14 October 2021
EMA/623887/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trodelvy

International non-proprietary name: sacituzumab govitecan

Procedure No. EMEA/H/C/005182/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

Abbreviation	Definition
10-OH-CPT	10-hydroxycamptothecin
Ab	antibody
ADA	anti-drug antibody
ADC	antibody-drug-conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	AEs of special interest
ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the concentration-versus-time curve
BM-ve	brain metastasis negative
BRCA	breast cancer susceptibility gene
CBR	clinical benefit rate
CDC	complement-dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAR	drug to antibody ratio
DNA	deoxyribonucleic acid
DOR	Duration of response
ECG	electrocardiogram
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
ER	estrogen receptor
Fc	heavy chain constant
G-CSF	granulocyte colony stimulating factor
GLP	Good Laboratory Practice
HER2	Human epidermal growth factor receptor 2
HNSTD	highest non-severely toxic dose
HPLC	high-performance liquid chromatography
HR+	hormone receptor positive
IC50	concentration producing 50% inhibition
IP	intraperitoneous(ly)
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous(ly)
KD	dissociation constant

LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MES	2-(N-morpholino) ethanesulfonic acid
mTNBC	metastatic triple-negative breast cancer
NK	natural killer
NOAEL	no observed adverse effect level
NZW	New Zealand white rabbits
ORR	objective response rate
OS	overall survival
PARPi	poly adenosine diphosphate ribose polymerase inhibitor
PBMC	peripheral blood mononuclear cell
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PR	progesterone receptor
PRAC	Pharmacovigilance Risk Assessment Committee
QTc	corrected QT
SAE	serious adverse event
SG	sacituzumab govitecan
SmPC	Summary of Product Characteristics
SN-38G	SN-38 glucuronide
t1/2	half-life
TAb	total antibody
TEAE	treatment-emergent adverse event
TK	toxicokinetic(s)
Tmax	time to maximum concentration
TNBC	triple-negative breast cancer
TPC	treatment of physician’s choice
Trop-2	trophoblast cell surface antigen 2
UGT	uridine diphosphate glucuronosyltransferase
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences Ireland UC submitted on 3 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Trodelvy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 .

The applicant applied for the following indication

Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) 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 applicant 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.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active substance status

The applicant requested the active substance sacituzumab govitecan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP on the development relevant for the indication from the CHMP on 1 April 2016 (EMEA/H/SA/3269/1/2016/SME/III). SAWP coordinators were Dr Pierre Démolis and Dr Joao Manuel Lopes de Oliveira. The Scientific advice pertained to the following non-clinical, and clinical aspects:

- The performance and timing of repeat-dose toxicity studies in NHPs;
- A sufficiency of a phase 2 single-arm study in a metastatic refractory TNBC population to support a CMA application;
- The overall design of a phase III randomised controlled study to support an MAA, and specifically the selection of 3L+ metastatic TNBC patients and choice of primary and secondary endpoints.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Sinan B. Sarac

The appointed co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	3 March 2021
Accelerated Assessment procedure was agreed-upon by CHMP on	25 February 2021
The procedure started on	25 March 2021
The Rapporteur's first Assessment Report was circulated to all CHMP members on	25 May 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	21 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 June 2021
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	25 May 2021

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 June 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 August 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	2 September 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 September 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trodelvy on	14 October 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially claimed indication was: "*TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease.*" Following recommendation by the CHMP the applicant agreed to a revised indication wording:

Trodelvy as monotherapy is indicated 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 (see section 5.1).

2.1.2. Epidemiology and risk factors

Triple-negative breast cancer (TNBC), accounts for approximately 15% of invasive breast cancers [*DeSantis et al, 2016; Plasilova et al, 2016; Kohler et al, 2015*]. 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*]

2.1.3. Biologic features Aetiology and pathogenesis

TNBC is defined by a lack of tumor-cell expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [*Anders et al, 2013*].

2.1.4. Clinical presentation, diagnosis and prognosis

TNBC is associated with aggressive tumour biology and a poor prognosis. TNBC is often associated with visceral metastases and mTNBC is incurable [*Kassam et al, 2009*].

