.1%)                                                            |
| Headache                                | 47 (17.1%)                                 | 33 (12.0%)                                  | 176 (18.3%)                      | 261 (13.1%)                                                            |
| Stomatitis                              | 42 (15.3%)                                 | 18 (6.5%)                                   | 102 (10.6%)                      | 194 (9.7%)                                                             |
| Abdominal pain                          | 41 (14.9%)                                 | 16 (5.8%)                                   | 179 (18.6%)                      | 356 (17.8%)                                                            |
| Blood alkaline phosphatase increased    | 36 (13.1%)                                 | 17 (6.2%)                                   | 103 (10.7%)                      | 169 (8.5%)                                                             |

| Preferred Term                    | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall mBC<br>(N = 963) | All Treated<br>(Expanded)<br>SG<br>(10 mg/kg)<br>(N = 1999) |
|-----------------------------------|-----------------------------------|------------------------------------|--------------------------|-------------------------------------------------------------|
| Upper respiratory tract infection | 34 (12.4%)                        | 16 (5.8%)                          | 103 (10.7%)              | 160 (8.0%)                                                  |
| Rash                              | 32 (11.6%)                        | 22 (8.0%)                          | 123 (12.8%)              | 229 (11.5%)                                                 |
| Lymphopenia                       | 31 (11.3%)                        | 28 (10.1%)                         | 108 (11.2%)              | 185 (9.3%)                                                  |
| Back pain                         | 29 (10.5%)                        | 23 (8.3%)                          | 138 (14.3%)              | 269 (13.5%)                                                 |
| Pyrexia                           | 29 (10.5%)                        | 27 (9.8%)                          | 132 (13.7%)              | 304 (15.2%)                                                 |
| Pruritus                          | 27 (9.8%)                         | 17 (6.2%)                          | 110 (11.4%)              | 223 (11.2%)                                                 |
| Urinary tract infection           | 27 (9.8%)                         | 40 (14.5%)                         | 116 (12.0%)              | 238 (11.9%)                                                 |
| Arthralgia                        | 26 (9.5%)                         | 33 (12.0%)                         | 134 (13.9%)              | 243 (12.2%)                                                 |
| Dyspnoea                          | 25 (9.1%)                         | 39 (14.1%)                         | 175 (18.2%)              | 354 (17.7%)                                                 |
| Hypokalaemia                      | 23 (8.4%)                         | 12 (4.3%)                          | 128 (13.3%)              | 252 (12.6%)                                                 |
| Dizziness                         | 22 (8.0%)                         | 19 (6.9%)                          | 108 (11.2%)              | 197 (9.9%)                                                  |
| Hypomagnesaemia                   | 15 (5.5%)                         | 12 (4.3%)                          | 97 (10.1%)               | 208 (10.4%)                                                 |
| Neuropathy peripheral             | 12 (4.4%)                         | 35 (12.7%)                         | 47 (4.9%)                | 87 (4.4%)                                                   |
| Thrombocytopenia                  | 12 (4.4%)                         | 78 (28.3%)                         | 71 (7.4%)                | 149 (7.5%)                                                  |

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; SG = sacituzumab govitecan; PT = preferred term; TPC = treatment of physician's choice

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Multiple AEs are counted only once per participant for each PT.

MedDRA Version 27.1 was used for coding.

PTs were presented by descending order of the frequency in the GS-US-592-6238 SG group.

The following terms are mapped: Neutrophil count decreased à Neutropenia, White blood cell count decreased à Leukopenia, Lymphocyte count decreased à Lymphopenia, Haemoglobin decreased à Anaemia, Red blood cell count decreased à Anaemia, Platelet count decreased à Thrombocytopenia, Asthenia à Fatigue, Typhlitis à Neutropenic colitis, Dyspnoea exertional à Dyspnoea.

### **Grade ≥ 3 Adverse Events**

**Table 54 Grade 3 or Higher Adverse Events Reported in ≥ 5% of Participants by Preferred Term (Study GS-US-592-6238 ISS Populations [Expanded])**

| Preferred Term                                            | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall mBC<br>(N = 963) | All Treated<br>(Expanded)<br>SG<br>(10 mg/kg)<br>(N = 1999) |
|-----------------------------------------------------------|-----------------------------------|------------------------------------|--------------------------|-------------------------------------------------------------|
| Number (%) of participants with any Grade 3 or higher AEs | 181 (65.8%)                       | 171 (62.0%)                        | 687 (71.3%)              | 1465 (73.3%)                                                |
| Neutropenia                                               | 118 (42.9%)                       | 112 (40.6%)                        | 468 (48.6%)              | 808 (40.4%)                                                 |
| Diarrhoea                                                 | 25 (9.1%)                         | 2 (0.7%)                           | 96 (10.0%)               | 224 (11.2%)                                                 |
| Leukopenia                                                | 20 (7.3%)                         | 35 (12.7%)                         | 92 (9.6%)                | 192 (9.6%)                                                  |
| Anaemia                                                   | 12 (4.4%)                         | 45 (16.3%)                         | 74 (7.7%)                | 210 (10.5%)                                                 |
| Febrile neutropenia                                       | 12 (4.4%)                         | 3 (1.1%)                           | 54 (5.6%)                | 142 (7.1%)                                                  |
| Lymphopenia                                               | 10 (3.6%)                         | 7 (2.5%)                           | 30 (3.1%)                | 50 (3.7%)                                                   |

|                                    |          |            |           |            |
|------------------------------------|----------|------------|-----------|------------|
| Alanine aminotransferase increased | 9 (3.3%) | 17 (6.2%)  | 17 (1.8%) | 29 (1.5%)  |
| Fatigue                            | 9 (3.3%) | 11 (4.0%)  | 56 (5.8%) | 181 (9.1%) |
| Thrombocytopenia                   | 2 (0.7%) | 33 (12.0%) | 12 (1.2%) | 26 (1.3%)  |

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Multiple AEs are counted only once per participant for each PT.

MedDRA Version 27.1 was used for coding.

PTs were presented by descending order of the frequency in the GS-US-592-6238 SG group.

The following terms are mapped: Neutrophil count decreased à Neutropenia, White blood cell count decreased à Leukopenia, Lymphocyte count decreased à Lymphopenia, Haemoglobin decreased à Anaemia, Red blood cell count decreased à Anaemia, Platelet count decreased à Thrombocytopenia, Asthenia à Fatigue, Typhlitis à Neutropenic colitis, Dyspnoea exertional à Dyspnoea.

### **Treatment-related Adverse Events**

**Table 55 Treatment-Related Adverse Events Reported in ≥ 10% of Participants in Selected ISS Populations by Preferred Term (Study GS-US-592-6238 ISS Populations [Expanded])**

| <b>Preferred Term</b>                                     | <b>GS-US-592-6238 SG<br/>(N = 275)</b> | <b>GS-US-592-6238 TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated (Expanded) SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|-----------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|----------------------------------------------------------------|
| Number (%) of participants with any treatment-related AEs | 271 (98.5%)                            | 258 (93.5%)                             | 942 (97.8%)                      | 1937 (96.9%)                                                   |
| Neutropenia                                               | 182 (66.2%)                            | 155 (56.2%)                             | 644 (66.9%)                      | 1113 (55.7%)                                                   |
| Nausea                                                    | 160 (58.2%)                            | 86 (31.2%)                              | 557 (57.8%)                      | 1051 (52.6%)                                                   |
| Alopecia                                                  | 149 (54.2%)                            | 74 (26.8%)                              | 453 (47.0%)                      | 877 (43.9%)                                                    |
| Diarrhoea                                                 | 136 (49.5%)                            | 43 (15.6%)                              | 527 (54.7%)                      | 1093 (54.7%)                                                   |
| Fatigue                                                   | 118 (42.9%)                            | 113 (40.9%)                             | 498 (51.7%)                      | 1032 (51.6%)                                                   |
| Anaemia                                                   | 97 (35.3%)                             | 133 (48.2%)                             | 348 (36.1%)                      | 734 (36.7%)                                                    |
| Leukopenia                                                | 69 (25.1%)                             | 69 (25.0%)                              | 184 (19.1%)                      | 371 (18.6%)                                                    |
| Constipation                                              | 63 (22.9%)                             | 45 (16.3%)                              | 194 (20.1%)                      | 347 (17.4%)                                                    |
| Vomiting                                                  | 56 (20.4%)                             | 24 (8.7%)                               | 257 (26.7%)                      | 507 (25.4%)                                                    |
| Alanine aminotransferase increased                        | 42 (15.3%)                             | 65 (23.6%)                              | 79 (8.2%)                        | 130 (6.5%)                                                     |
| Decreased appetite                                        | 38 (13.8%)                             | 23 (8.3%)                               | 178 (18.5%)                      | 446 (22.3%)                                                    |
| Stomatitis                                                | 38 (13.8%)                             | 18 (6.5%)                               | 94 (9.8%)                        | 175 (8.8%)                                                     |
| Aspartate aminotransferase increased                      | 34 (12.4%)                             | 59 (21.4%)                              | 71 (7.4%)                        | 106 (5.3%)                                                     |
| Lymphopenia                                               | 31 (11.3%)                             | 24 (8.7%)                               | 101 (10.5%)                      | 166 (8.3%)                                                     |
| Abdominal pain                                            | 28 (10.2%)                             | 9 (3.3%)                                | 109 (11.3%)                      | 195 (9.8%)                                                     |
| Thrombocytopenia                                          | 12 (4.4%)                              | 77 (27.9%)                              | 64 (6.6%)                        | 136 (6.8%)                                                     |
| Neuropathy peripheral                                     | 8 (2.9%)                               | 34 (12.3%)                              | 30 (3.1%)                        | 56 (2.8%)                                                      |

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and Unrelated'.

Multiple AEs are counted only once per participant for each PT.

MedDRA Version 27.1 was used for coding.

The following terms are mapped: Neutrophil count decreased à Neutropenia, White blood cell count decreased à Leukopenia, Lymphocyte count decreased à Lymphopenia, Haemoglobin decreased à Anaemia, Red blood cell count

decreased à Anaemia, Platelet count decreased à Thrombocytopenia, Asthenia à Fatigue, Typhlitis à Neutropenic colitis, Dyspnoea exertional à Dyspnoea.

Source: ISS (Expanded), [Adhoc 202348 Table 14.3.2.3.2.2](#)

MedDRA Version 27.1 was used for coding.

The following terms are mapped: Neutrophil count decreased à Neutropenia, White blood cell count decreased à Leukopenia, Lymphocyte count decreased à Lymphopenia, Haemoglobin decreased à Anaemia, Red blood cell count decreased à Anaemia, Platelet count decreased à Thrombocytopenia, Asthenia à Fatigue, Typhlitis à Neutropenic colitis, Dyspnoea exertional à Dyspnoea.

## **Treatment-related Grade ≥3 Adverse Events**

**Table 56 Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (excerpt from Study GS-US-592-6238 ISS)**

| System Organ Class<br>Preferred Term                                                                      | GS-US-592-6238<br>SG<br>(N=275) | GS-US-592-6238<br>TPC<br>(N=276) | Overall mBC<br>(N=963) | All Treated<br>SG (10 mg/kg)<br>(N=1354) |
|-----------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------------|------------------------|------------------------------------------|
| Number (%) of Participants with Any Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events | 167 ( 60.7%)                    | 147 ( 53.3%)                     | 615 ( 63.9%)           | 854 ( 63.1%)                             |
| Blood and lymphatic system disorders                                                                      | 133 ( 48.4%)                    | 128 ( 46.4%)                     | 516 ( 53.6%)           | 697 ( 51.5%)                             |
| Neutropenia                                                                                               | 118 ( 42.9%)                    | 108 ( 39.1%)                     | 465 ( 48.3%)           | 605 ( 44.7%)                             |
| Leukopenia                                                                                                | 20 ( 7.3%)                      | 34 ( 12.3%)                      | 91 ( 9.4%)             | 140 ( 10.3%)                             |
| Febrile neutropenia                                                                                       | 12 ( 4.4%)                      | 3 ( 1.1%)                        | 52 ( 5.4%)             | 77 ( 5.7%)                               |
| Anaemia                                                                                                   | 10 ( 3.6%)                      | 41 ( 14.9%)                      | 63 ( 6.5%)             | 112 ( 8.3%)                              |
| Lymphopenia                                                                                               | 10 ( 3.6%)                      | 5 ( 1.8%)                        | 28 ( 2.9%)             | 42 ( 3.1%)                               |
| Thrombocytopenia                                                                                          | 2 ( 0.7%)                       | 32 ( 11.6%)                      | 12 ( 1.2%)             | 16 ( 1.2%)                               |
| Gastrointestinal disorders                                                                                | 36 ( 13.1%)                     | 4 ( 1.4%)                        | 128 ( 13.3%)           | 195 ( 14.4%)                             |
| Diarrhoea                                                                                                 | 21 ( 7.6%)                      | 1 ( 0.4%)                        | 87 ( 9.0%)             | 126 ( 9.3%)                              |
| Nausea                                                                                                    | 4 ( 1.5%)                       | 1 ( 0.4%)                        | 20 ( 2.1%)             | 34 ( 2.5%)                               |
| Neutropenic colitis                                                                                       | 4 ( 1.5%)                       | 0                                | 12 ( 1.2%)             | 18 ( 1.3%)                               |
| Vomiting                                                                                                  | 4 ( 1.5%)                       | 3 ( 1.1%)                        | 16 ( 1.7%)             | 22 ( 1.6%)                               |
| Colitis                                                                                                   | 2 ( 0.7%)                       | 0                                | 5 ( 0.5%)              | 7 ( 0.5%)                                |
| Stomatitis                                                                                                | 2 ( 0.7%)                       | 0                                | 6 ( 0.6%)              | 10 ( 0.7%)                               |
| Abdominal pain                                                                                            | 1 ( 0.4%)                       | 0                                | 6 ( 0.6%)              | 9 ( 0.7%)                                |
| Dysphagia                                                                                                 | 1 ( 0.4%)                       | 0                                | 1 ( 0.1%)              | 1 ( <0.1%)                               |
| Oesophagitis                                                                                              | 1 ( 0.4%)                       | 0                                | 1 ( 0.1%)              | 1 ( <0.1%)                               |

## **Adverse Drug Reactions (ADR) in the SmPC**

Section 4.8 of the SmPC is updated to include the GS-US-592-6238 (ASCENT-03) study population of patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours do not express PD-L1 or patients previously treated with anti-PD-(L)1 agents in the early setting whose tumours do express PD-L1 receiving SG as monotherapy, into the current 'Overall mBC SG' pooled safety dataset.

The below encompasses the adverse reactions included in Table 3 'List of adverse reactions' of the SmPC with related frequency categories from the latest monotherapy safety pooled dataset 'Overall mBC SG' studies (N= 963) as follows:

- Study IMMU-132-01<sup>a</sup>
- Study IMMU-132-05<sup>b</sup>
- Study IMMU-132-09<sup>b</sup>
- Study GS-US-592-6238<sup>b</sup>.