2.1.5. Management

Targeted therapies have benefited patients with other subtypes of breast cancer and several targeted therapies for hormone receptor positive (HR+) and HER2-positive breast cancer are available; however, sequential single-agent chemotherapy remains the standard of care for patients with mTNBC [*Cardoso et al,*

2020]. There is no preferred or standard regimen used and in general, patients first receive standard chemotherapy regimens that include either a taxane and/or anthracycline.

However, a majority of patients have disease progression after receiving first-line therapy and standard therapeutic options are limited to chemotherapy (eg, capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens for patients who present with visceral crisis). Standard chemotherapy is associated with low response rates (10 to 15%) and short progression-free survival (PFS) (2 to 3 months) among patients with pretreated mTNBC [*Brufsky et al, 2012; Perez et al, 2010; Twelves et al, 2016; Park et al, 2019*]. Overall survival (OS) among patients with this form of breast cancer has not changed over the past 20 years and patients with mTNBC continue to have a considerably worse OS when compared with their metastatic breast cancer counterparts [*Zeichner et al, 2016*].

For patients whose tumours are programmed death-ligand 1 (PD-L1) positive, atezolizumab in combination with nab-paclitaxel has been approved for mTNBC while the poly-adenosine diphosphate-ribose polymerase inhibitors (PARPi), olaparib and talazoparib, have been approved for patients with TNBC who harbour a germline BRCA 1 or 2 mutation and have been previously treated with chemotherapy.

Treatment options are limited for patients who have received 2 or more regimens in the metastatic setting, highlighting the need for advances in therapeutic options for these patients.

About the product

Sacituzumab govitecan (hereafter referred to as SG) is a trophoblast cell surface antigen-2 (Trop-2)-directed antibody and topoisomerase inhibitor conjugate (ie, an antibody-drug conjugate) composed of the following 3 components:

1. The humanised monoclonal antibody, hRS7 IgG1κ, that binds to Trop-2, a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers, including triple-negative breast cancer (TNBC)
2. The camptothecin-derived agent, SN-38, a topoisomerase I inhibitor
3. A hydrolyzable linker, with the company designation as CL2A, which links the humanised monoclonal antibody to SN-38.

Binding of Trop-2 by the parental RS7 antibody has been shown to result in internalisation and processing of the antibody by the targeted cells [*Shih et al, 1994; Stein et al, 1995*]. Because of its hydrolyzable linker, SG will release its SN-38 payload both intra- and extra-cellularly in the tumor microenvironment [*Govindan et al, 2013; Goldenberg et al, 2015*]. SG delivers significantly greater amounts of SN-38 to a Trop-2-expressing tumor than conventional irinotecan chemotherapy [*Sharkey et al, 2015*]. The extracellular release of SN-38 from SG also allows for by-stander killing of Trop-2 negative tumor cells [*Lopez et al, 2020; Perrone et al, 2020; Zeybek et al, 2020*].

Thus, SG can deliver cytotoxic chemotherapy to tumors, 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.

SG belongs to the Anatomic Therapeutic Class 1 of antineoplastic and immunomodulating agents.

The claimed indication for SG is for the treatment of adult patients with metastatic TNBC who have received at least 2 prior therapies for metastatic disease. SG for injection is a powder for intravenous (IV) use in a 50 mL clear glass single-dose vial that delivers 200 mg SG each. The recommended dose of SG is 10 mg/kg administered as an IV infusion once weekly on Days 1 and 8 of 21-day treatment cycles. SG treatment is to be continued until disease progression or unacceptable toxicity.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the provided Phase III study data which demonstrated a clinically meaningful improvement in progression free and overall survival compared to physician´s choice of SOC chemotherapy. Sacituzumab govitecan was considered to have the potential to fulfil the unmet medical need in the sought patient population.

2.2. Quality aspects

2.2.1. Introduction

Sacituzumab govitecan, the active substance contained in Trodelvy, is an antibody-drug conjugate (ADC). Sacituzumab is a humanised monoclonal antibody (hRS7 IgG1κ) produced from a Sp2/0 cell line and recognises Trop-2. The small molecule, SN38, is a topoisomerase I inhibitor which is covalently attached to the antibody by a hydrolysable linker, CL2A.