<sup>a</sup> Only participants who received a starting dose of SG 10 mg/kg monotherapy were included

<sup>b</sup> All SG-treated participants from the study were included in the pooled analysis

**Table 57 List of adverse reactions**

| <b>System organ class (SOC)</b>             | <b>Frequency</b> | <b>Adverse reactions</b>                                                                                |
|---------------------------------------------|------------------|---------------------------------------------------------------------------------------------------------|
| <b>Infections and infestations</b>          |                  |                                                                                                         |
|                                             | Very common      | Urinary tract infection<br>Upper respiratory tract infection                                            |
|                                             | Common           | Sepsis<br>Pneumonia<br>Influenza<br>Bronchitis<br>Nasopharyngitis<br>Sinusitis<br>Oral herpes           |
| <b>Blood and lymphatic system disorders</b> |                  |                                                                                                         |
|                                             | Very common      | Neutropenia <sup>1</sup><br>Anaemia <sup>2</sup><br>Leukopenia <sup>3</sup><br>Lymphopenia <sup>4</sup> |
|                                             | Common           | Febrile neutropenia<br>Thrombocytopenia <sup>5</sup>                                                    |
| <b>Immune system disorders</b>              |                  |                                                                                                         |
|                                             | Very common      | Hypersensitivity <sup>6</sup>                                                                           |
| <b>Metabolism and nutrition disorders</b>   |                  |                                                                                                         |
|                                             | Very common      | Decreased appetite<br>Hypokalaemia<br>Hypomagnesaemia                                                   |
|                                             | Common           | Dehydration<br>Hyperglycaemia<br>Hypophosphataemia<br>Hypocalcaemia<br>Hyponatraemia                    |
| <b>Psychiatric disorders</b>                |                  |                                                                                                         |
|                                             | Common           | Insomnia<br>Anxiety                                                                                     |

| System organ class (SOC)                               | Frequency   | Adverse reactions                                                                                                                            |
|--------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Nervous system disorders</b>                        |             |                                                                                                                                              |
|                                                        | Very common | Headache<br>Dizziness                                                                                                                        |
|                                                        | Common      | Dysgeusia                                                                                                                                    |
| <b>Vascular disorders</b>                              |             |                                                                                                                                              |
|                                                        | Common      | Hypotension                                                                                                                                  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |             |                                                                                                                                              |
|                                                        | Very common | Dyspnoea <sup>7</sup><br>Cough                                                                                                               |
|                                                        | Common      | Epistaxis<br>Productive cough<br>Rhinorrhoea<br>Nasal congestion<br>Upper airway cough syndrome                                              |
| <b>Gastrointestinal disorders</b>                      |             |                                                                                                                                              |
|                                                        | Very common | Diarrhoea<br>Vomiting<br>Constipation<br>Stomatitis<br>Nausea<br>Abdominal Pain                                                              |
|                                                        | Common      | Neutropenic colitis <sup>8</sup><br>Colitis<br>Abdominal pain upper<br>Dyspepsia<br>Gastrooesophageal reflux disease<br>Abdominal distension |
|                                                        | Uncommon    | Enteritis                                                                                                                                    |
| <b>Skin and subcutaneous tissue disorders</b>          |             |                                                                                                                                              |

| System organ class (SOC)                                    | Frequency   | Adverse reactions                                                                                            |
|-------------------------------------------------------------|-------------|--------------------------------------------------------------------------------------------------------------|
|                                                             | Very common | Alopecia<br>Rash<br>Pruritus                                                                                 |
|                                                             | Common      | Rash maculopapular<br>Skin hyperpigmentation<br>Dermatitis acneiform<br>Dry skin                             |
| <b>Musculoskeletal and connective tissue disorders</b>      |             |                                                                                                              |
|                                                             | Very common | Back pain<br>Arthralgia                                                                                      |
|                                                             | Common      | Musculoskeletal chest pain<br>Muscle spasms                                                                  |
| <b>Renal and urinary disorders</b>                          |             |                                                                                                              |
|                                                             | Common      | Haematuria<br>Proteinuria<br>Dysuria                                                                         |
| <b>General disorders and administration site conditions</b> |             |                                                                                                              |
|                                                             | Very common | Fatigue <sup>9</sup>                                                                                         |
|                                                             | Common      | Pain<br>Chills                                                                                               |
| <b>Investigations</b>                                       |             |                                                                                                              |
|                                                             | Very common | Blood alkaline phosphatase increased                                                                         |
|                                                             | Common      | Weight decreased<br>Activated partial thromboplastin time prolonged<br>Blood lactate dehydrogenase increased |
| <b>Injury, poisoning and procedural complications</b>       |             |                                                                                                              |
|                                                             | Common      | Infusion related reaction                                                                                    |

1: Includes the following preferred terms: neutropenia; neutrophil count decreased.

2: Includes the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.

3: Includes the following preferred terms: leukopenia; white blood cell count decreased.

4: Includes the following preferred terms: lymphopenia; lymphocyte count decreased.

5: Includes the following preferred terms: thrombocytopenia; platelet count decreased.

6: Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: rash, infusion related reaction, hypersensitivity, periorbital oedema, catheter site dermatitis, contrast media reaction, dermatitis allergic, dermatitis contact, eczema, rash erythematous, urticaria, anaphylactic reaction, bronchospasm, conjunctivitis allergic, dermatitis, dermatitis acneiform, dermatitis

exfoliative generalised, drug hypersensitivity, infusion related hypersensitivity reaction, rash macular, rash maculo-papular, rash papular, rash pustular, rhinitis allergic, swelling face, swelling of eyelid, swollen tongue, Type IV hypersensitivity reaction, cough with pruritus, cough with rash, dyspnoea with pruritus, dyspnoea with rash, dyspnoea with wheezing and rash, hypotension with dyspnoea

7: Includes the following preferred terms: dyspnoea; dyspnoea exertional

8: Includes the preferred term of neutropenic colitis and events reported as typhlitis

9: Includes the following preferred terms: fatigue, asthenia

As a consequence of the updated 'Overall mBC SG' pooled safety dataset, the frequency of the following ADRs has been revised in section 4.8 of the SmPC as follows:

- 'Insomnia' from 'Very common' to 'Common'
- 'Stomatitis' from 'Common' to 'Very common'
- 'Blood alkaline phosphatase increased' from 'Common' to 'Very common'
- 'Infusion related reaction' from 'Uncommon' to 'Common'.

## Serious adverse event/deaths/other significant events

### Serious Adverse Events (SAEs)

**Table 58 Serious Adverse Events in  $\geq 1\%$  of the Participants in Selected ISS Populations by Preferred Term (Study GS-US-592-6238 ISS Populations [Expanded])**

| Preferred Term                                                                | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall<br>mBC<br>(N = 963) | All Treated<br>(Expanded)<br>SG<br>(10 mg/kg)<br>(N = 1999) |
|-------------------------------------------------------------------------------|-----------------------------------|------------------------------------|-----------------------------|-------------------------------------------------------------|
| Number (%) of participants with any treatment-emergent serious adverse events | 71 (25.8%)                        | 67 (24.3%)                         | 266 (27.6%)                 | 763 (38.2%)                                                 |
| Febrile neutropenia                                                           | 10 (3.6%)                         | 2 (0.7%)                           | 43 (4.5%)                   | 119 (6.0%)                                                  |
| Neutropenia                                                                   | 10 (3.6%)                         | 8 (2.9%)                           | 28 (2.9%)                   | 73 (3.7%)                                                   |
| Diarrhoea                                                                     | 9 (3.3%)                          | 1 (0.4%)                           | 36 (3.7%)                   | 99 (5.0%)                                                   |
| Pneumonia                                                                     | 6 (2.2%)                          | 9 (3.3%)                           | 20 (2.1%)                   | 50 (2.5%)                                                   |
| Neutropenic colitis                                                           | 4 (1.5%)                          | 0                                  | 11 (1.1%)                   | 26 (1.3%)                                                   |
| Sepsis                                                                        | 4 (1.5%)                          | 4 (1.4%)                           | 10 (1.0%)                   | 35 (1.8%)                                                   |
| Dehydration                                                                   | 3 (1.1%)                          | 0                                  | 9 (0.9%)                    | 11 (0.6%)                                                   |
| Pleural effusion                                                              | 3 (1.1%)                          | 1 (0.4%)                           | 10 (1.0%)                   | 17 (0.9%)                                                   |
| Pulmonary embolism                                                            | 3 (1.1%)                          | 6 (2.2%)                           | 8 (0.8%)                    | 18 (0.9%)                                                   |
| Pyrexia                                                                       | 3 (1.1%)                          | 4 (1.4%)                           | 9 (0.9%)                    | 29 (1.5%)                                                   |
| Urinary tract infection                                                       | 2 (0.7%)                          | 1 (0.4%)                           | 8 (0.8%)                    | 33 (1.7%)                                                   |
| Vomiting                                                                      | 2 (0.7%)                          | 0                                  | 15 (1.6%)                   | 31 (1.6%)                                                   |
| Abdominal pain                                                                | 1 (0.4%)                          | 0                                  | 11 (1.1%)                   | 23 (1.2%)                                                   |

| Preferred Term            | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall<br>mBC<br>(N = 963) | All Treated<br>(Expanded)<br>SG<br>(10 mg/kg)<br>(N = 1999) |
|---------------------------|-----------------------------------|------------------------------------|-----------------------------|-------------------------------------------------------------|
| Acute kidney injury       | 1 (0.4%)                          | 1 (0.4%)                           | 5 (0.5%)                    | 25 (1.3%)                                                   |
| Anaemia                   | 1 (0.4%)                          | 6 (2.2%)                           | 8 (0.8%)                    | 22 (1.1%)                                                   |
| Dyspnoea                  | 1 (0.4%)                          | 1 (0.4%)                           | 11<br>(1.1%)                | 22 (1.1%)                                                   |
| Vascular device infection | 1 (0.4%)                          | 3 (1.1%)                           | 3 (0.3%)                    | 5 (0.3%)                                                    |
| Fatigue                   | 0                                 | 0                                  | 5 (0.5%)                    | 19 (1.0%)                                                   |
| Thrombocytopenia          | 0                                 | 10 (3.6%)                          | 4 (0.4%)                    | 8 (0.4%)                                                    |

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Multiple AEs are counted only once per participant for each PT.

MedDRA Version 27.1 was used for coding.

PTs were presented by descending order of the frequency in the GS-US-592-6238 SG group.

The following terms are mapped: Neutrophil count decreased à Neutropenia, White blood cell count decreased à Leukopenia, Lymphocyte count decreased à Lymphopenia, Haemoglobin decreased à Anaemia, Red blood cell count decreased à Anaemia, Platelet count decreased à Thrombocytopenia, Asthenia à Fatigue, Typhilitis à Neutropenic colitis, Dyspnoea exertional à Dyspnoea.

## Deaths

**Table 59 Summary of Deaths (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                                                   | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall<br>mBC<br>(N = 963) | All Treated<br>(Expanded)<br>SG<br>(10 mg/kg)<br>(N = 1999) |
|-------------------------------------------------------------------|-----------------------------------|------------------------------------|-----------------------------|-------------------------------------------------------------|
| All deaths                                                        | 101 (36.7%)                       | 102 (37.0%)                        | 665<br>(69.1%)              | 1426<br>(71.3%)                                             |
| Adverse event                                                     | 9 (3.3%)                          | 3 (1.1%)                           | 21 (2.2%)                   | 73 (3.7%)                                                   |
| Progressive disease                                               | 82 (29.8%)                        | 89 (32.2%)                         | 606<br>(62.9%)              | 1255<br>(62.8%)                                             |
| During long-term follow-up and not related to study drug          | 10 (3.6%)                         | 10 (3.6%)                          | 10 (1.0%)                   | 24 (1.2%)                                                   |
| Other                                                             | 0                                 | 0                                  | 27 (2.8%)                   | 70 (3.5%)                                                   |
| Missing                                                           | 0                                 | 0                                  | 1 (0.1%)                    | 4 (0.2%)                                                    |
| Deaths within 30 days of the last dose of study drug <sup>a</sup> | 10 (3.6%)                         | 8 (2.9%)                           | 53 (5.5%)                   | 165 (8.3%)                                                  |
| Adverse event                                                     | 7 (2.5%)                          | 1 (0.4%)                           | 15 (1.6%)                   | 64 (3.2%)                                                   |
| Progressive disease                                               | 3 (1.1%)                          | 7 (2.5%)                           | 37 (3.8%)                   | 95 (4.8%)                                                   |
| During long-term follow-up and not related to study drug          | 0                                 | 0                                  | 0                           | 0                                                           |
| Other                                                             | 0                                 | 0                                  | 1 (0.1%)                    | 5 (0.3%)                                                    |
| Missing                                                           | 0                                 | 0                                  | 0                           | 1 (< 0.1%)                                                  |
| Deaths after 30 days of the last dose of study drug <sup>a</sup>  | 91 (33.1%)                        | 94 (34.1%)                         | 612<br>(63.6%)              | 1261<br>(63.1%)                                             |
| Adverse event                                                     | 2 (0.7%)                          | 2 (0.7%)                           | 6 (0.6%)                    | 9 (0.5%)                                                    |
| Progressive disease                                               | 79 (28.7%)                        | 82 (29.7%)                         | 569<br>(59.1%)              | 1160<br>(58.0%)                                             |

|                                                                   | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall<br/>mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|-------------------------------------------------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------|------------------------------------------------------------------------|
| During long-term follow-up and not related to study drug          | 10 (3.6%)                                  | 10 (3.6%)                                   | 10 (1.0%)                            | 24 (1.2%)                                                              |
| Other                                                             | 0                                          | 0                                           | 26 (2.7%)                            | 65 (3.3%)                                                              |
| Missing                                                           | 0                                          | 0                                           | 1 (0.1%)                             | 3 (0.2%)                                                               |
| Deaths within 60 days of the last dose of study drug <sup>a</sup> | 25 (9.1%)                                  | 22 (8.0%)                                   | 119 (12.4%)                          | 356 (17.8%)                                                            |
| Adverse event                                                     | 8 (2.9%)                                   | 2 (0.7%)                                    | 20 (2.1%)                            | 70 (3.5%)                                                              |
| Progressive disease                                               | 17 (6.2%)                                  | 17 (6.2%)                                   | 98 (10.2%)                           | 271 (13.6%)                                                            |
| During Long-term follow-up and not related to study drug          | 0                                          | 3 (1.1%)                                    | 0                                    | 1 (< 0.1%)                                                             |
| Other                                                             | 0                                          | 0                                           | 1 (0.1%)                             | 12 (0.6%)                                                              |
| Missing                                                           | 0                                          | 0                                           | 0                                    | 2 (0.1%)                                                               |
| Deaths after 60 days of the last dose of study drug <sup>a</sup>  | 76 (27.6%)                                 | 80 (29.0%)                                  | 546 (56.7%)                          | 1070 (53.5%)                                                           |
| Adverse event                                                     | 1 (0.4%)                                   | 1 (0.4%)                                    | 1 (0.1%)                             | 3 (0.2%)                                                               |
| Progressive disease                                               | 65 (23.6%)                                 | 72 (26.1%)                                  | 508 (52.8%)                          | 984 (49.2%)                                                            |
| During long-term follow-up and not related to study drug          | 10 (3.6%)                                  | 7 (2.5%)                                    | 10 (1.0%)                            | 23 (1.2%)                                                              |
| Other                                                             | 0                                          | 0                                           | 26 (2.7%)                            | 58 (2.9%)                                                              |
| Missing                                                           | 0                                          | 0                                           | 1 (0.1%)                             | 2 (0.1%)                                                               |

ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Percentages are based on the total number of participants in the corresponding column.

For summary of all deaths, deaths occurring in the crossover phase are included for the GS-US-592-6238 TPC group.

a For the GS-US-592-6238 TPC group, study drug refers to the drug taken in the randomized phase.

**Table 60 Adverse Events Leading to Death by System Organ Class and Preferred Term (Study GS-US-592-6238 ISS Populations [Expanded])**

| <b>System Organ Class<br/>Preferred Term</b>             | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|----------------------------------------------------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| Number (%) of participants with any AEs leading to death | 7 (2.5%)                                   | 1 (0.4%)                                    | 15 (1.6%)                        | 63 (3.2%)                                                              |
| Blood and lymphatic system disorders                     | 0                                          | 0                                           | 0                                | 2 (0.1%)                                                               |
| Febrile neutropenia                                      | 0                                          | 0                                           | 0                                | 1 (< 0.1%)                                                             |
| Leukopenia                                               | 0                                          | 0                                           | 0                                | 1 (< 0.1%)                                                             |
| Cardiac disorders                                        | 0                                          | 0                                           | 1 (0.1%)                         | 4 (0.2%)                                                               |
| Arrhythmia                                               | 0                                          | 0                                           | 1 (0.1%)                         | 1 (< 0.1%)                                                             |
| Cardiac arrest                                           | 0                                          | 0                                           | 0                                | 1 (< 0.1%)                                                             |
| Cardiac failure                                          | 0                                          | 0                                           | 0                                | 1 (< 0.1%)                                                             |
| Myocardial ischaemia                                     | 0                                          | 0                                           | 0                                | 1 (< 0.1%)                                                             |
| Gastrointestinal disorders                               | 1 (0.4%)                                   | 0                                           | 1 (0.1%)                         | 3 (0.2%)                                                               |
| Neutropenic colitis                                      | 1 (0.4%)                                   | 0                                           | 1 (0.1%)                         | 2 (0.1%)                                                               |
| Haematemesis                                             | 0                                          | 0                                           | 0                                | 1 (< 0.1%)                                                             |
| General disorders and administration                     | 0                                          | 0                                           | 0                                | 2 (0.1%)                                                               |

| <b>System Organ Class<br/>Preferred Term</b>                        | <b>GS-US-592-62<br/>38<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-<br/>6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|---------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| site conditions                                                     |                                                 |                                                  |                                  |                                                                        |
| Death                                                               | 0                                               | 0                                                | 0                                | 2 (0.1%)                                                               |
| Hepatobiliary disorders                                             | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Hepatobiliary disease                                               | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Infections and infestations                                         | 5 (1.8%)                                        | 0                                                | 8 (0.8%)                         | 28 (1.4%)                                                              |
| Sepsis                                                              | 3 (1.1%)                                        | 0                                                | 3 (0.3%)                         | 9 (0.5%)                                                               |
| Pneumonia                                                           | 1 (0.4%)                                        | 0                                                | 2 (0.2%)                         | 3 (0.2%)                                                               |
| Septic shock                                                        | 1 (0.4%)                                        | 0                                                | 2 (0.2%)                         | 6 (0.3%)                                                               |
| COVID-19                                                            | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| COVID-19 pneumonia                                                  | 0                                               | 0                                                | 1 (0.1%)                         | 1 (< 0.1%)                                                             |
| Enterocolitis infectious                                            | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Neutropenic sepsis                                                  | 0                                               | 0                                                | 0                                | 4 (0.2%)                                                               |
| Pneumonia aspiration                                                | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Pseudomonal sepsis                                                  | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Pulmonary sepsis                                                    | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Metabolism and nutrition disorders                                  | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Hypoglycaemia                                                       | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0                                               | 0                                                | 1 (0.1%)                         | 2 (0.1%)                                                               |
| Metastases to central nervous system                                | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Metastases to spine                                                 | 0                                               | 0                                                | 1 (0.1%)                         | 1 (< 0.1%)                                                             |
| Nervous system disorders                                            | 0                                               | 0                                                | 1 (0.1%)                         | 4 (0.2%)                                                               |
| Cerebral infarction                                                 | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Cerebrovascular accident                                            | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Ischaemic stroke                                                    | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Nervous system disorder                                             | 0                                               | 0                                                | 1 (0.1%)                         | 1 (< 0.1%)                                                             |
| Psychiatric disorders                                               | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Completed suicide                                                   | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Renal and urinary disorders                                         | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Acute kidney injury                                                 | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Respiratory, thoracic and mediastinal disorders                     | 1 (0.4%)                                        | 1 (0.4%)                                         | 3 (0.3%)                         | 14 (0.7%)                                                              |
| Acute respiratory failure                                           | 1 (0.4%)                                        | 0                                                | 1 (0.1%)                         | 1 (< 0.1%)                                                             |
| Acute respiratory distress syndrome                                 | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Apnoea                                                              | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Epistaxis                                                           | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Hypoxia                                                             | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Pleural effusion                                                    | 0                                               | 1 (0.4%)                                         | 0                                | 0                                                                      |
| Pulmonary embolism                                                  | 0                                               | 0                                                | 1 (0.1%)                         | 2 (0.1%)                                                               |
| Respiratory distress                                                | 0                                               | 0                                                | 0                                | 1 (< 0.1%)                                                             |
| Respiratory failure                                                 | 0                                               | 0                                                | 1 (0.1%)                         | 6 (0.3%)                                                               |

AE = adverse event; COVID-19 = coronavirus disease 2019; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TPC = treatment of physician's choice  
Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.  
Multiple AEs are counted only once per participant for each SOC and PT.  
MedDRA Version 27.1 was used for coding.

SOCs were presented alphabetically and PTs within SOC were presented by descending order of the frequency in the GS-US-592-6238 SG group.

The following terms are mapped: Neutrophil count decreased = Neutropenia, White blood cell count decreased = Leukopenia, Lymphocyte count decreased = Lymphopenia, Haemoglobin decreased = Anaemia, Red blood cell count decreased = Anaemia, Platelet count decreased = Thrombocytopenia, Asthenia = Fatigue, Typhlitis = Neutropenic colitis, Dyspnoea exertional = Dyspnoea.

Fatal infections secondary to neutropenia (including neutropenic colitis) occurred in 0.6% of patients in the Overall mBC pool.

### **Other significant events - Adverse Events of Special Interest (AESI)**

**Table 61 Definition of Adverse Events of Special Interest**

| <b>AESI Category</b>                        | <b>Definition</b>                                                                                                       |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Serious infections secondary to neutropenia | PTs under SOC: Infection and Infestations <sup>a</sup><br>(Serious infections occurring after any grade AE Neutropenia) |
| Severe diarrhea                             | PT: Diarrhea (Grade 3 or higher)                                                                                        |
| Hypersensitivity <sup>b</sup>               | PTs under: Hypersensitivity SMQ (narrow) and Anaphylactic Reaction SMQ (broad and narrow) <sup>c</sup>                  |
| Neutropenia <sup>d</sup>                    | PTs: neutropenia, neutrophil count decreased, febrile neutropenia                                                       |

AE = Adverse Events; AESI = Adverse Events of Special Interest; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SMQ = Standardised MedDRA Query; SOC = System Organ Class

a SAEs from SOC of Infections and Infestations that occurred within 11 days of neutropenia, febrile neutropenia or neutrophil count decreased.

b For the category of Hypersensitivity, only events whose onset dates are on the day of or 1 day after study drug administration are included.

c Anaphylactic Reaction SMQ (broad and narrow) is an algorithmic SMQ.

d Grouped AE terms

All AESI definitions are based on MedDRA version 27.1 or higher.

**Table 62 Adverse Events of Special Interest For SG: Overall Summary (Study GS-US-592-6238 ISS Populations [Expanded])**

| <b>AESI</b>                                 | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG (10<br/>mg/kg)<br/>(N = 1999)</b> |
|---------------------------------------------|--------------------------------------------|---------------------------------------------|----------------------------------|------------------------------------------------------------------------|
| Serious infections secondary to neutropenia | 9 (3.3%)                                   | 4 (1.4%)                                    | 28 (2.9%)                        | 73 (3.7%)                                                              |
| Severe diarrhea                             | 25 (9.1%)                                  | 2 (0.7%)                                    | 96 (10.0%)                       | 224 (11.2%)                                                            |
| Hypersensitivity                            | 21 (7.6%)                                  | 34 (12.3%)                                  | 123 (12.8%)                      | 237 (11.9%)                                                            |
| Neutropenia                                 | 187 (68.0%)                                | 158 (57.2%)                                 | 663 (68.8%)                      | 1185 (59.3%)                                                           |

AE = adverse event; AESI = adverse event of special interest; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

## Serious Infections Secondary to Neutropenia

**Table 63 Adverse Event of Special Interest for SG: Serious Infections Secondary to Neutropenia (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                                          | <b>GS-US-592-6238 SG<br/>(N = 275)</b> | <b>GS-US-592-6238 TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated (Expanded) SG<br/>(10 mg/kg)<br/>(N = 1999)</b> |
|----------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|----------------------------------------------------------------|
| <b>AESI: Serious Infections Secondary to Neutropenia</b> |                                        |                                         |                                  |                                                                |
| AEs                                                      | 9 (3.3%)                               | 4 (1.4%)                                | 28 (2.9%)                        | 73 (3.7%)                                                      |
| Grade 3 or higher                                        | 8 (2.9%)                               | 4 (1.4%)                                | 27 (2.8%)                        | 71 (3.6%)                                                      |
| Treatment-related AEs                                    | 4 (1.5%)                               | 2 (0.7%)                                | 15 (1.6%)                        | 46 (2.3%)                                                      |
| AEs leading to study drug dose reduction                 | 1 (0.4%)                               | 2 (0.7%)                                | 3/801 (0.4%) <sup>a</sup>        | 7/1597 (0.4%) <sup>a</sup>                                     |
| AEs leading to study drug interruption                   | 3 (1.1%)                               | 2 (0.7%)                                | 11 (1.1%)                        | 32 (1.6%)                                                      |
| AEs leading to study drug withdrawal/discontinuation     | 0                                      | 0                                       | 2 (0.2%)                         | 8 (0.4%)                                                       |
| AEs leading to death                                     | 1 (0.4%)                               | 0                                       | 1 (0.1%)                         | 11 (0.6%)                                                      |
| Treatment-related AEs leading to death                   | 1 (0.4%)                               | 0                                       | 1 (0.1%)                         | 10 (0.5%)                                                      |

AE = adverse event; AESI = adverse events of special interest; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

<sup>a</sup> AEs leading to study drug dose reduction were not collected in IMMU-132-01; therefore, IMMU-132-01 participants were excluded from the denominators for percentages of TEAEs leading to study drug dose reduction for the last 2 columns.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and 'Unrelated'. Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe;

4 = Life-Threatening; 5 = Death.

See definitions of Adverse Events of Special Interest in the Statistical Analysis Plan, CSR, and/or Summary of Clinical Safety.

## Time to Onset and Duration of Serious Infections Secondary to Neutropenia

The median time to first onset of serious infections secondary to neutropenia was similar in the study GS-US-592-6238 SG group (20 days) compared with the All Treated (Expanded) SG pool (17 days). The median time to onset of the first event of Grade 3 or higher serious infections secondary to neutropenia in the study GS-US-592-6238 SG group (45 days) was longer than in the All Treated (Expanded) SG pool (17 days) (GS-US-592-6238 ISS [Expanded]).

The median durations of serious infections secondary to neutropenia of any grade and Grade 3 or higher serious infections secondary to neutropenia were longer in the study GS-US-592-6238 SG group (13 and 12 days, respectively) than in the All Treated (Expanded) SG pool (7 days and 7 days, respectively).

## Severe Diarrhoea

**Table 64 Adverse Event of Special Interest for SG: Severe Diarrhoea (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                                      | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall<br/>mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG (10<br/>mg/kg)<br/>(N = 1999)</b> |
|------------------------------------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------|------------------------------------------------------------------------|
| <b>AESI: Severe Diarrhea</b>                         |                                            |                                             |                                      |                                                                        |
| AEs                                                  | 25 (9.1%)                                  | 2 (0.7%)                                    | 96 (10.0%)                           | 224 (11.2%)                                                            |
| Treatment-related AEs                                | 21 (7.6%)                                  | 1 (0.4%)                                    | 87 (9.0%)                            | 206 (10.3%)                                                            |
| SAEs                                                 | 9 (3.3%)                                   | 1 (0.4%)                                    | 30 (3.1%)                            | 86 (4.3%)                                                              |
| AEs leading to study drug dose reduction             | 11 (4.0%)                                  | 0                                           | 28/801<br>(3.5%) <sup>a</sup>        | 72/1597<br>(4.5%) <sup>a</sup>                                         |
| AEs leading to study drug interruption               | 7 (2.5%)                                   | 1 (0.4%)                                    | 23 (2.4%)                            | 51 (2.6%)                                                              |
| AEs leading to study drug withdrawal/discontinuation | 1 (0.4%)                                   | 0                                           | 3 (0.3%)                             | 9 (0.5%)                                                               |
| AEs leading to death                                 | 0                                          | 0                                           | 0                                    | 0                                                                      |

AE = adverse event; AESI = adverse event of special interest; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

a AEs leading to study drug dose reduction were not collected in IMMU-132-01; therefore, IMMU-132-01 participants were excluded from the denominators for percentages of TEAEs leading to study drug dose reduction for the last 2 columns.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and 'Unrelated'. Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-Threatening; 5 = Death.

See definitions of Adverse Events of Special Interest in the Statistical Analysis Plan, CSR, and/or Summary of Clinical Safety.

## Time to Onset and Duration of Severe Diarrhoea

The median time from first dose of the study drug to onset of the first event of severe (Grade 3 or higher) diarrhoea was longer in the study GS-US-592-6238 SG group (67 days) than in the All Treated (Expanded) SG (15 days) pool.

The median duration of severe diarrhoea was similar between the study GS-US-592-6238 SG group (6 days) and the All Treated (Expanded) SG (7 days) pool (GS-US-592-6238 ISS [Expanded]).

## Hypersensitivity

**Table 65 Adverse Event of Special Interest for SG: Hypersensitivity (Study GS-US-592-6238 ISS Populations [Expanded])**

|                               | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall<br/>mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG (10 mg/kg)<br/>(N = 1999)</b> |
|-------------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------|--------------------------------------------------------------------|
| <b>AESI: Hypersensitivity</b> |                                            |                                             |                                      |                                                                    |
| AEs                           | 21 (7.6%)                                  | 34 (12.3%)                                  | 123<br>(12.8%)                       | 237 (11.9%)                                                        |
| Grade 3 or higher             | 0                                          | 4 (1.4%)                                    | 5 (0.5%)                             | 9 (0.5%)                                                           |

|                                                      |           |            |                    |                              |
|------------------------------------------------------|-----------|------------|--------------------|------------------------------|
| Treatment-related AEs                                | 15 (5.5%) | 31 (11.2%) | 86 (8.9%)          | 170 (8.5%)                   |
| SAEs                                                 | 0         | 1 (0.4%)   | 1 (0.1%)           | 5 (0.3%)                     |
| AEs leading to study drug dose reduction             | 0         | 0          | 0/801 <sup>a</sup> | 1/1597 (< 0.1%) <sup>a</sup> |
| AEs leading to study drug interruption               | 3 (1.1%)  | 8 (2.9%)   | 5 (0.5%)           | 19 (1.0%)                    |
| AEs leading to study drug withdrawal/discontinuation | 1 (0.4%)  | 4 (1.4%)   | 2 (0.2%)           | 7 (0.4%)                     |
| AEs leading to death                                 | 0         | 0          | 0                  | 0                            |

AE = adverse event; AESI = adverse event of special interest; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

a AEs leading to study drug dose reduction were not collected in IMMU-132-01; therefore, IMMU-132-01 participants were excluded from the denominators for percentages of TEAEs leading to study drug dose reduction for the last 2 columns.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and 'Unrelated'. Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe;

4 = Life-Threatening; 5 = Death.

See definitions of Adverse Events of Special Interest in the Statistical Analysis Plan, CSR, and/or Summary of Clinical Safety.

### Time to Onset and Duration of Hypersensitivity

The median time to first onset of hypersensitivity was similar between the study GS-US-592-6238 SG group, the All Treated (Expanded) SG pool.

The median duration of hypersensitivity was lower in the study GS-US-592-6238 SG group than in the All Treated (Expanded) SG pool (8 vs 14 days, respectively)

### Neutropenia

**Table 66 Adverse Event of Special Interest for SG: Neutropenia (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                                      | <b>GS-US-592-6238<br/>SG<br/>(N = 275)</b> | <b>GS-US-592-6238<br/>TPC<br/>(N = 276)</b> | <b>Overall<br/>mBC<br/>(N = 963)</b> | <b>All Treated<br/>(Expanded)<br/>SG (10 mg/kg)<br/>(N = 1999)</b> |
|------------------------------------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------|--------------------------------------------------------------------|
| <b>AESI: Neutropenia<sup>a</sup></b>                 |                                            |                                             |                                      |                                                                    |
| AEs                                                  | 187 (68.0%)                                | 158 (57.2%)                                 | 663 (68.8%)                          | 1185 (59.3%)                                                       |
| Grade 3 or higher                                    | 124 (45.1%)                                | 113 (40.9%)                                 | 491 (51.0%)                          | 893 (44.7%)                                                        |
| Treatment-related AEs                                | 186 (67.6%)                                | 156 (56.5%)                                 | 658 (68.3%)                          | 1174 (58.7%)                                                       |
| Grade 3 or higher                                    | 124 (45.1%)                                | 109 (39.5%)                                 | 487 (50.6%)                          | 881 (44.1%)                                                        |
| SAEs                                                 | 20 (7.3%)                                  | 10 (3.6%)                                   | 70 (7.3%)                            | 187 (9.4%)                                                         |
| AEs leading to study drug dose reduction             | 54 (19.6%)                                 | 54 (19.6%)                                  | 131/801 (16.4%) <sup>b</sup>         | 241/1597 (15.1%) <sup>b</sup>                                      |
| AEs leading to study drug interruption               | 119 (43.3%)                                | 102 (37.0%)                                 | 429 (44.5%)                          | 699 (35.0%)                                                        |
| AEs leading to study drug withdrawal/discontinuation | 1 (0.4%)                                   | 3 (1.1%)                                    | 4 (0.4%)                             | 22 (1.1%)                                                          |
| AEs leading to death                                 | 0                                          | 0                                           | 0                                    | 1 (< 0.1%)                                                         |

AE = adverse event; AESI = adverse event of special interest; CSR = clinical study report CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; PT

= preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

- a TEAE of neutropenia combines 2 PTs: neutropenia, neutrophil count decreased. AESI neutropenia combines 3 PTs: neutropenia, febrile neutropenia, neutrophil count decreased.
- b AEs leading to study drug dose reduction were not collected in IMMU-132-01; therefore, IMMU-132-01 participants were excluded from the denominators for percentages of TEAEs leading to study drug dose reduction for the last 2 columns.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and 'Unrelated'. Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe;

4 = Life-Threatening; 5 = Death.

See definitions of Adverse Events of Special Interest in the Statistical Analysis Plan, CSR, and/or Summary of Clinical Safety.

## Time to Onset and Duration of Neutropenia

The median time to first onset of any grade neutropenia and first onset of Grade 3 or higher neutropenia were longer in the study GS-US-592-6238 SG group (both 22 days) compared to the All Treated (Expanded) SG pool (both 15 days). The median time to onset of neutropenia (including febrile neutropenia) following the start of the first treatment cycle was 20 days in the Overall mBC pool. Median duration of any grade neutropenia was 10 days in the Overall mBC pool.

## Management of Neutropenia

G-CSF use at any time during the study was higher in the study GS-US-592-6238 SG group than in the All Treated (Expanded) SG pool (58.9% vs 46.0%, respectively). These results suggest the increased use of G-CSF in study GS-US-592-6238 and adherence to protocol-specified guidance for the management of neutropenia. G-CSF use in the study GS-US-592-6238 SG group for both treatment and prophylaxis was also higher than those in the All Treated (Expanded) SG pool (treatment: 37.5% vs 29.9%; prophylaxis: 44.0% vs 26.6%).

However, then an update of protocol specified guidance for the management of neutropenia (G-CSF use) was implemented late in this study, in November 2024. Therefore, this change most likely had no further effect on the severity and number of infections in this study.