Trodelvy is presented as 200 mg powder for concentrate for solution for infusion in a vial. It is formulated with 2-(N-morpholino)ethane sulfonic acid (MES) monohydrate (novel excipient), polysorbate 80 and trehalose dihydrate.

2.2.2. Active Substance

The quality of sacituzumab, CL2A-SN38 and sacituzumab govitecan is described in separate sections:

- Sacituzumab intermediate (hRS7 IgG1κ);

- CL2A-SN38 drug-linker intermediate;

- Sacituzumab govitecan active substance.

2.2.2.1. Sacituzumab intermediate (hRS7 IgG1κ)

General Information

hRS7 IgG1 κ is a recombinant heterotetrameric humanised mouse IgG1 monoclonal antibody with two kappa light chains and two gamma one heavy chains. There is one N-glycosylation site on the heavy chain (301) and it is predominantly occupied with a core fucosylated bi-antennary glycan, typically found with monoclonal antibodies produced by Sp2/0 murine myeloma cells, with 0, 1 or 2 terminal galactose residues.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

The monoclonal antibody intermediate is manufactured in accordance with EU GMP.

hRS7 IgG1κ antibody intermediate (hRS7 IgG1κ) is manufactured from a Sp2/0-AG14 cell line using a fed-batch bioreactor process, consisting of thaw and inoculum expansion, cell culture expansion and production in a bioreactor, followed by harvest. The intact IgG is purified from the cell culture broth by a series of column chromatography and filtration steps.

Thaw and inoculum expansion are described in sufficient detail and appropriate process parameters and in-process controls (IPCs) are in place. Production and harvest process have been thoroughly described. Fill weight is controlled. The purification process has been adequately described, including the sanitisation procedures. Resin lifetime has been identified as a key operational parameter (KOP), with a pre-determined number of cycles. An overview of the process control strategy has been provided, where the process parameters and in-process controls have been described. In process hold times have been validated by studying the chemical stability and microbial control of media holds performed on the specific storage vessels. Antibody intermediate bulk solution is shipped for manufacturing of sacituzumab govitecan bulk active substance.

The description of the manufacturing process and process controls are considered acceptable.

Control of materials

Compendial and non-compendial raw materials, disposable equipment, resins and filters are listed. Certificates of analysis for all incoming materials are reviewed to ensure they comply with the manufacturer specifications. Additional testing is performed on specific raw materials. In-house specifications for raw materials were provided.

Sufficient information on the gene construct and cell line is provided. A conventional two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) has been established. Cell bank manufacturing and storage is described. The cell banks have been characterised and tested. The generation and qualification of the WCB is described. The limit of *in vitro* cell age (LIVCA) is established as of total *in vitro* age from the MCB, given the harvest from a production run after thaw of the WCB and of additional culture, included in the manufacture of the WCB. The acceptability of a LIVCA from the MCB is supported by all data generated for the upstream process performance and product quality, and also genetic stability data.

Control of materials is considered acceptable.

Control of critical steps and intermediates

An overview of the process parameters and IPCs of the antibody intermediate manufacturing process was presented. Steps with CPPs and/or critical IPCs are considered the critical steps. CPPs impacting critical quality attributes (CQAs) are defined for the manufacturing process. It is indicated which in-process tests are to adjust the process and which are related to product quality/or process performance indicators. Target range and acceptable range are provided. A strategy is in place to manage excursions from acceptable ranges and excursion actions based upon parameter criticality are clarified. This is acceptable.

Process validation

A lifecycle approach has been used for validation of the commercial manufacturing process of hRS7 IgG1κ; Process Design, Process Verification (also referred to as PPQ) and ongoing process verification. These batches

were manufactured under a pre-approved protocol and acceptance criteria to show that the manufacturing process can consistently produce product meeting quality criteria. The performance parameter results obtained during process validation demonstrate that the cell culture and purification processes are under control and can be considered successfully validated. Deviations to the PPQ protocol are described in sufficient detail and were determined not to adversely affect the product or the process, and therefore not to impact the PPQ. Commercial scale process equipment cleaning validation was successfully executed with no process deviations.