## Laboratory findings

**Table 67 Grade 3 or 4 Laboratory Abnormalities That Occurred in ≥ 5% of Participants in the Study GS-US-592-6238 SG or TPC Groups (Study GS-US-592-6238 ISS Populations [Expanded])**

| Maximum Postbaseline Toxicity Grade  | GS-US-592-6238 SG (N = 275) | GS-US-592-6238 TPC (N = 276) | Overall mBC (N = 963) | All Treated (Expanded) SG (10 mg/kg) (N = 1999) |
|--------------------------------------|-----------------------------|------------------------------|-----------------------|-------------------------------------------------|
| Participants with postbaseline value | 274                         | 272                          | 954                   | 1970                                            |
| Grade 3 or 4                         | 182 (66.4%)                 | 162 (59.6%)                  | 606 (63.5%)           | 1184 (60.1%)                                    |
| Grade 3                              | 104 (38.0%)                 | 95 (34.9%)                   | 368 (38.6%)           | 727 (36.9%)                                     |
| Grade 4                              | 78 (28.5%)                  | 67 (24.6%)                   | 238 (24.9%)           | 457 (23.2%)                                     |
| Hematology                           |                             |                              |                       |                                                 |
| Hemoglobin (anemia)                  | 274                         | 272                          | 954                   | 1966                                            |
| Grade 3 or 4                         | 19 (6.9%)                   | 51 (18.8%)                   | 73 (7.7%)             | 197 (10.0%)                                     |
| Grade 3                              | 19 (6.9%)                   | 51 (18.8%)                   | 73 (7.7%)             | 197 (10.0%)                                     |

| <b>Maximum Postbaseline Toxicity Grade</b>                    | <b>GS-US-592-6238 SG (N = 275)</b> | <b>GS-US-592-6238 TPC (N = 276)</b> | <b>Overall mBC (N = 963)</b> | <b>All Treated (Expanded) SG (10 mg/kg) (N = 1999)</b> |
|---------------------------------------------------------------|------------------------------------|-------------------------------------|------------------------------|--------------------------------------------------------|
| Leukocytes (white blood cell decreased)                       | 274                                | 272                                 | 954                          | 1966                                                   |
| Grade 3 or 4                                                  | 79 (28.8%)                         | 90 (33.1%)                          | 327 (34.3%)                  | 575 (29.2%)                                            |
| Grade 3                                                       | 55 (20.1%)                         | 76 (27.9%)                          | 248 (26.0%)                  | 408 (20.8%)                                            |
| Grade 4                                                       | 24 (8.8%)                          | 14 (5.1%)                           | 79 (8.3%)                    | 167 (8.5%)                                             |
| Lymphocytes (lymphocyte count decreased)                      | 274                                | 272                                 | 950                          | 1942                                                   |
| Grade 3 or 4                                                  | 45 (16.4%)                         | 53 (19.5%)                          | 194 (20.4%)                  | 456 (23.5%)                                            |
| Grade 3                                                       | 39 (14.2%)                         | 46 (16.9%)                          | 173 (18.2%)                  | 397 (20.4%)                                            |
| Grade 4                                                       | 6 (2.2%)                           | 7 (2.6%)                            | 21 (2.2%)                    | 59 (3.0%)                                              |
| Neutrophils (neutrophil count decreased)                      | 274                                | 272                                 | 953                          | 1962                                                   |
| Grade 3 or 4                                                  | 128 (46.7%)                        | 118 (43.4%)                         | 444 (46.6%)                  | 759 (38.7%)                                            |
| Grade 3                                                       | 71 (25.9%)                         | 73 (26.8%)                          | 274 (28.8%)                  | 452 (23.0%)                                            |
| Grade 4                                                       | 57 (20.8%)                         | 45 (16.5%)                          | 170 (17.8%)                  | 307 (15.6%)                                            |
| Platelets (platelet count decreased)                          | 274                                | 272                                 | 954                          | 1965                                                   |
| Grade 3 or 4                                                  | 16 (5.8%)                          | 45 (16.5%)                          | 33 (3.5%)                    | 68 (3.5%)                                              |
| Grade 3                                                       | 9 (3.3%)                           | 27 (9.9%)                           | 14 (1.5%)                    | 27 (1.4%)                                              |
| Grade 4                                                       | 7 (2.6%)                           | 18 (6.6%)                           | 19 (2.0%)                    | 41 (2.1%)                                              |
| Chemistry                                                     |                                    |                                     |                              |                                                        |
| Alanine aminotransferase (alanine aminotransferase increased) | 274                                | 272                                 | 953                          | 1965                                                   |
| Grade 3 or 4                                                  | 11 (4.0%)                          | 16 (5.9%)                           | 18 (1.9%)                    | 25 (1.3%)                                              |
| Grade 3                                                       | 11 (4.0%)                          | 16 (5.9%)                           | 18 (1.9%)                    | 25 (1.3%)                                              |
| Magnesium (hypermagnesemia)                                   | 274                                | 272                                 | 949                          | 1962                                                   |
| Grade 3 or 4                                                  | 14 (5.1%)                          | 5 (1.8%)                            | 18 (1.9%)                    | 31 (1.6%)                                              |
| Grade 3                                                       | 13 (4.7%)                          | 5 (1.8%)                            | 16 (1.7%)                    | 25 (1.3%)                                              |
| Grade 4                                                       | 1 (0.4%)                           | 0                                   | 2 (0.2%)                     | 6 (0.3%)                                               |
| Potassium (hypokalemia)                                       | 274                                | 272                                 | 952                          | 1966                                                   |
| Grade 3 or 4                                                  | 14 (5.1%)                          | 7 (2.6%)                            | 42 (4.4%)                    | 66 (3.4%)                                              |
| Grade 3                                                       | 10 (3.6%)                          | 3 (1.1%)                            | 37 (3.9%)                    | 58 (3.0%)                                              |
| Grade 4                                                       | 4 (1.5%)                           | 4 (1.5%)                            | 5 (0.5%)                     | 8 (0.4%)                                               |

CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TE = treatment emergent; TPC = treatment of physician's choice

Severity grades were defined by the CTCAE Version 5.0.

For maximum postbaseline toxicity grade, the most severe graded abnormality from all tests was counted for each participant.

For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.

A TE laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last study drug dose plus 30 days or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurs first. If the baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above (TE window) will be considered TE. Percentages were based on participant with nonmissing postbaseline values within the TE window.

## ***Safety in special populations***

### **Race**

Analysis of the safety data in the racial subgroups include the following findings:

- Grade 3 or higher AEs were lower in the GS-US-592-6238 SG group versus the All Treated (Expanded) SG Pool in White participants (63.4% vs 72.8%) and Asian participants (65.2% vs 77.4%), whereas the reverse was true in Black or African American participants (88.9% vs 74.3%).
- SAEs were lower in the GS-US-592-6238 SG group versus the All Treated (Expanded) SG Pool in White participants (26.3% vs 38.6%), Asian participants (21.2% vs 34.4%), and Other participants (32.0% vs 40.3%) and were similar in Black or African American participants (33.3% vs 31.4%).
- AEs leading to study drug dose reduction were higher in the GS-US-592-6238 SG group versus the All Treated (Expanded) SG Pool in Black or African American participants (55.6% vs 35.3%).
- AEs leading to study drug discontinuation were lower in the GS-US-592-6238 SG group versus the All Treated (Expanded) SG Pool in White participants (3.4% vs 8.6%), Black or African American participants (0 vs 4.3%), Asian participants (4.5% vs 9.4%), and Other participants (4.0% vs 10.7%).
- Rates of AEs leading to death were low across racial subgroups, with no notable trends comparing the GS-US-592-6238 SG group versus the All Treated (Expanded) SG Pool.
- Interpretation is limited in the Black or African American, American Indian or Alaska Native, and Other race subgroups given then low number of participants.

### **Age**

Median age was similar in the All Treated (Expanded) SG pool and the original All Treated SG pool (61 and 58 years, respectively). Median age was lower in the study GS-US-592-6238 SG group (56 years) compared to the All Treated (Expanded) SG pool (61 years). In all populations, most participants were < 65 years of age.

Median duration of treatment was consistent between the All Treated (Expanded) SG Pool and the original All Treated SG pool within age subgroups. The median duration of SG treatment was longer in the study GS-US-592-6238 SG group than in the All Treated (Expanded) SG pool in participants < 65 and ≥ 65 years of age but was the same in participants ≥ 75 years of age. (GS-US-592-6238 ISS [Expanded],

- < 65 years: 8.79 months (SG group; n = 212) and 4.60 months (All Treated [Expanded] SG Pool; n = 1209)
- ≥ 65 years: 6.97 months (SG group; n = 63) and 3.71 months (All Treated [Expanded] SG Pool; n = 790)
- **≥ 75 years: 3.14 months (SG group; n = 20), and 3.14 months (All Treated [Expanded] SG Pool; n = 232).**

Within the study GS-US-592-6238 SG group, median duration of treatment was longer in the < 65 years subgroup than in the ≥ 65 years and ≥ 75 subgroups, with the ≥ 75 subgroup having a greater magnitude of difference.

The incidence of SAEs in the study GS-US-592-6238 SG group was also higher in the  $\geq 75$  years and  $\geq 65$  years subgroup than in the  $< 65$  years subgroup. A similar trend was seen in the All Treated (Expanded) SG Pool:

- **$< 65$  years: 21.7% (SG group) and 32.9% (All Treated [Expanded] SG Pool)**
- **$\geq 65$  years: 39.7% (SG group) and 46.2% (All Treated [Expanded] SG Pool)**
- **$\geq 75$  years: 50% (SG group) and 55.2% (All Treated [Expanded] SG Pool).**

A similar trend was also seen in Grade 3 or higher AEs in the All Treated (Expanded) SG Pool.

The incidence of any AEs leading to discontinuation in the study GS-US-592-6238 SG group was higher in the  $\geq 75$  years and  $\geq 65$  years subgroups than in the  $< 65$  years subgroup. A similar trend was seen in the All Treated (Expanded) SG Pool:

- $< 65$  years: 2.4% (SG group) and 5.8% (All Treated [Expanded] SG Pool)
- $\geq 65$  years: 7.9% (SG group) and 13.5% (All Treated [Expanded] SG Pool)
- **$\geq 75$  years: 25.0% (SG group) and 15.5% (All Treated [Expanded] SG Pool).**

**Table 68 Treatment-Emergent Adverse Events: Overall Summary by Age Group**

| Age group                                                | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall<br>mBC<br>(N = 963) | All Treated<br>SG<br>(10 mg/kg)<br>(N = 1354) |
|----------------------------------------------------------|-----------------------------------|------------------------------------|-----------------------------|-----------------------------------------------|
| Age Group: $< 50$ years                                  | 89                                | 99                                 | 301                         | 336                                           |
| All TEAEs                                                | 87 ( 97.8%)                       | <b>94 ( 94.9%)</b>                 | 299 ( 99.3%)                | 334 ( 99.4%)                                  |
| Grade 3 or higher                                        | 54 ( 60.7%)                       | 55 ( 55.6%)                        | 209 ( 69.4%)                | 230 ( 68.5%)                                  |
| Death                                                    | 2 ( 2.2%)                         | 0                                  | 3 ( 1.0%)                   | 3 ( 0.9%)                                     |
| SAEs                                                     | 18 ( 20.2%)                       | 21 ( 21.2%)                        | 74 ( 24.6%)                 | 85 ( 25.3%)                                   |
| Age Group: 50-64 years                                   | 123                               | 99                                 | 447                         | 608                                           |
| All TEAEs                                                | 123 (100.0%)                      | 98 ( 99.0%)                        | 446 ( 99.8%)                | 607 ( 99.8%)                                  |
| Grade 3 or higher                                        | 76 ( 61.8%)                       | 64 ( 64.6%)                        | 315 ( 70.5%)                | 440 ( 72.4%)                                  |
| Death                                                    | 1 ( 0.8%)                         | 1 ( 1.0%)                          | 3 ( 0.7%)                   | 11 ( 1.8%)                                    |
| SAEs                                                     | 28 ( 22.8%)                       | 27 ( 27.3%)                        | 116 ( 26.0%)                | 189 ( 31.1%)                                  |
| <b>Age Group: <math>&lt;65</math> years</b>              | <b>212</b>                        | <b>198</b>                         | <b>748</b>                  | <b>944</b>                                    |
| All TEAEs                                                | 210 ( 99.1%)                      | 192 ( 97.0%)                       | 745 ( 99.6%)                | 941 ( 99.7%)                                  |
| Grade 3 or higher                                        | <b>130 ( 61.3%)</b>               | 119 ( 60.1%)                       | 524 ( 70.1%)                | 670 ( 71.0%)                                  |
| Death                                                    | <b>3 ( 1.4%)</b>                  | 1 (0.5%)                           | 6 ( 0.8%)                   | 14 ( 1.5%)                                    |
| SAE                                                      | <b>46 ( 21.7%)</b>                | 48 ( 24.2%)                        | 190 ( 25.4%)                | 274 ( 29.0%)                                  |
| TEAEs Leading to Study Drug Withdrawal / Discontinuation | <b>5 ( 2.4%)</b>                  | 26 ( 13.1%)                        | 27 ( 3.6%)                  | 46 ( 4.9%)                                    |
| TEAEs Leading to Study Drug Dose Reduction               | <b>68 ( 32.1%)</b>                | 82 ( 41.4%)                        | 171/617 ( 27.7%)            | 193/678 ( 28.5%)                              |
| TEAEs Leading to Study Drug Interruption                 | <b>139 ( 65.6%)</b>               | 114 ( 57.6%)                       | 467 ( 62.4%)                | <b>567 ( 60.1%)</b>                           |
| <b>Age Group: <math>\geq 65</math> years</b>             | <b>63</b>                         | <b>78</b>                          | <b>215</b>                  | <b>410</b>                                    |
| All TEAEs                                                | <b>63 (100.0%)</b>                | <b>77 ( 98.7%)</b>                 | 215 (100.0)                 | 408 ( 99.5%)                                  |

| Age group                                                   | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall<br>mBC<br>(N = 963) | All Treated<br>SG<br>(10 mg/kg)<br>(N = 1354) |
|-------------------------------------------------------------|-----------------------------------|------------------------------------|-----------------------------|-----------------------------------------------|
| Grade 3 or higher                                           | <b>51 ( 81.0%)</b>                | 52 ( 66.7%)                        | 163<br>(75.8%)              | 331 ( 80.7%)                                  |
| Death                                                       | <b>4 ( 6.3%)</b>                  | 0                                  | 10 ( 4.7%)                  | 16 (3.9%)                                     |
| SAE                                                         | <b>25 ( 39.7%)</b>                | 19 ( 24.4%)                        | 76 ( 35.3%)                 | 170 ( 41.5%)                                  |
| TEAEs Leading to Study Drug<br>Withdrawal / Discontinuation | <b>5 ( 7.9%)</b>                  | 7 ( 9.0%)                          | 18 ( 8.4%)                  | 48 ( 11.7%)                                   |
| TEAEs Leading to Study Drug<br>Dose Reduction               | 33 ( 52.4%)                       | 42 ( 53.8%)                        | 78/184 ( 42.4%)             | 120/274 ( 43.8%)                              |
| TEAEs Leading to Study Drug<br>Interruption                 | 42 ( 66.7%)                       | 57 ( 73.1%)                        | 131<br>(60.9%)              | 244 ( 59.5%)                                  |
| <b>Age Group: 65 -74 years</b>                              | <b>43</b>                         | <b>58</b>                          | <b>167</b>                  | <b>282</b>                                    |
| All TEAEs                                                   | <b>43 (100.0%)</b>                | <b>57 ( 98.3%)</b>                 | 167<br>(100.0%)             | 280 ( 99.3%)                                  |
| Grade 3 or higher                                           | 35 ( 81.4%)                       | 38 ( 65.5%)                        | 124 ( 74.3%)                | 220 ( 78.0%)                                  |
| Death                                                       | 2 ( 4.7%)                         | 0                                  | 8 ( 4.8%)                   | 14 ( 5.0%)                                    |
| SAEs                                                        | 15 ( 34.9%)                       | 16 ( 27.6%)                        | 51 ( 30.5%)                 | 102 ( 36.2%)                                  |
| TEAEs Leading to Study Drug<br>Withdrawal / Discontinuation | <b>0</b>                          | 5 ( 8.6%)                          | 10 ( 6.0%)                  | 22 ( 7.8%)                                    |
| TEAEs Leading to Study Drug<br>Dose Reduction               | <b>22 ( 51.2%)</b>                | 30 ( 51.7%)                        | 58/140 ( 41.4%)             | 79/186 ( 42.5%)                               |
| TEAEs Leading to Study Drug<br>Interruption                 | <b>29 ( 67.4%)</b>                | 41 ( 70.7%)                        | 102 ( 61.1%)                | <b>171 ( 60.6%)</b>                           |
| <b>Age Group: &gt;=75years</b>                              | <b>20</b>                         | <b>20</b>                          | <b>48</b>                   | <b>128</b>                                    |
| All TEAEs                                                   | 20 (100.0%)                       | 20 (100.0%)                        | 48<br>(100.0%)              | 128 (100.0%)                                  |
| Grade 3 or higher                                           | <b>16 ( 80.0%)</b>                | 14 ( 70.0%)                        | 39 ( 81.3%)                 | 111 ( 86.7%)                                  |
| Death                                                       | <b>2 ( 10.0%)</b>                 | 0                                  | 2 ( 4.2%)                   | 2 ( 1.6%)                                     |
| SAEs                                                        | <b>10 ( 50.0%)</b>                | 3 ( 15.0%)                         | 25 ( 52.1%)                 | 68 ( 53.1%)                                   |
| TEAEs Leading to Study Drug<br>Withdrawal / Discontinuation | <b>5 ( 25.0%)</b>                 | 2 ( 10.0%)                         | 8 ( 16.7%)                  | 26 ( 20.3%)                                   |
| TEAEs Leading to Study Drug<br>Dose Reduction               | 11 ( 55.0%)                       | 12 ( 60.0%)                        | 20/44 ( 45.5%)              | 41/88 ( 46.6%)                                |
| TEAEs Leading to Study Drug<br>Interruption                 | 13 ( 65.0%)                       | 16 ( 80.0%)                        | 29 ( 60.4%)                 | 73 ( 57.0%)                                   |

**Table 69 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age Group (Assessors table blue >=65, red>=75)**

| System Organ Class<br>Preferred Term                    | GS-US-592-6238<br>SG<br>(N=275) | GS-US-592-6238<br>TPC<br>(N=276) | Overall mBC<br>(N=963) | All Treated<br>SG (10 mg/kg)<br>(N=1354) |
|---------------------------------------------------------|---------------------------------|----------------------------------|------------------------|------------------------------------------|
| Age Group: < 65 years                                   | 212                             | 198                              | 748                    | 944                                      |
| Participants with Any Treatment-Emergent Adverse Events | 210 ( 99.1%)                    | 192 ( 97.0%)                     | 745 ( 99.6%)           | 941 ( 99.7%)                             |
| Blood and lymphatic system disorders                    | 165 ( 77.8%)                    | 140 ( 70.7%)                     | 594 ( 79.4%)           | 734 ( 77.8%)                             |
| Neutropenia                                             | <b>145 ( 68.4%)</b>             | 112 ( 56.6%)                     | 514 ( 68.7%)           | 607 ( 64.3%)                             |
| Anaemia                                                 | 82 ( 38.7%)                     | 93 ( 47.0%)                      | 288 ( 38.5%)           | 368 ( 39.0%)                             |
| Leukopenia                                              | 54 ( 25.5%)                     | 54 ( 27.3%)                      | 152 ( 20.3%)           | 191 ( 20.2%)                             |
| Lymphopenia                                             | 26 ( 12.3%)                     | 22 ( 11.1%)                      | 84 ( 11.2%)            | 101 ( 10.7%)                             |
| Febrile neutropenia                                     | 8 ( 3.8%)                       | 3 ( 1.5%)                        | 39 ( 5.2%)             | 50 ( 5.3%)                               |
| Thrombocytopenia                                        | 7 ( 3.3%)                       | 52 ( 26.3%)                      | 49 ( 6.6%)             | 64 ( 6.8%)                               |
| Eosinophilia                                            | 2 ( 0.9%)                       | 0                                | 2 ( 0.3%)              | 2 ( 0.2%)                                |
| Leukocytosis                                            | 2 ( 0.9%)                       | 6 ( 3.0%)                        | 7 ( 0.9%)              | 9 ( 1.0%)                                |
| Thrombocytosis                                          | 2 ( 0.9%)                       | 0                                | 2 ( 0.3%)              | 2 ( 0.2%)                                |
| Disseminated intravascular coagulation                  | 1 ( 0.5%)                       | 0                                | 1 ( 0.1%)              | 1 ( 0.1%)                                |
| Iron deficiency anaemia                                 | 1 ( 0.5%)                       | 0                                | 2 ( 0.3%)              | 3 ( 0.3%)                                |
| Lymphadenitis                                           | 1 ( 0.5%)                       | 0                                | 1 ( 0.1%)              | 1 ( 0.1%)                                |
| Lymphadenopathy                                         | 1 ( 0.5%)                       | 0                                | 5 ( 0.7%)              | 5 ( 0.5%)                                |
| Neutrophilia                                            | 1 ( 0.5%)                       | 3 ( 1.5%)                        | 2 ( 0.3%)              | 2 ( 0.2%)                                |

|                                                         |             |             |              |              |
|---------------------------------------------------------|-------------|-------------|--------------|--------------|
| Age Group: >= 65 years                                  | 63          | 78          | 215          | 410          |
| Participants with Any Treatment-Emergent Adverse Events | 63 (100.0%) | 77 (98.7%)  | 215 (100.0%) | 408 (99.5%)  |
| Blood and lymphatic system disorders                    | 46 (73.0%)  | 59 (75.6%)  | 170 (79.1%)  | 312 (76.1%)  |
| Neutropenia                                             | 38 (60.3%)  | 45 (57.7%)  | 134 (62.3%)  | 237 (57.8%)  |
| Anaemia                                                 | 25 (39.7%)  | 45 (57.7%)  | 98 (45.6%)   | 175 (42.7%)  |
| Leukopenia                                              | 16 (25.4%)  | 16 (20.5%)  | 36 (16.7%)   | 79 (19.3%)   |
| Lymphopenia                                             | 5 (7.9%)    | 6 (7.7%)    | 24 (11.2%)   | 43 (10.5%)   |
| Thrombocytopenia                                        | 5 (7.9%)    | 26 (33.3%)  | 22 (10.2%)   | 36 (8.8%)    |
| Age Group: >= 75 years                                  | 20          | 20          | 48           | 128          |
| Participants with Any Treatment-Emergent Adverse Events | 20 (100.0%) | 20 (100.0%) | 48 (100.0%)  | 128 (100.0%) |
| Blood and lymphatic system disorders                    | 13 (65.0%)  | 17 (85.0%)  | 37 (77.1%)   | 96 (75.0%)   |
| Neutropenia                                             | 11 (55.0%)  | 12 (60.0%)  | 31 (64.6%)   | 70 (54.7%)   |
| Anaemia                                                 | 8 (40.0%)   | 13 (65.0%)  | 18 (37.5%)   | 48 (37.5%)   |
| Leukopenia                                              | 5 (25.0%)   | 4 (20.0%)   | 9 (18.8%)    | 30 (23.4%)   |
| Febrile neutropenia                                     | 2 (10.0%)   | 0           | 6 (12.5%)    | 16 (12.5%)   |
| Lymphopenia                                             | 1 (5.0%)    | 1 (5.0%)    | 5 (10.4%)    | 14 (10.9%)   |
| Cardiac disorders                                       | 11 (5.2%)   | 13 (6.6%)   | 60 (8.0%)    | 71 (7.5%)    |
| Palpitations                                            | 4 (1.9%)    | 4 (2.0%)    | 16 (2.1%)    | 19 (2.0%)    |
| Tachycardia                                             | 4 (1.9%)    | 1 (0.5%)    | 20 (2.7%)    | 24 (2.5%)    |
| Atrial fibrillation                                     | 2 (0.9%)    | 1 (0.5%)    | 4 (0.5%)     | 4 (0.4%)     |
| Sinus tachycardia                                       | 1 (0.5%)    | 3 (1.5%)    | 11 (1.5%)    | 13 (1.4%)    |
| Cardiac disorders                                       | 8 (12.7%)   | 4 (5.1%)    | 27 (12.6%)   | 48 (11.7%)   |
| Atrial fibrillation                                     | 2 (3.2%)    | 0           | 3 (1.4%)     | 6 (1.5%)     |
| Sinus tachycardia                                       | 2 (3.2%)    | 0           | 9 (4.2%)     | 11 (2.7%)    |
| Arrhythmia                                              | 1 (1.6%)    | 0           | 2 (0.9%)     | 2 (0.5%)     |
| Cardiac failure                                         | 1 (1.6%)    | 1 (1.3%)    | 3 (1.4%)     | 4 (1.0%)     |
| Right ventricular enlargement                           | 1 (1.6%)    | 0           | 1 (0.5%)     | 1 (0.2%)     |
| Tachycardia                                             | 1 (1.6%)    | 0           | 6 (2.8%)     | 16 (3.9%)    |
| Cardiac disorders                                       | 4 (20.0%)   | 3 (15.0%)   | 9 (18.8%)    | 16 (12.5%)   |
| Atrial fibrillation                                     | 1 (5.0%)    | 0           | 1 (2.1%)     | 4 (3.1%)     |
| Cardiac failure                                         | 1 (5.0%)    | 1 (5.0%)    | 1 (2.1%)     | 1 (0.8%)     |
| Right ventricular enlargement                           | 1 (5.0%)    | 0           | 1 (2.1%)     | 1 (0.8%)     |
| Tachycardia                                             | 1 (5.0%)    | 0           | 2 (4.2%)     | 4 (3.1%)     |
| Gastrointestinal disorders                              | 188 (88.7%) | 125 (63.1%) | 690 (92.2%)  | 874 (92.6%)  |
| Nausea                                                  | 127 (59.9%) | 71 (35.9%)  | 477 (63.8%)  | 618 (65.5%)  |
| Diarrhoea                                               | 107 (50.5%) | 36 (18.2%)  | 425 (56.8%)  | 555 (58.8%)  |
| Constipation                                            | 75 (35.4%)  | 48 (24.2%)  | 271 (36.2%)  | 358 (37.9%)  |
| Vomiting                                                | 53 (25.0%)  | 26 (13.1%)  | 244 (32.6%)  | 329 (34.9%)  |
| Stomatitis                                              | 34 (16.0%)  | 14 (7.1%)   | 81 (10.8%)   | 92 (9.7%)    |
| Abdominal pain                                          | 33 (15.6%)  | 13 (6.6%)   | 142 (19.0%)  | 194 (20.6%)  |
| Abdominal pain upper                                    | 17 (8.0%)   | 14 (7.1%)   | 53 (7.1%)    | 61 (6.5%)    |
| Dyspepsia                                               | 15 (7.1%)   | 7 (3.5%)    | 49 (6.6%)    | 56 (5.9%)    |
| Gastrooesophageal reflux disease                        | 9 (4.2%)    | 3 (1.5%)    | 43 (5.7%)    | 49 (5.2%)    |
| Abdominal distension                                    | 6 (2.8%)    | 4 (2.0%)    | 38 (5.1%)    | 48 (5.1%)    |
| Toothache                                               | 6 (2.8%)    | 1 (0.5%)    | 13 (1.7%)    | 16 (1.7%)    |
| Haemorrhoids                                            | 4 (1.9%)    | 1 (0.5%)    | 22 (2.9%)    | 26 (2.8%)    |
| Colitis                                                 | 3 (1.4%)    | 1 (0.5%)    | 9 (1.2%)     | 11 (1.2%)    |
| Dental caries                                           | 3 (1.4%)    | 0           | 6 (0.8%)     | 7 (0.7%)     |
| Gastrointestinal disorders                              | 57 (90.5%)  | 49 (62.8%)  | 198 (92.1%)  | 369 (90.0%)  |
| Diarrhoea                                               | 41 (65.1%)  | 19 (24.4%)  | 152 (70.7%)  | 283 (69.0%)  |
| Nausea                                                  | 40 (63.5%)  | 24 (30.8%)  | 121 (56.3%)  | 241 (58.8%)  |
| Constipation                                            | 29 (46.0%)  | 20 (25.6%)  | 82 (38.1%)   | 144 (35.1%)  |
| Vomiting                                                | 16 (25.4%)  | 9 (11.5%)   | 57 (26.5%)   | 119 (29.0%)  |
| Abdominal pain                                          | 8 (12.7%)   | 3 (3.8%)    | 37 (17.2%)   | 84 (20.5%)   |
| Stomatitis                                              | 8 (12.7%)   | 4 (5.1%)    | 21 (9.8%)    | 32 (7.8%)    |
| Gastrointestinal disorders                              | 19 (95.0%)  | 14 (70.0%)  | 46 (95.8%)   | 116 (90.6%)  |
| Gastrointestinal disorders (cont)                       |             |             |              |              |
| Nausea                                                  | 15 (75.0%)  | 6 (30.0%)   | 32 (66.7%)   | 76 (59.4%)   |
| Diarrhoea                                               | 11 (55.0%)  | 7 (35.0%)   | 35 (72.9%)   | 87 (68.0%)   |
| Constipation                                            | 9 (45.0%)   | 5 (25.0%)   | 21 (43.8%)   | 44 (34.4%)   |
| Vomiting                                                | 6 (30.0%)   | 4 (20.0%)   | 9 (18.8%)    | 27 (21.1%)   |
| Stomatitis                                              | 3 (15.0%)   | 2 (10.0%)   | 4 (8.3%)     | 8 (6.3%)     |
| Dry mouth                                               | 2 (10.0%)   | 1 (5.0%)    | 2 (4.2%)     | 6 (4.7%)     |
| General disorders and administration site conditions    | 126 (59.4%) | 120 (60.6%) | 534 (71.4%)  | 684 (72.5%)  |
| Fatigue                                                 | 91 (42.9%)  | 91 (46.0%)  | 418 (55.9%)  | 529 (56.0%)  |
| Pyrexia                                                 | 25 (11.8%)  | 18 (9.1%)   | 114 (15.2%)  | 150 (15.9%)  |
| Oedema peripheral                                       | 15 (7.1%)   | 14 (7.1%)   | 59 (7.9%)    | 83 (8.8%)    |
| Malaise                                                 | 10 (4.7%)   | 4 (2.0%)    | 23 (3.1%)    | 25 (2.6%)    |
| Chest pain                                              | 7 (3.3%)    | 5 (2.5%)    | 24 (3.2%)    | 40 (4.2%)    |
| Pain                                                    | 7 (3.3%)    | 4 (2.0%)    | 42 (5.6%)    | 48 (5.1%)    |

|                                                             |             |             |              |              |
|-------------------------------------------------------------|-------------|-------------|--------------|--------------|
| General disorders and administration site conditions        | 46 ( 73.0%) | 48 ( 61.5%) | 156 ( 72.6%) | 306 ( 74.6%) |
| Fatigue                                                     | 39 ( 61.9%) | 38 ( 48.7%) | 135 ( 62.8%) | 267 ( 65.1%) |
| General disorders and administration site conditions (cont) |             |             |              |              |
| Oedema peripheral                                           | 9 ( 14.3%)  | 11 ( 14.1%) | 30 ( 14.0%)  | 70 ( 17.1%)  |
| Influenza like illness                                      | 4 ( 6.3%)   | 0           | 5 ( 2.3%)    | 5 ( 1.2%)    |
| Pyrexia                                                     | 4 ( 6.3%)   | 9 ( 11.5%)  | 18 ( 8.4%)   | 53 ( 12.9%)  |
| Chest pain                                                  | 2 ( 3.2%)   | 1 ( 1.3%)   | 6 ( 2.8%)    | 15 ( 3.7%)   |
| Chills                                                      | 2 ( 3.2%)   | 0           | 9 ( 4.2%)    | 27 ( 6.6%)   |
| Malaise                                                     | 2 ( 3.2%)   | 4 ( 5.1%)   | 5 ( 2.3%)    | 10 ( 2.4%)   |
| Pain                                                        | 2 ( 3.2%)   | 1 ( 1.3%)   | 15 ( 7.0%)   | 23 ( 5.6%)   |

|                                                      |             |             |             |              |
|------------------------------------------------------|-------------|-------------|-------------|--------------|
| General disorders and administration site conditions | 17 ( 85.0%) | 13 ( 65.0%) | 41 ( 85.4%) | 100 ( 78.1%) |
| Fatigue                                              | 12 ( 60.0%) | 10 ( 50.0%) | 34 ( 70.8%) | 86 ( 67.2%)  |
| Oedema peripheral                                    | 5 ( 25.0%)  | 4 ( 20.0%)  | 12 ( 25.0%) | 27 ( 21.1%)  |
| Pyrexia                                              | 2 ( 10.0%)  | 3 ( 15.0%)  | 3 ( 6.3%)   | 19 ( 14.8%)  |
| Chest pain                                           | 1 ( 5.0%)   | 1 ( 5.0%)   | 2 ( 4.2%)   | 5 ( 3.9%)    |

|                                   |              |              |              |              |
|-----------------------------------|--------------|--------------|--------------|--------------|
| Infections and infestations       | 116 ( 54.7%) | 102 ( 51.5%) | 361 ( 48.3%) | 452 ( 47.9%) |
| Upper respiratory tract infection | 24 ( 11.3%)  | 13 ( 6.6%)   | 80 ( 10.7%)  | 94 ( 10.0%)  |