The commercial process for the manufacture of hRS7 IgG1 κ is considered validated.

The applicant follows a comprehensive control strategy linking the control provided by each unit operation with control provided by raw materials, procedural elements, environmental factors, process parameters, in-process and release testing and stability monitoring.

Characterisation

An exhaustive characterisation exercise was performed that include determination of the primary, secondary and tertiary structures, glycosylation profile analysis, purity and biological activity studies. Overall, the methods used are considered adequate for their intended use.

To control process-derived impurities, the applicant follows a strategy based on risk assessments, release testing and capacity of the purification process to efficiently remove impurities to acceptable levels. Overall, this is considered adequate.

Overall, characterisation of hRS7 IgG1κ is considered acceptable.

Specifications

Specifications for the hRS7 IgG1κ monoclonal antibody intermediate include control of identity, purity and impurities, potency and other general tests.

The applicant has justified the ranges of acceptance criteria for each quality attribute included in the sacituzumab specification. The acceptance criteria reflect the results of characterisation, stability and variability in the analytical results. The proposed acceptance criteria ensure that all variants are controlled to levels that do not affect biological activity or safety. The specifications take into account the fact that hRS7 IgG1κ is an intermediate and also additional controls are in place for sacituzumab govitecan. The specifications for hRS7 IgG1κ are considered acceptable.

The applicant states that specifications will be re-evaluated after enough commercial lots are manufactured to provide statistical power for robust analyses. This is considered adequate.

Analytical methods

Descriptions of non-compendial methods are provided by the applicant. The methods were validated in accordance with ICH guideline for specificity, accuracy, repeatability, intermediate precision, linearity, range, and robustness. Results indicate that the methods are suitable for release purposes.

Batch analysis

Batch analysis data is provided for commercial scale batches produced and the PPQ batches. All results are within the set specification at the time of release. Batches manufactured according to the commercial process demonstrate consistency of the manufacturing process. Supportive batch analysis data is provided.

Reference Material

The applicant has described the reference standards used in sufficient detail. A two-tiered reference standard system has been implemented and the corresponding qualification data is included in the dossier.

Container closure

The applicant has given an acceptable description of the container closure system. Container specification was provided. Stability study on PPQ batches, has been initiated.

Stability

Stability data is presented for hRS7 IgG1 κ batches;. The tested conditions apply to long term, accelerated and stressed conditions.

Presently, data are provided for the PPQ batches. No trends were observed in any of the parameters tested. Accordingly, the shelf life has been set. The shelf life will be updated primarily based on the long-term stability data.

The applicant commits that at least one lot of hRS7 IgG1 κ will be placed on stability yearly.

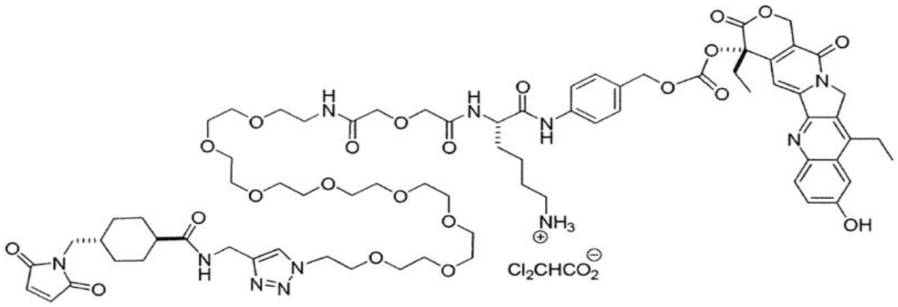
In conclusion, the proposed shelf life is considered acceptable.

2.2.2.2. CL2A-SN38 drug-linker intermediate

General Information

SN-38 is a potent topoisomerase I inhibitor and the active metabolite of irinotecan. CL2A links the humanised monoclonal antibody hRS7 IgG1 κ to SN-38. The structure of CL2A-SN38 (Figure 1) was confirmed by spectral analysis and by elemental analysis and general properties were updated during the procedure. The molecular formula and average mass for CL2A-SN38 are $C_{73}H_{97}N_{11}O_{22}$ and 1479.7 Da.