|                                    |            |             |             |              |
|------------------------------------|------------|-------------|-------------|--------------|
| Infections and infestations (cont) |            |             |             |              |
| Urinary tract infection            | 20 ( 9.4%) | 24 ( 12.1%) | 91 ( 12.2%) | 121 ( 12.8%) |
| COVID-19                           | 16 ( 7.5%) | 11 ( 5.6%)  | 26 ( 3.5%)  | 28 ( 3.0%)   |
| Influenza                          | 13 ( 6.1%) | 9 ( 4.5%)   | 22 ( 2.9%)  | 23 ( 2.4%)   |
| Nasopharyngitis                    | 13 ( 6.1%) | 10 ( 5.1%)  | 30 ( 4.0%)  | 33 ( 3.5%)   |
| Bronchitis                         | 12 ( 5.7%) | 2 ( 1.0%)   | 26 ( 3.5%)  | 28 ( 3.0%)   |
| Pneumonia                          | 12 ( 5.7%) | 12 ( 6.1%)  | 31 ( 4.1%)  | 45 ( 4.8%)   |
| Pharyngitis                        | 10 ( 4.7%) | 4 ( 2.0%)   | 11 ( 1.5%)  | 12 ( 1.3%)   |
| Cystitis                           | 7 ( 3.3%)  | 4 ( 2.0%)   | 9 ( 1.2%)   | 10 ( 1.1%)   |
| Rhinitis                           | 7 ( 3.3%)  | 1 ( 0.5%)   | 13 ( 1.7%)  | 17 ( 1.8%)   |
| Conjunctivitis                     | 5 ( 2.4%)  | 3 ( 1.5%)   | 10 ( 1.3%)  | 10 ( 1.1%)   |
| Candida infection                  | 4 ( 1.9%)  | 1 ( 0.5%)   | 7 ( 0.9%)   | 8 ( 0.8%)    |
| Oral herpes                        | 4 ( 1.9%)  | 3 ( 1.5%)   | 14 ( 1.9%)  | 14 ( 1.5%)   |
| Paronychia                         | 4 ( 1.9%)  | 4 ( 2.0%)   | 5 ( 0.7%)   | 5 ( 0.5%)    |
| Respiratory tract infection        | 4 ( 1.9%)  | 3 ( 1.5%)   | 9 ( 1.2%)   | 11 ( 1.2%)   |
| Herpes zoster                      | 3 ( 1.4%)  | 3 ( 1.5%)   | 10 ( 1.3%)  | 11 ( 1.2%)   |
| Sinusitis                          | 3 ( 1.4%)  | 2 ( 1.0%)   | 22 ( 2.9%)  | 29 ( 3.1%)   |
| Skin infection                     | 3 ( 1.4%)  | 2 ( 1.0%)   | 9 ( 1.2%)   | 9 ( 1.0%)    |
| Viral infection                    | 3 ( 1.4%)  | 1 ( 0.5%)   | 5 ( 0.7%)   | 8 ( 0.8%)    |

|                                    |             |             |             |             |
|------------------------------------|-------------|-------------|-------------|-------------|
| Infections and infestations (cont) |             |             |             |             |
| Upper respiratory tract infection  | 10 ( 15.9%) | 3 ( 3.8%)   | 23 ( 10.7%) | 41 ( 10.0%) |
| Urinary tract infection            | 7 ( 11.1%)  | 16 ( 20.5%) | 25 ( 11.6%) | 56 ( 13.7%) |
| Nasopharyngitis                    | 6 ( 9.5%)   | 4 ( 5.1%)   | 15 ( 7.0%)  | 18 ( 4.4%)  |
| COVID-19                           | 3 ( 4.8%)   | 5 ( 6.4%)   | 7 ( 3.3%)   | 10 ( 2.4%)  |
| Pneumonia                          | 3 ( 4.8%)   | 9 ( 11.5%)  | 10 ( 4.7%)  | 21 ( 5.1%)  |
| Sepsis                             | 3 ( 4.8%)   | 1 ( 1.3%)   | 7 ( 3.3%)   | 13 ( 3.2%)  |
| Sinusitis                          | 3 ( 4.8%)   | 1 ( 1.3%)   | 6 ( 2.8%)   | 9 ( 2.2%)   |

|                                   |             |            |             |             |
|-----------------------------------|-------------|------------|-------------|-------------|
| Infections and infestations       | 11 ( 55.0%) | 9 ( 45.0%) | 28 ( 58.3%) | 66 ( 51.6%) |
| Sepsis                            | 2 ( 10.0%)  | 0          | 5 ( 10.4%)  | 9 ( 7.0%)   |
| Upper respiratory tract infection | 2 ( 10.0%)  | 0          | 6 ( 12.5%)  | 9 ( 7.0%)   |
| Urinary tract infection           | 2 ( 10.0%)  | 5 ( 25.0%) | 9 ( 18.8%)  | 26 ( 20.3%) |

|                                                 |             |             |              |              |
|-------------------------------------------------|-------------|-------------|--------------|--------------|
| Respiratory, thoracic and mediastinal disorders | 73 ( 34.4%) | 63 ( 31.8%) | 337 ( 45.1%) | 442 ( 46.8%) |
| Cough                                           | 37 ( 17.5%) | 26 ( 13.1%) | 144 ( 19.3%) | 182 ( 19.3%) |
| Dyspnoea                                        | 17 ( 8.0%)  | 22 ( 11.1%) | 136 ( 18.2%) | 181 ( 19.2%) |
| Oropharyngeal pain                              | 12 ( 5.7%)  | 6 ( 3.0%)   | 37 ( 4.9%)   | 46 ( 4.9%)   |
| Pulmonary embolism                              | 9 ( 4.2%)   | 5 ( 2.5%)   | 20 ( 2.7%)   | 27 ( 2.9%)   |

|                                                 |             |             |             |              |
|-------------------------------------------------|-------------|-------------|-------------|--------------|
| Respiratory, thoracic and mediastinal disorders | 26 ( 41.3%) | 31 ( 39.7%) | 96 ( 44.7%) | 193 ( 47.1%) |
| Cough                                           | 12 ( 19.0%) | 9 ( 11.5%)  | 35 ( 16.3%) | 69 ( 16.8%)  |
| Dyspnoea                                        | 8 ( 12.7%)  | 17 ( 21.8%) | 39 ( 18.1%) | 81 ( 19.8%)  |
| Oropharyngeal pain                              | 4 ( 6.3%)   | 1 ( 1.3%)   | 13 ( 6.0%)  | 19 ( 4.6%)   |
| Epistaxis                                       | 3 ( 4.8%)   | 5 ( 6.4%)   | 11 ( 5.1%)  | 22 ( 5.4%)   |
| Pulmonary embolism                              | 3 ( 4.8%)   | 2 ( 2.6%)   | 9 ( 4.2%)   | 18 ( 4.4%)   |
| Rhinorrhoea                                     | 3 ( 4.8%)   | 2 ( 2.6%)   | 10 ( 4.7%)  | 25 ( 6.1%)   |

|                                                 |             |            |             |             |
|-------------------------------------------------|-------------|------------|-------------|-------------|
| Respiratory, thoracic and mediastinal disorders | 10 ( 50.0%) | 6 ( 30.0%) | 24 ( 50.0%) | 60 ( 46.9%) |
| Dyspnoea                                        | 6 ( 30.0%)  | 3 ( 15.0%) | 12 ( 25.0%) | 28 ( 21.9%) |
| Cough                                           | 4 ( 20.0%)  | 4 ( 20.0%) | 8 ( 16.7%)  | 20 ( 15.6%) |
| Interstitial lung disease                       | 2 ( 10.0%)  | 0          | 2 ( 4.2%)   | 3 ( 2.3%)   |
| Pulmonary embolism                              | 2 ( 10.0%)  | 0          | 4 ( 8.3%)   | 7 ( 5.5%)   |
| Dysphonia                                       | 1 ( 5.0%)   | 0          | 3 ( 6.3%)   | 7 ( 5.5%)   |
| Epistaxis                                       | 1 ( 5.0%)   | 1 ( 5.0%)  | 3 ( 6.3%)   | 6 ( 4.7%)   |
| Productive cough                                | 1 ( 5.0%)   | 0          | 1 ( 2.1%)   | 2 ( 1.6%)   |
| Pulmonary hypertension                          | 1 ( 5.0%)   | 0          | 1 ( 2.1%)   | 1 ( 0.8%)   |

**Table 70 Summary of Select TEAEs by Age (ISS All Treated [Expanded] SG)**

|                                             | ISS All Treated (Expanded) SG<br>(N = 1999) |                         |                         |
|---------------------------------------------|---------------------------------------------|-------------------------|-------------------------|
|                                             | < 65 Years<br>(N = 1209)                    | ≥ 65 Years<br>(N = 790) | ≥ 75 Years<br>(N = 232) |
| <b>Febrile neutropenia</b>                  |                                             |                         |                         |
| Any TEAEs                                   | 71 (5.9%)                                   | 72 (9.1%)               | 30 (12.9%)              |
| Grade 3 or higher TEAEs                     | 70 (5.8%)                                   | 72 (9.1%)               | 30 (12.9%)              |
| SAEs                                        | 56 (4.6%)                                   | 63 (8.0%)               | 25 (10.8%)              |
| TEAEs leading to study drug discontinuation | 4 (0.3%)                                    | 7 (0.9%)                | 3 (1.3%)                |
| TEAEs leading to death                      | 1 (< 0.1%)                                  | 0                       | 0                       |
| <b>Sepsis</b>                               |                                             |                         |                         |
| Any TEAEs                                   | 17 (1.4%)                                   | 28 (3.5%)               | 15 (6.5%)               |
| Grade 3 or higher TEAEs                     | 15 (1.2%)                                   | 28 (3.5%)               | 15 (6.5%)               |
| SAEs                                        | 10 (0.8%)                                   | 25 (3.2%)               | 14 (6.0%)               |
| TEAEs leading to study drug discontinuation | 3 (0.2%)                                    | 5 (0.6%)                | 1 (0.4%)                |
| TEAEs leading to death                      | 1 (< 0.1%)                                  | 8 (1.0%)                | 4 (1.7%)                |
| <b>Diarrhoea</b>                            |                                             |                         |                         |
| Any TEAEs                                   | 681 (56.3%)                                 | 511 (64.7%)             | 155 (66.8%)             |
| Grade 3 or higher TEAEs                     | 105 (8.7%)                                  | 119 (15.1%)             | 45 (19.4%)              |
| SAEs                                        | 40 (3.3%)                                   | 59 (7.5%)               | 28 (12.1%)              |
| TEAEs leading to study drug discontinuation | 6 (0.5%)                                    | 5 (0.6%)                | 3 (1.3%)                |
| TEAEs leading to death                      | 0                                           | 0                       | 0                       |
| <b>Fatigue</b>                              |                                             |                         |                         |
| Any TEAEs                                   | 677 (56.0%)                                 | 488 (61.8%)             | 148 (63.8%)             |
| Grade 3 or higher TEAEs                     | 79 (6.5%)                                   | 102 (12.9%)             | 34 (14.7%)              |
| SAEs                                        | 8 (0.7%)                                    | 11 (1.4%)               | 5 (2.2%)                |
| TEAEs leading to study drug discontinuation | 3 (0.2%)                                    | 9 (1.1%)                | 4 (1.7%)                |
| TEAEs leading to death                      | 0                                           | 0                       | 0                       |
| <b>Anaemia</b>                              |                                             |                         |                         |
| Any TEAEs                                   | 497 (41.1%)                                 | 353 (44.7%)             | 93 (40.1%)              |
| Grade 3 or higher TEAEs                     | 101 (8.4%)                                  | 109 (13.8%)             | 30 (12.9%)              |
| SAEs                                        | 9 (0.7%)                                    | 13 (1.6%)               | 2 (0.9%)                |
| TEAEs leading to study drug discontinuation | 1 (< 0.1%)                                  | 3 (0.4%)                | 0                       |
| TEAEs leading to death                      | 0                                           | 0                       | 0                       |

ISS = integrated summary of safety; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event

**Table 71 Overall Summary of Adverse Events by UGT1A1 Genotype in Participants Treated With SG (Study GS-US-592-6238 ISS Populations [Expanded])**

|                                                      | <b>GS-US-592-6238 SG (N = 275)</b> | <b>Overall mBC (N = 963)</b> | <b>All Treated (Expanded) SG (10 mg/kg) (N = 1999)</b> |
|------------------------------------------------------|------------------------------------|------------------------------|--------------------------------------------------------|
| <b>UGT1A1 Genotype: *1/*1</b>                        | 111                                | 396                          | 723                                                    |
| AEs                                                  | 111 (100.0%)                       | 396 (100.0%)                 | 722 (99.9%)                                            |
| Grade 3 or higher                                    | 72 (64.9%)                         | 266 (67.2%)                  | 497 (68.7%)                                            |
| Treatment-related AEs                                | 110 (99.1%)                        | 391 (98.7%)                  | 706 (97.6%)                                            |
| SAEs                                                 | 23 (20.7%)                         | 93 (23.5%)                   | 243 (33.6%)                                            |
| AEs leading to death                                 | 3 (2.7%)                           | 4 (1.0%)                     | 20 (2.8%)                                              |
| Treatment-related AEs leading to death               | 3 (2.7%)                           | 3 (0.8%)                     | 8 (1.1%)                                               |
| AEs leading to study drug withdrawal/discontinuation | 3 (2.7%)                           | 16 (4.0%)                    | 51 (7.1%)                                              |
| AEs leading to study drug dose reduction             | 40 (36.0%)                         | 86/327 (26.3%) <sup>a</sup>  | 161/575 (28.0%) <sup>a</sup>                           |
| AEs leading to study drug interruption               | 69 (62.2%)                         | 245 (61.9%)                  | 425 (58.8%)                                            |
| <b>UGT1A1 Genotype: *1/*28</b>                       | 103                                | 375                          | 701                                                    |
| AEs                                                  | 101 (98.1%)                        | 372 (99.2%)                  | 697 (99.4%)                                            |
| Grade 3 or higher                                    | 67 (65.0%)                         | 272 (72.5%)                  | 517 (73.8%)                                            |
| Treatment-related AEs                                | 101 (98.1%)                        | 362 (96.5%)                  | 675 (96.3%)                                            |
| SAEs                                                 | 28 (27.2%)                         | 106 (28.3%)                  | 250 (35.7%)                                            |
| AEs leading to death                                 | 3 (2.9%)                           | 9 (2.4%)                     | 21 (3.0%)                                              |
| Treatment-related AEs leading to death               | 3 (2.9%)                           | 4 (1.1%)                     | 7 (1.0%)                                               |
| AEs leading to study drug withdrawal/discontinuation | 4 (3.9%)                           | 17 (4.5%)                    | 48 (6.8%)                                              |
| AEs leading to study drug dose reduction             | 42 (40.8%)                         | 111/318 (34.9%) <sup>a</sup> | 190/551 (34.5%) <sup>a</sup>                           |
| AEs leading to study drug interruption               | 71 (68.9%)                         | 232 (61.9%)                  | 422 (60.2%)                                            |
| <b>UGT1A1 Genotype: *28/*28</b>                      | 23                                 | 94                           | 184                                                    |
| AEs                                                  | 23 (100.0%)                        | 94 (100.0%)                  | 183 (99.5%)                                            |
| Grade 3 or higher                                    | 16 (69.6%)                         | 78 (83.0%)                   | 150 (81.5%)                                            |
| Treatment-related AEs                                | 23 (100.0%)                        | 93 (98.9%)                   | 176 (95.7%)                                            |
| SAEs                                                 | 5 (21.7%)                          | 37 (39.4%)                   | 92 (50.0%)                                             |
| AEs leading to death                                 | 0                                  | 1 (1.1%)                     | 6 (3.3%)                                               |
| Treatment-related AEs leading to death               | 0                                  | 0                            | 3 (1.6%)                                               |
| AEs leading to study drug withdrawal/discontinuation | 2 (8.7%)                           | 7 (7.4%)                     | 18 (9.8%)                                              |
| AEs leading to study drug dose reduction             | 4 (17.4%)                          | 26/82 (31.7%) <sup>a</sup>   | 48/148 (32.4%) <sup>a</sup>                            |
| AEs leading to study drug interruption               | 15 (65.2%)                         | 61 (64.9%)                   | 123 (66.8%)                                            |

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

<sup>a</sup> AEs leading to study drug dose reduction were not collected in IMMU-132-01; therefore, IMMU-132-01 participants were excluded from the denominators for percentages of TEAEs leading to study drug dose reduction for the last 2 columns.

Percentages are based on the total number of participants in the corresponding subgroup.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. It excluded 'Unlikely Related', 'Not Related', and 'Unrelated'. Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-Threatening; 5 = Death.

### Serious Adverse Events

In the study GS-US-592-6238 SG group, SAEs were reported in a larger proportion of participants who were heterozygous for the UGT1A1\*28 allele compared with participants who were homozygous for the UGT1A1\*28 allele or the UGT1A1\*1 allele (27.2% vs 21.7%, and 20.7%, respectively).

Neutropenia, febrile neutropenia, and diarrhoea were the only SAEs that occurred in  $\geq 3.0\%$  of participants in any genotype:

- UGT1A1\*1/\*1: febrile neutropenia (3.6%)
- UGT1A1\*1/\*28: diarrhea (4.9%), febrile neutropenia (3.9%), neutropenia (3.9%)
- UGT1A1\*28/\*28: neutropenia (4.3%), diarrhea (4.3%), neutropenic colitis (4.3%), colitis (4.3%), stomatitis (4.3%), pneumonia bacterial (4.3%), erysipelas (4.3%)
- UGT1A1\*1/\*6: febrile neutropenia (7.7%), septic shock (7.7%), herpes zoster (7.7%), pleural effusion (7.7%), dyspnea (7.7%), acute respiratory failure (7.7%).

Serious AEs were reported in a larger proportion of participants who were homozygous for the UGT1A1\*28 allele compared with participants who were either heterozygous for the UGT1A1\*28 allele or homozygous for the UGT1A1\*1 allele in the Overall mBC pool (39.4% vs 28.3% and 23.5%, respectively) and the All Treated (Expanded) SG pool (50.0% vs 35.7% and 33.6%, respectively).

### ***Safety related to drug-drug interactions and other interactions***

General considerations made about DDI for SG are valid also for this extension of indication. No dedicated DDI studies have been performed.

### ***Discontinuation due to adverse events***

**Table 72 Adverse Events Leading to Discontinuation of Any Study Drug in  $\geq 2$  Participants in Study GS-US-592-6238 by Preferred Term (Study GS-US-592-6238 ISS Populations)**

| <b>Preferred Term</b>                                                            | <b>GS-US-592-6238 SG<br/>(N = 275)</b> | <b>GS-US-592-6238 TPC<br/>(N = 276)</b> | <b>Overall mBC<br/>(N = 963)</b> | <b>All Treated SG<br/>(10 mg/kg)<br/>(N = 1354)</b> |
|----------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|-----------------------------------------------------|
| Number (%) of participants with any AEs leading to discontinuation of study drug | 10 (3.6%)                              | 33 (12.0%)                              | 45 (4.7%)                        | 94 (6.9%)                                           |
| Thrombocytopenia                                                                 | 0                                      | 9 (3.3%)                                | 1 (0.1%)                         | 1 (< 0.1%)                                          |
| Fatigue                                                                          | 0                                      | 3 (1.1%)                                | 4 (0.4%)                         | 9 (0.7%)                                            |
| Interstitial lung disease                                                        | 3 (1.1%)                               | 0                                       | 3 (0.3%)                         | 3 (0.2%)                                            |
| Neutropenia                                                                      | 0                                      | 3 (1.1%)                                | 3 (0.3%)                         | 6 (0.4%)                                            |
| Infusion related reaction                                                        | 1 (0.4%)                               | 2 (0.7%)                                | 1 (0.1%)                         | 1 (< 0.1%)                                          |
| Anaemia                                                                          | 0                                      | 2 (0.7%)                                | 1 (0.1%)                         | 1 (< 0.1%)                                          |
| Hypersensitivity                                                                 | 0                                      | 2 (0.7%)                                | 0                                | 0                                                   |
| Neuropathy peripheral                                                            | 0                                      | 2 (0.7%)                                | 0                                | 1 (< 0.1%)                                          |
| Peripheral sensory neuropathy                                                    | 0                                      | 2 (0.7%)                                | 0                                | 0                                                   |

| Preferred Term                        | GS-US-592-6238<br>SG<br>(N = 275) | GS-US-592-6238<br>TPC<br>(N = 276) | Overall<br>mBC<br>(N = 963) | All Treated<br>SG<br>(10 mg/kg)<br>(N = 1354) |
|---------------------------------------|-----------------------------------|------------------------------------|-----------------------------|-----------------------------------------------|
| Colitis                               | 1 (0.4%)                          | 0                                  | 2 (0.2%)                    | 3 (0.2%)                                      |
| Diarrhoea                             | 1 (0.4%)                          | 0                                  | 4 (0.4%)                    | 9 (0.7%)                                      |
| Febrile neutropenia                   | 1 (0.4%)                          | 0                                  | 1 (0.1%)                    | 5 (0.4%)                                      |
| Neutropenic colitis                   | 1 (0.4%)                          | 0                                  | 2 (0.2%)                    | 2 (0.1%)                                      |
| Alanine aminotransferase increased    | 0                                 | 0                                  | 1 (0.1%)                    | 2 (0.1%)                                      |
| Aspartate aminotransferase increased  | 0                                 | 0                                  | 1 (0.1%)                    | 2 (0.1%)                                      |
| Breast pain                           | 0                                 | 0                                  | 1 (0.1%)                    | 2 (0.1%)                                      |
| General physical health deterioration | 0                                 | 0                                  | 2 (0.2%)                    | 2 (0.1%)                                      |
| Leukopenia                            | 0                                 | 0                                  | 1 (0.1%)                    | 2 (0.1%)                                      |
| Pneumonia                             | 0                                 | 0                                  | 3 (0.3%)                    | 7 (0.5%)                                      |
| Pruritus                              | 0                                 | 0                                  | 0                           | 3 (0.2%)                                      |
| Rash maculo-papular                   | 0                                 | 0                                  | 0                           | 2 (0.1%)                                      |
| Sepsis                                | 0                                 | 0                                  | 1 (0.1%)                    | 4 (0.3%)                                      |
| Vomiting                              | 0                                 | 0                                  | 0                           | 2 (0.1%)                                      |

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date up to and including 30 days after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Multiple AEs were counted only once per participant for each PT.

MedDRA Version 27.1 was used for coding.

PTs were presented by descending order of total frequency in Study GS-US-592-6238.

The following terms are mapped: Neutrophil count decreased = Neutropenia, White blood cell count decreased = Leukopenia, Lymphocyte count decreased = Lymphopenia, Haemoglobin decreased = Anaemia, Red blood cell count decreased = Anaemia, Platelet count decreased = Thrombocytopenia, Asthenia = Fatigue, Typhlitis = Neutropenic colitis, Dyspnoea exertional = Dyspnoea.

### Adverse Events Leading to Dose Reduction

In study GS-US-592-6238, the incidence of AEs leading to dose reduction of SG or TPC was lower in the SG group than in the TPC group (36.7% vs 44.9%).

The most commonly reported ( $\geq 5\%$  of participants in either treatment group) AEs leading to dose reduction of SG or TPC by treatment were as follows:

- **SG: neutropenia (17.5%) and diarrhea (5.5%)**
- **TPC: neutropenia (19.2%), thrombocytopenia (7.6%), and anemia (6.9%).**

The most commonly reported AEs leading to SG dose reduction in the study GS-US-592-6238 SG group were similar to those in the Overall mBC and All Treated SG pools.

### Adverse Events Leading to Study Drug Interruption

In study GS-US-592-6238, the incidence of AEs leading to interruption of any study drug was similar between the SG group and the TPC group (65.8% vs 62.0%).

The most commonly reported AEs leading to interruption of any study drug by treatment group were as follows:

- **SG: neutropenia (43.3%), diarrhoea (5.8%), leukopenia (5.1%), and COVID 19 (5.1%)**
- **TPC: neutropenia (37.0%), thrombocytopenia (18.8%), and anaemia (13.4%).**

Neutropenia was also the most frequently reported AE leading to study drug interruption in the Overall mBC and All Treated SG pools.

## ***Post marketing experience***

Cumulative patient exposure to Trodelvy from the first marketing approval in the US on 22 April 2020 up to 21 April 2025 is estimated to be 66,804 patients, including 21,518 patients in the EU.

### **2.5.1. Discussion on clinical safety**

The safety population of interest are patients from the pivotal study GS-US-592-6238 (n=275 who received SG). Additional Safety data has been provided for 963 patients that received SG 10 mg/kg in the metastatic breast cancer pool (mBC pool). The size of the safety data available in breast cancer patients who have received SG at the proposed dose of 10 mg/kg on Days 1 and 8 Q3W is considered acceptable. In addition, data of an expanded all treated population (including data from metastatic Urothelial Carcinoma (mUC) and metastatic Non Small Cell Lung Cancer (mNSCLC) trials) were provided. The median treatment duration was longer in the SG arm than in the TPC arm i.e. 8.31 months (range: 0.03, 28.68) vs 5.78 months (range: 0.03, 24.18). Approximately 60% of the patients in the SG arm were treated for more than 6 months; however, only half of them for more than 12 months. The dose of SG was reduced in approximately 36% of patients; therefore, the relative dose intensity was above 90% in only about 50% of the patients.

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study GS-US-592-6238 and the most frequently observed adverse events in the SG arm vs the TPC arm were neutropenia (66.5% vs 56.9%), nausea (60.7% vs 34.4%) and alopecia (54.8% vs 27.2%), diarrhoea (53.8% vs 19.9%) and fatigue (47.3% vs 46.7%).

**Treatment-related AEs** (ADRs) with SG vs TPC were also neutropenia (66.2% vs 56.2%), nausea (58.2% vs 26.6%), alopecia (54.2% vs 26.8%) and diarrhoea (56.7% vs 16.9%). In general, Gastrointestinal toxicity was markedly increased with SG vs TPC, whereas haematological toxicities occurred in both treatment arms.

**Grade  $\geq 3$  AEs** in the SG arm vs the TPC arm were: neutropenia (42.9% and 40.6.0%), diarrhoea (9.1% vs 0.7%), leukopenia (7.3% vs 12.7%), anaemia (4.4% and 16.1%) and febrile neutropenia (4.4% vs 1.1%). Treatment-related grade  $\geq 3$  adverse events were more frequent in the SG arm compared to the TPC arm (60.7% vs. 53.3%).

**Adverse events of special interest** (AESI) included neutropenia (including febrile neutropenia), infections secondary to neutropenia, diarrhoea and hypersensitivity, which are important known risks of treatment with SG.

**Neutropenia** was as expected commonly observed in both the pivotal study GS US592 6238 (68.0%), the mBC pool (68.8%) and the All Treated (Expanded) SG population (59.3%). These events were often of grade 3 or higher (45.1% vs 40.9%) in the study GS-US-592-6238. The majority of these events were assessed to be treatment-related and often led to study drug interruptions and reductions. G-CSF use at any time during the study was higher in the study GS-US-592-6238 SG group than in the All Treated (Expanded) SG pool (58.9% vs 46.0%, respectively). These results could suggest the increased use of G-CSF in study GS-US-592-6238, reflecting the better knowledge of neutropenia and management of neutropenia, as a common adverse event for SG. Protocol specified guidance for the

management of neutropenia was changed with Amendment 4 (dated November 2024). This late implementation does not suggest an additional effect on incidences and severity of neutropenia in study GS-US-592-6238. **Febrile neutropenia** was observed as grade 3 or higher and the incidences were similar in the SG arm, the mBC pool and the All Treated (Expanded) SG population, 4.4% vs 5.6 vs 7.1% respectively.

Adverse events and treatment-related AEs of **severe diarrhoea** occurred almost exclusively in participants in the SG group (9.1% and 7.6%, respectively) compared to the TPC group (0.7% and 0.4%, respectively) in study GS-US-592-6238. One participant (0.4%) discontinued SG treatment in study GS-US-592-6238 because of diarrhoea. Incidences and severity of diarrhoea are similar in the SG arm compared to the mBC pool and the All Treated (Expanded) SG population.

**Serious Adverse events (SAEs)** were observed with 25.8% in the SG arm compared to 24.3% in the TPC arm, which is similar to the incidences observed in the mBC pool (27.6%) and lower compared to the All Treated (Expanded) SG population (38.2%). The most commonly observed SAEs in the SG arm, the mBC pool and the All Treated (Expanded) SG Population were febrile neutropenia (3.6% vs 4.5% vs. 6.0%), neutropenia (3.6% vs 2.9% vs 3.7%, respectively), diarrhoea (3.3% vs 3.7% vs 5.0%, respectively) and pneumonia (2.2% vs 2.1% vs 2.5%, respectively).

Remarkably, approximately 10% of SAEs are infections and infestations and approximately 2% of patients experienced sepsis or a septic shock. In the TPC arm the most common SAEs were pneumonia (3.3%) and neutropenia (2.9%).

In the SG arm in GS-US-592-6238, 36.7% had **died**: 29.8% of disease progression and 3.3% of an adverse event. In comparison, more patients had died in the TPC arm with 37.0%; 32.2% died of disease progression and 1.1% died from an adverse event. Hence, treatment with SG seems to carry more severe toxicity, which is outweighed by fewer cases of disease progression and death compared to standard of care (TPC). Causes of death were mostly infections (sepsis, pneumonia).

In study GS-US-592-6238, 3.6% of the patients in the SG arm **discontinued treatment** due to adverse events, which is significantly lower compared to the TPC arm (12.0%) and comparable to the rate for the mBC pool (4.7%) and lower compared to the All Treated Population (6.9%).

Discontinuations rates appear really low, taking the high SAE rates into consideration.

**Dose reductions** of SG were common and the rates were similar in both the SG arm (36.7%) and the TPC arm (44.9%). Most frequent AEs leading to dose reductions were neutropenia and diarrhoea, which is consistent with the known safety profile of SG.

**Dose interruptions** were similar in the SG arm (65.8%) and the TPC arm (62%). Most frequent AEs leading to dose interruptions were neutropenia, diarrhoea, leukopenia, and COVID19. The rate of dose reductions and dose interruptions with SG are high but acceptable considering the targeted non-curative setting.

Laboratory findings were in line with the reported AEs.

Available data in the **elderly population (>65 years)** are limited especially in over 75 years. Increasing toxicity of SG could be observed with increasing age regarding serious adverse events (SAEs) both in the GS-US-592-6238 study, the mBC pool and the All Treated (Expanded) SG Population. In GS-US-592-6238 study, the incidences of grade  $\geq 3$ , SAEs and deaths were 81.0%, 39.7% and 6.3%, respectively, in patients 65 years or older compared to 61.3%, 21.7% and 1.4%, respectively, in patients younger than 65 years which raises concerns about the B/R in the elderly patient population. In addition, the tolerability of the chemotherapy regimen of the TPC arm in the elderly population with 66.7% of Grade  $\geq 3$  AEs, 24.4% of SAEs and no deaths does not indicate a significantly worse safety profile of this regimen in the elderly population. The higher discontinuation

rate due to ADRs, the increased risk of febrile neutropenia, severe diarrhoea and fatal infections in older patients are now reflected in section 4.8 of the SmPC.

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1. The UGT1A1\*28 allele is associated with decreased rates of transcription, initiation, expression, and enzyme activity of UDP-glucuronosyltransferase 1-1. With a decrease in enzyme activity, SN-38 metabolism and hence, detoxification, is reduced and the exposure time of active SN-38 in the intestines is prolonged. Individuals who are homozygous for the UGT1A1\*28 allele are potentially at increased risk for toxicities from SG. Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1\*28 allele. Incidences of AEs were high in patients regardless of genotype, however, Grade 3 or higher AEs were reported in a significantly higher percentage of participants who were homozygous for the UGT1A1\*28 allele compared with participants who were either heterozygous or were homozygous for the UGT1A1\*1 allele in the mBC pool and the All Treated (Expanded) SG Population (83.0%/81.5% vs 72.5%/73.8% vs 67.2%/68.7%). This applies also to the serious AEs which were reported in half of participants who were homozygous for the UGT1A1\*28 allele (50.0%) compared with participants who were either heterozygous (35.7%) or homozygous for the UGT1A1\*1 allele (33.6%) in the All Treated (Expanded) SG Population.

Approximately 0.2% of the Black population, 0.3% of the White population, and 27% of the East Asian population are heterozygous for the UGT1A1\*6 allele. Data were provided for SAEs and the UGT1A1\*6 allele where notably high incidences of febrile neutropenia (7.7%), septic shock (7.7%), herpes zoster (7.7%), pleural effusion (7.7%), dyspnoea (7.7%), acute respiratory failure (7.7%) were reported in GS-US-592-6238 study. The genotype UGT1A1\*1/\*6 seems to be associated with increased risk of ADRs comparable to the risk for UGT1A1\*28/\*28 genotype (52% SAEs, 20% drug discontinuations, 10% death). Although information is limited based on the sample size of UGT1A1\*1/\*6 genotypes, there is a biological rationale for increased safety risks for patients with this genotype.

The higher incidence of Grade 3-4 neutropenia, febrile neutropenia, and anaemia observed in patients homozygous for the UGT1A1\*28 allele and patients heterozygous for the UGT1A1\*6 allele compared to patients homozygous for the wild-type allele has been reflected in sections 4.4 and 4.8 of the SmPC.

### **2.5.2. Conclusions on clinical safety**

The overall toxicity observed with SG 10 mg/kg is considered manageable and in line with what has previously been observed in other clinical trials and the incidences reflected in the mBC pool and the All Treated Expanded SG population. No new toxicities were observed in the pivotal study GS-US-592-6238. The safety profile of SG is considered rather unfavourable compared to the standard chemotherapy arm mainly due to fatal events secondary to neutropenia and gastrointestinal disorders (severe diarrhoea); nonetheless, toxicities can be regarded as manageable by support with G-CSF and dose modifications and overall the safety profile of SG can be considered acceptable in the proposed indication.