Figure 1 – *Structural formula of CL2A-SN38*



Manufacture, process controls and characterisation

Flow diagrams of the chemical synthesis and narrative descriptions have been provided including standard quantities of used raw materials, solvents and reagents reflecting the representative batch scale for commercial manufacture as well as pH values, reaction and drying temperatures and times. The expected yields are given. Information about reprocessing is adequate.

Control of materials

Specifications, analytical procedures as well as analytical data have also been presented.

Analytical procedures have been described and batch analysis data for impurities control have been presented.

The other raw materials used are listed and minimum specifications are included regarding identity and sometimes assay/purity. Viral and/or TSE safety data are not required. The content and purity specifications have been included.

Information about CPPs and the corresponding process steps is considered justified in conjunction with S.2.6, Manufacturing process development.

Control of critical steps and intermediates

The review of process parameters and operating ranges concluded that appropriate process monitoring, and process control mechanisms have been designed into the manufacturing process to ensure production of CL2A-SN38 of acceptable quality. In addition to the quality control of the starting materials and key reagents, these mechanisms include the incorporation of IPC tests and processing instructions that define actions to take based upon observations during batch production.

Process validation

The CL2A-SN38 manufacturing process does not involve aseptic processing or sterilisation so no process validation information is required for this intermediate. Only shipment conditions have been adequately validated. The results have been presented.

Manufacturing process development

The history of manufacturing process development provides enough details and summarises the main changes during the process development. The control strategy was established based on a combination of risk-assessment and use of Design of Experiments (DoE) to characterise each major stage in the manufacture of CL2A-SN38.

Characterisation

CL2A-SN38 has been sufficiently characterised. Elemental analysis data comply with the theoretical values of the molecular formula for CL2A-SN38. 1H NMR and 13C NMR IR, UV/Vi data and spectra including interpretation are provided. The results are consistent with the chemical structure.

Additionally, the MS results for major intermediates (starting materials and intermediates of CL2A-SN38) and CL2A-SN38 itself have been provided and sufficiently discussed.

The process-related organic impurities, residual solvent impurities and the elemental impurities are shortly discussed. Overall, the discussion is acceptable for the other set of impurities which are not conjugatable.

Specification

The CL2A-SN38 specification is based on results obtained and general requirements of Ph. Eur. The results presented justify all the proposed limits.

Analytical methods

All methods used are described in detail. The applied methods are in accordance with current technical and scientific requirements. The validation data provided for the methods used are in accordance with the requirements of the relevant ICH guidelines.

Batch analysis

Test results for batches of CL2A-SN38 have been presented. Batch analysis results confirm batch-to-batch consistency. Furthermore, the results show a steady improvement in the manufacturing process. Purity increases over time.

Reference Material

Sufficient information on the reference standard is provided.

Container closure

The container is characterised and the applicant has confirmed that the container is in compliance with all the applicable Ph. Eur. requirements. Specifications/analytical procedures are provided.

Stability

Stability studies have been performed in line with CPMP/QWP/122/02, rev 1 corr.

The results of stability studies confirm that the intermediate CL2A-SN38 is sufficiently stable.

A retest period is justified based on the stability data reported.

2.2.2.3. Sacituzumab govitecan

General Information

Sacituzumab govitecan (Figure 2) results from the conjugation via thioether bonds of the following intermediates:

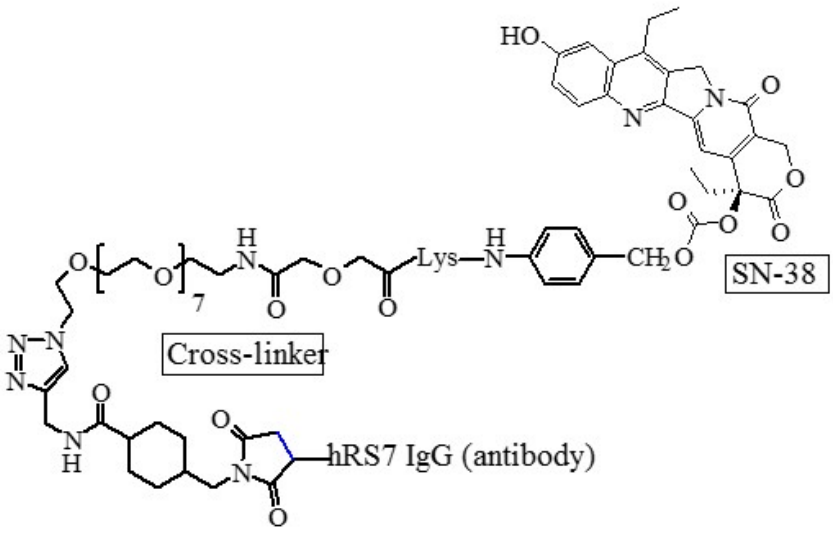
- Sacituzumab, a humanised monoclonal antibody (hRS7 IgG1κ);

- CL2A-SN38, a drug linker comprised of SN-38, a camptothecin-derived agent (topoisomerase I inhibitor) and CL2A, a hydrolysable linker.

Binding of Trop-2 by the parental hRS7 antibody has been shown to result in the internalisation and processing of the antibody by the targeted cells. Because of its hydrolysable linker, the active substance will release its SN38 payload both intra- and extra-cellularly in the tumour microenvironment. The extracellular release of SN-38 also allows for by-stander killing of Trop-2 negative tumour cells.

The ADC has an average molar drug to antibody ratio (DAR) of approximately 7 to 8 drug molecules per antibody, and a molecular weight of approximately 160 kDa.

***Figure 2* – Structure of sacituzumab govitecan**



Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Sacituzumab govitecan is manufactured at BSP Pharmaceuticals S.p.A., Italy by a straightforward process.

Control of materials

The raw materials, solvents, and reagents used for conjugation and purification of sacituzumab govitecan are provided. For non-compendial raw materials, quality standards are provided.

Control of critical steps and intermediates

The quantity of the antibody and the CL2A-SN38 used in the conjugation is controlled as a process input in the master batch record. The microbial control strategy is deemed acceptable considering the limits set for IPCs and release of sacituzumab govitecan active substance.

Manufacturing steps having a significant impact on CQAs or have essential roles in controlling CQAs need to be controlled. Steps with CPPs and/or critical IPCs are considered the critical steps.

Process validation

The sacituzumab govitecan active substance process validation strategy was designed to demonstrate that the commercial process is capable of consistently delivering active substance with the required quality. The process validation strategy included consecutive PPQ batches of active substance, manufactured according to the commercial process. The process performance parameter results obtained during process qualification demonstrate that the active substance manufacturing process consistently meets criteria for process performance and product quality specifications for active substance. Ongoing process verification will be followed in stage 3, to monitor the process in order to assure that the process remains in a state of control during commercial manufacture, in compliance with the validated parameters.

Information on the history of the manufacturing process is described, including development of the linker, scale-up and early development of the manufacturing process. The control strategy for the active

manufacturing process is composed of a variety of elements including raw material controls, procedural and environmental controls, process parameter controls, in-process controls, release testing, stability testing and process validation. Combinations of these control elements are applied, as appropriate, to provide a high degree of assurance that the defined properties for the CQAs are achieved. The integrated strategy for control of sacituzumab govitecan active substance was developed by assessing the criticality of product quality attributes and ranking the process variables based on risk to CQAs and process consistency. Each quality attribute was rated for criticality using a risk assessment tool that evaluates severity of impact and the uncertainty of this evaluation. The outcome of the sacituzumab govitecan active substance CQA risk assessment is considered adequate. The medium and high-risk quality attributes were conservatively categorised as CQAs. To rank the process variables based on their risk to impact CQAs and process consistency, a process capability risk assessment was performed and each parameter of the various unit operations was evaluated for their impact in a FMEA. The Risk Priority Numbers (RPNs) were calculated considering the severity, occurrence and detectability rankings. High and medium Risk parameters were identified as potential CPPs and a risk mitigation strategy was defined, and validation studies, adjustments to master batch records, or control strategies were implemented. The presented overall control strategy is deemed acceptable.