### **2.5.3. PSUR cycle**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **2.6. Risk management plan**

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

## ***Safety concerns***

**Table 73 Summary of Safety Concerns**

|                                   |                                                                              |
|-----------------------------------|------------------------------------------------------------------------------|
| <b>Important Identified Risks</b> | Serious infections secondary to neutropenia                                  |
| <b>Important Potential Risks</b>  | None                                                                         |
| <b>Missing Information</b>        | Use in patients with moderate or severe hepatic impairment<br>Immunogenicity |

## ***Pharmacovigilance plan***

**Table 74 Ongoing and Planned Additional Pharmacovigilance Activities**

| <b>Study Status</b>                                                                                                                                                                                                                                                           | <b>Summary of Objectives</b>                                                                                                                                                                                                                                                                                                                                       | <b>Safety Concerns Addressed</b>                           | <b>Milestones</b>      | <b>Due Dates</b> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|------------------------|------------------|
| <b>Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation</b>                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                    |                                                            |                        |                  |
| None                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                    |                                                            |                        |                  |
| <b>Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances</b>                                             |                                                                                                                                                                                                                                                                                                                                                                    |                                                            |                        |                  |
| None                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                    |                                                            |                        |                  |
| <b>Category 3 - Required additional pharmacovigilance activities</b>                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                    |                                                            |                        |                  |
| Study IMMU-132-15<br>A Phase 1,<br>Open-Label,<br>Dose-Escalation<br>Study to Determine<br>an Appropriate<br>Starting Dose of<br>Sacituzumab<br>Govitecan in<br>Subjects with<br>Advanced or<br>Metastatic Solid<br>Tumour and<br>Moderate Liver<br>Impairment<br><br>Ongoing | To identify the safe starting dose of SG in subjects with solid tumour and moderate hepatic impairment.<br>To evaluate the PK of SG, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment.<br>To assess the occurrences of human antibodies against SG in subjects with solid tumour and moderate hepatic impairment. | Use in patients with moderate or severe hepatic impairment | Protocol finalised     | 30-Oct-2020      |
|                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                    |                                                            | First subject enrolled | Apr-2021         |
|                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                    |                                                            | Last subject completed | Dec-2026         |
|                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                    |                                                            | CSR filing             | Jun-2027         |

CSR= clinical study report; SG=sacituzumab govitecan; PK=pharmacokinetics

## Risk minimisation measures

**Table 75 Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern**

| Safety Concern                                             | Risk Minimisation Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Pharmacovigilance Activities                                                                                                                                                                                                                                                    |
|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Important identified risk</b>                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                 |
| Serious infections secondary to neutropenia                | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> <li>Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) should be considered starting in the first cycle in patients at increased risk of febrile neutropenia in SmPC sections 4.2 and 4.4</li> <li>Dose modifications based on severity and occurrence in SmPC section 4.2</li> <li>Warnings of severe or life-threatening neutropenia, including fatal infections in the setting of neutropenia observed in clinical studies with SG primarily in the first two cycles of treatment, in SmPC section 4.4</li> <li>Warning for UGT1A1*28 allele homozygous patients in SmPC section 4.4</li> <li>Adverse reaction in SmPC section 4.8</li> <li>Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9</li> <li>Warning in PL section 2</li> <li>Side effect in PL section 4</li> <li>Restricted medical prescription</li> </ul> <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none"> <li>None</li> </ul> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> <li>None</li> </ul> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>None</li> </ul>              |
| <b>Important potential risk(s)</b>                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                 |
| None                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                 |
| <b>Missing information</b>                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                 |
| Use in patients with moderate or severe hepatic impairment | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> <li>Guidance that no dose adjustment is necessary for mild hepatic impairment in SmPC Section 4.2</li> <li>Guidance that TRODELVY should be avoided in patients with moderate or severe hepatic impairment in SmPC Section 4.2</li> <li>Information on SG exposure is similar in patients with mild hepatic impairment (bilirubin <math>\leq</math> ULN and AST <math>&gt;</math> ULN, or bilirubin <math>&gt; 1.0</math> to <math>\leq 1.5</math> ULN and AST of any level) to patients with normal hepatic function (bilirubin and AST <math>\leq</math> ULN) in SmPC Section 5.2</li> <li>Guidance for the patient to talk to their doctor or nurse if they have liver problems in PL Section 2</li> <li>Restricted medical prescription</li> </ul> <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none"> <li>None</li> </ul>                                                                                                                         | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> <li>None</li> </ul> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>Study IMMU-132-15</li> </ul> |
| Immunogenicity                                             | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> <li>Available clinical data on SG immunogenicity SG SmPC section 4.8</li> <li>Restricted medical prescription</li> </ul> <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none"> <li>None</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> <li>None</li> </ul> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>None</li> </ul>              |

## **2.7. Update of the Product information**

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

In addition, the MAH took the opportunity to make corrections to the BG, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IT, IS, LT, LV, MT, NL, NO, PL, PT, SE, SK, SV translations.

### **2.7.1. User consultation**

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the package leaflet has been amended to reflect the new indication for the treatment of first-line metastatic TNBC in adult patients but the updates are considered slight. The key safety messages as well as the design and layout of the package leaflet are not significantly affected.

## **3. Benefit-Risk Balance**

### **3.1. Therapeutic Context**

The recommended indication reflecting the data evaluated is:

*Trodelvy is indicated as monotherapy for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy (see section 5.1).*

#### **3.1.1. Disease or condition**

TNBC is defined by a lack of ER, PR, and HER2 expression in tumour cells, and accounts for approximately 15% of invasive breast cancers. It is characterized by a more aggressive tumour biology and shorter overall survival with a low 5-year survival rate of approximately 12% (American Cancer Society 2023<sup>12</sup>). Approximately 33% of patients with metastatic TNBC present with de novo metastatic disease (Punie et al. 2024<sup>13</sup>), and TNBC is most commonly associated with visceral metastases affecting the liver, lung, and brain (O'Reilly et al. 2021<sup>14</sup>).

#### **3.1.2. Available therapies and unmet medical need**

Current standard treatment for recurrent/metastatic TNBC varies by subtypes. For patients with de novo metastatic TNBC or recurrence of >6-12 months after the end of (neo)adjuvant immune checkpoint inhibitors (ICI) most recent ESMO guidance recommends a combination of chemotherapy with an ICI for PD-L1 positive patients. PD-L1 negative patients with germline BRCA 1/2 mutations should be treated with a PARP inhibitor and gBRCA-wt PD-L1 negative patients should receive chemotherapy (ESMO living guideline<sup>15</sup>).

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<sup>12</sup> American Cancer Society. Triple-negative Breast Cancer. Available at: <https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html>. Last Updated: 01 March. 2023

<sup>13</sup> Punie K et al. Evolution of characteristics, real-world treatment landscape, and survival outcomes in patients with previously untreated mTNBC in the United States [Abstract]. ESMO Breast Cancer; 2024

<sup>14</sup> O'Reilly D et al. Overview of recent advances in metastatic triple negative breast cancer. World J Clin Oncol 2021

<sup>15</sup> ESMO Living Guideline for Triple-negative metastatic breast cancer; G Curigliano et al., Ann Oncol. 2025.

The subset of patients with PD L1 positive metastatic TNBC (CPS  $\geq 10$ ) accounts for approximately 40% of patients with metastatic TNBC and the prevalence of germline BRCA mutations is only 9.3% to 15.4% among patients with TNBC (Armstrong et al. 2019). For the majority of patients, first-line treatment remains chemotherapy which is associated with a short median PFS of 5.6 months and median OS of 16 months (Cortes et al. 2022). Therefore, there is still significant unmet need for treatments for the subgroup of patients with TNBC who are not candidates for ICI (or PARPi).

### **3.1.3. Main clinical studies**

Study ASCENT-03 is a global, open-label phase 3 study to evaluate the efficacy and safety of SG compared with TPC chemotherapy in participants with locally advanced unresectable or metastatic TNBC who have not received previous systemic therapy for advanced disease. The study enrolled participants with tumours that were PD-L1 negative (CPS < 10) and planned to recruit participants with PD-L1 positive tumours if they previously received a PD-1 or PD-L1 inhibitor in the (neo)adjuvant or had a comorbidity precluding treatment with a PD-(L)1inhibitor.

558 participants were randomized 1:1 to receive SG (10 mg/kg D1 and D8, Q3W) or TPC (paclitaxel, nab-paclitaxel or gemcitabine plus carboplatin). All but two patients had PD-L1 negative tumours. The primary endpoint was PFS as assessed by BICR. Participants in the control group were eligible to receive SG through the study in the crossover phase upon disease progression verified by BICR.

### **3.2. Favourable effects**

At the time of the primary analysis of **PFS** (DCO: 02 April 2025 with a median duration of follow-up of 13.2 months), the ASCENT-03 study demonstrated a statistically significant PFS improvement of SG compared to TPC (HR: 0.623; 95% CI: 0.501, 0.775; 2-sided  $P < 0.0001$ ). The median PFS was 9.69 months (95% CI: 8.15, 11.14) in the SG group and 6.93 months (95% CI: 5.62, 8.25) in the TPC group. Sensitivity analysis of PFS were consistent with the primary analysis.

**OS** data from the first OS interim analysis based on an OS maturity rate of 50.7% (DCO: 27 October 2025 with a median duration of follow-up of 17.7 months) showed similar results in both treatment arms (HR: 0.953; 95% CI: 0.755, 1.205,  $P = 0.6860$ ). The median OS was 21.45 months (95% CI: 18.86, 26.55) in the SG group and 21.26 months (95% CI: 18.69, 25.17) in the TPC group. The OS KM curves largely overlapped until month 24 when they began to separate in favour of SG. Of note, numbers of events beyond 24 months were limited.

### **3.3. Uncertainties and limitations about favourable effects**

- Interpretation of OS data is hampered by the high cross-over rate; at OS IA1, 55.2% participants in the TPC group received SG in the second line setting, 44.8% received SG through the crossover phase of the study. Data in elderly are limited, especially in patients older than 75 years.
- The study population did not represent patients with PD-L1 positive disease who have a comorbidity precluding treatment with ICI or cannot be rechallenged with ICI upon disease recurrence. Nonetheless, it can be assumed that tumour PD-L1 expression is not an effect modifier and that study results from ASCENT-03 are also relevant for these PD-L1 positive patients for whom chemotherapy would be the choice of therapy, therefore the final indication reflects the extended population of patients who are not candidates for PD-1 or PD-L1 inhibitor therapy. The study population characteristics are presented in section 5.1 of the SmPC.

### 3.4. Unfavourable effects

Common AEs observed in the GS-US-592-6238 study in the SG arm were neutropenia (66.5%), nausea (60.7%), alopecia (54.9%), diarrhoea (53.8%) and fatigue (47.3%). Grade  $\geq 3$  AEs were neutropenia (42.9%), diarrhoea (9.1%), leukopenia (7.3%), anaemia (4.4%) and febrile neutropenia (4.4%) **Adverse events of special interest (AESI)** included neutropenia (including febrile neutropenia), infections secondary to neutropenia, diarrhoea and hypersensitivity.

**Serious adverse events (SAEs)** were observed with 25.8% in the SG arm in the GS-US-592-6238 study. The most commonly observed SAEs in the SG arm were febrile neutropenia (3.6%), neutropenia (3.6%), diarrhoea (3.3%) and pneumonia (2.2%).

In the GS-US-592-6238 study, 3.3% of patients in the SG arm **died** due to an AE.

### 3.5. Uncertainties and limitations about unfavourable effects

Data in elderly are limited, especially in patients older than 75 years. Higher incidences of febrile neutropenia, severe diarrhoea, fatal infections and discontinuations due to adverse reactions were observed in patients aged 65 years or older compared with younger patients with metastatic breast cancer. There was a higher incidence rate of serious adverse events in patients aged 75 years or older (50.0%) compared to patients aged 65 years or older (39.7%) and patients younger than 65 years (21.7%) in the GS-US-592-6238 study.

### 3.6. Effects Table

**Table 76 Effects Table for Trodelvy for the 1L treatment of patients with unresectable locally advanced or metastatic TNBC who are not candidates for PD-(L)1 inhibitor therapy (DCO: 02 April 2025 for PFS analysis and safety, DCO: 27 October 2025 for OS IA)**

| Effect               | Short description              | Unit       | Treatment SG      | TPC Control | Uncertainties / Strength of evidence                                                                         | References    |
|----------------------|--------------------------------|------------|-------------------|-------------|--------------------------------------------------------------------------------------------------------------|---------------|
| Favourable Effects   |                                |            |                   |             |                                                                                                              |               |
| PFS                  | Median, by BICR per RECIST 1.1 | Months     | 9.7               | 6.9         | Statistical significance was met for primary PFS endpoint (p<0.0001);                                        | CSR ASCENT-03 |
|                      |                                | HR, 95% CI | 0.62 (0.50, 0.78) |             |                                                                                                              |               |
| OS                   | Median                         | Months     | 21.5              | 21.3        | Interpretation of OS data confounded by high rate of participants (55%) who received SG in 2L in control arm |               |
|                      |                                | HR, 95% CI | 0.95 (0.76, 1.21) |             |                                                                                                              |               |
| Unfavourable Effects |                                |            |                   |             |                                                                                                              |               |
| Drug-related AEs     |                                | %          | 98.5              | 93.5        | Safety in elderly is limited                                                                                 |               |
| G 3-5 AEs            |                                | %          | 65.8              | 62.0        |                                                                                                              |               |
| SAEs                 |                                | %          | 25.8              | 24.3        |                                                                                                              |               |
| Death due to         |                                | %          | 2.2               | 0.4         |                                                                                                              |               |

| Effect | Short description                       | Unit | Treatment SG | TPC Control | Uncertainties / Strength of evidence | References |
|--------|-----------------------------------------|------|--------------|-------------|--------------------------------------|------------|
|        | drug-related AEs                        |      |              |             |                                      |            |
|        | Discontinuation due to drug-related AEs | %    | 2.9          | 11.2        |                                      |            |
|        | Neutropenia                             | %    | 66.5         | 56.9        |                                      |            |
|        | Nausea                                  | %    | 60.7         | 34.4        |                                      |            |
|        | Alopecia                                | %    | 54.9         | 27.2        |                                      |            |
|        | Diarrhoea                               | %    | 53.8         | 19.9        |                                      |            |

Abbreviations: PFS=progression free survival; OS=overall survival; RECIST= Response Evaluation Criteria In Solid Tumors; BICR=blinded independent central review; HR=hazard ratio; G=grade; AE=adverse event; SAE=serious adverse event; PD=progression.

### 3.7. Benefit-risk assessment and discussion

#### 3.7.1. Importance of favourable and unfavourable effects

The ASCENT-03 study demonstrated a statistically significant improvement in PFS for SG compared to first-line chemotherapy in patients with PD-L1 negative TNBC. This improvement can also be considered clinically relevant. However, the study did not show an OS benefit, with an OS maturity rate of 55%. The interpretation of OS data is complicated by the fact that a large proportion of patients (55%) in the control arm received SG after disease progression. Nonetheless, administering SG after the failure of 1L treatment reflects standard clinical practice. The OS data can be considered sufficiently mature to rule out a detrimental effect; however they do not demonstrate an OS benefit in patients with TNBC when SG is administered in the first-line setting compared with later-lines of treatment.

The overall safety profile of SG in ASCENT-03 study is in line with what has been observed previously with SG. No new ADRs and no new risks have been identified in the RMP. The safety profile of SG is considered rather unfavourable compared to the chemotherapeutic agents of the control arm, mainly due to high rates of infections secondary to neutropenia (e.g. sepsis) and gastrointestinal disorders (e.g. severe diarrhoea); nonetheless, toxicities can be regarded as manageable by support with G-CSF and dose modifications.

#### 3.7.2. Balance of benefits and risks

In view of the demonstrated benefit in PFS for SG and its manageable safety profile, SG can be considered a viable treatment option for first-line therapy in patients with TNBC.

#### 3.7.3. Additional considerations on the benefit-risk balance

N/A

### 3.8. Conclusions

The overall B/R of Trodelvy in the new claimed indication is positive.

## 4. Recommendations

### Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| Variation accepted |                                                                                     | Type              | Annexes affected |
|--------------------|-------------------------------------------------------------------------------------|-------------------|------------------|
| C.I.6.a            | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II | I and IIIB       |

Extension of indication for Trodelvy as monotherapy for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy, based on the results from study GS-US-592-6238 (ASCENT-03), which is a phase 3 study of sacituzumab govitecan (IMMU-132) versus treatment of physician's choice (TPC) in patients with previously untreated, locally advanced, inoperable or metastatic triple-negative breast cancer whose tumours do not express PD-L1 or in patients previously treated with anti-PD-(L)1 agents in the early setting whose tumours do express PD-L1. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been agreed. In addition, the MAH took the opportunity to bring the PI in line with the QRD template version 10.4 and to implement corrections to the BG, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IT, IS, LT, LV, MT, NL, NO, PL, PT, SE, SK, SV translations.

### Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.