In the context of process characterisation, a series of DoE experiments were performed to identify or confirm the appropriate setpoints and operating ranges for key or critical process parameters. Sacituzumab govitecan has been evaluated in the pivotal IMMU-132-01 Phase I/II and in the confirmatory Phase III ASCENT clinical trials.

Characterisation

Elucidation of structure

The active substance has been adequately characterised. The reduction method has consistently resulted in 8 sulfhydryl groups derived from the four inter-chain disulfide bridges, while intra-domain disulfides if reduced are expected to refold due to their juxtaposition within the Ig-fold. This is supported by peptide mapping showing that 99% of the attached payload is coupled specifically to the 8 sulfhydryl groups involved in interchain disulfide bridges. Occupancy at non-specific sites is low (<1%).

Impurities

Different sources of potential impurities in sacituzumab govitecan were considered, including impurities originating from raw materials, solvents and reagents used in the manufacturing processes, as well as product-related impurities. Process-related impurities are introduced into the active substance process either directly or from the antibody and CL2A-SN38. Elemental impurities have been determined.

Specification

Specifications have been set as per ICH Q6A and ICH Q6B and include control of identity, purity and impurities, potency and other general tests.

Assays have been developed for monitoring the biological activity of sacituzumab govitecan. Justification for the specification is based on an assessment of the variability in the analytical results obtained for each specification.

The control strategy is appropriate and characteristics identified by risk analysis are largely covered. Reference to Ph. Eur. and internal method identification number is provided.

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Analytical methods

The non-compendial analytical procedures have been validated in accordance with ICH and found suitable for their intended purposes. The methods have been demonstrated to be fit for purpose.

Batch analysis

Batch analysis data for sacituzumab govitecan active substance manufactured with the different processes are provided. Batches were tested by the methods valid at time of release and the acceptance criteria were met. The data support consistency of the material.

Reference Standard

Refer to the finished product section.

Container closure

Suitability of the container closure system for the active substance is supported by stability data.

Stability

No trends were observed in any of the parameters tested for the duration of the study under long-term conditions. The proposed shelf life is further supported by prediction modelling of long term data, by stability data under accelerated conditions of batches.

The applicant provided appropriate a commitment that commercial stability studies for sacituzumab govitecan bulk active substance will be completed as per the protocol. Any confirmed out-of-specification result, or significant negative trend, should be reported to EMA. In addition, one batch of sacituzumab govitecan bulk active substance will be placed on stability annually.

The active substance was subjected to various stress conditions of thermal, low and high pH, oxidative stress, and photo stress.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the finished product

Sacituzumab govitecan finished product, also referred to as IMMU-132, is a lyophilisate for solution for infusion in a vial. The target amount of sacituzumab govitecan is 200 mg (target fill amount per vial), to obtain a sacituzumab govitecan concentration of 10 mg/mL upon reconstitution with 20 mL of sodium chloride (not supplied). The reconstituted solution is diluted with sodium chloride injection, to obtain a sacituzumab govitecan concentration in the range of 1.1 to 3.4 mg/mL in a solution for IV infusion not exceeding 500 mL.

The finished product is packaged in a 50R Ph. Eur. Type I clear glass vial, stoppered with an elastomeric stopper and sealed with a 20 mm aluminium flip-off overseal.

The composition of the finished product both before and after reconstitution were provided. Sacituzumab govitecan is formulated with 2 compendial excipients, trehalose dihydrate (stabiliser/bulking agent) and

polysorbate 80 (stabiliser/surfactant), and a novel excipient 2-(N-morpholino)ethane sulfonic acid (MES) hydrate, pH 6.5 (buffer).

The formulation was developed to minimise in-process (bulk active substance and finished product) degradation, facilitate lyophilisation, ensure acceptable finished product stability, and provide suitable in-use stability and handling properties.

Pharmaceutical development

The comprehensive control strategy links the control provided by each unit operation with control provided by raw materials, procedural elements, environmental factors, process parameters, in-process and release testing and stability monitoring.

The critical process steps and process parameters for the finished product manufacturing have been identified through design space studies and accumulated manufacturing experience.

Manufacture of the product and process controls

Manufacture

Sacituzumab govitecan finished product is manufactured and tested for release.

Process validation

The process validation strategy for sacituzumab govitecan finished product is based on a lifecycle management approach that includes a process design stage, a PPQ stage and an ongoing process verification.

finished product batches were successfully manufactured by the PPQ criteria, demonstrating homogeneity and reproducibility of the manufacturing process based on the validation data collected.

Control of excipients

Trehalose dihydrate and polysorbate 80 are of compendial grade and are tested against compendial specifications. Reference to Ph. Eur. is accepted.

The data provided to support the use of MES monohydrate as novel excipient for Trodelvy is considered acceptable for approval.

Batch release data and data to support qualification of compendial methods and validation of non-compendial methods are included.

Product specification

Specifications for sacituzumab govitecan finished product are set in accordance with the principles defined in ICH Q6B. They include control of identity, purity and impurities, potency and other general tests.

Data from all clinical lots, all applicable real-time stability data, data that is representative of current analytical methods were used to justify the set acceptance criteria. The overall approach to establish and justify the commercial specifications is based on an assessment of the variability in the analytical results obtained for each specification and clinical relevance.

The defined acceptance criteria are found acceptable.

Analytical methods

The analytical methods description is adequate and descriptions are presented for non-compendial analytical methods exclusively applied to the finished product, including the preparation of samples for analysis, the conditions of analysis and the calculation formulas. Compendial analytical procedures follow the current edition of the referenced pharmacopeia and reference to the corresponding monograph is provided. All compendial methods used for active substance and finished product testing were successfully verified.

A detailed risk assessment according to ICH Q3D (R1) was conducted in relation to the potential presence of elemental impurities in the finished product, using component assessment approach for all phases of production, from conjugation to filling along with excipients. Given the "low" overall risk, as described in the ICH Q3D, the absence of additional controls is found acceptable.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been provided, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

The risk of the presence of nitrosamine impurities in Trodelvy from the chemically synthesised linker CL2A-SN38, from the raw materials used in the biological components of Trodelvy and from the primary packaging materials was assessed.

Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis

Sacituzumab govitecan finished product batch analysis data are provided. The presented data support consistency of the Process C finished product.

Reference standard

Reference standard used for finished product testing is the same as for the active substance.

A two-tiered reference standard programme (primary and working reference standards) has been established from lots representative of production and clinical materials to ensure consistency and continuity of the active substance and finished product quality. Qualification data was provided. A requalification protocol based on pre-specified criteria was provided.

Container closure

The primary packaging components, Type I colourless, clear glass 50-mL vial and 20-mm elastomeric stopper meet Ph. Eur. compendial requirements for glass containers for pharmaceutical use and elastomeric closures for injection.

Stability of the product

Stability studies were conducted in accordance with ICH Q5C under approved stability protocols. Batches that have been placed on stability are summarised and the acceptance criteria are provided. Beside long-term storage condition (5°C ± 3°C), accelerated conditions and stress conditions.

According to the SmPC instructions for administration of sacituzumab govitecan finished product, the lyophilised product is reconstituted with 20 mL of normal saline, providing a 10 mg/mL solution and further diluted to 1.1 - 3.4 mg/mL in normal saline in an IV bag. Compatibility studies demonstrate that the finished product at 1.1 and 3.4 mg/mL is compatible with polyvinyl chloride infusion containers. The infusion bag containing the diluted solution can be stored in a refrigerator (2°C to 8°C) for up to 4 hours, protected from light.

In conclusion, the acceptable shelf life for the finished product is 36 months when stored at 2°C - 8°C protected from light.

Adventitious agents

No materials of animal or human origin were used during cell banking or are used in the manufacturing process. None of the excipients is of human or animal origin. The MCB, WCB and cells at LIVCA have been tested sufficiently for adventitious viruses as well as retroviruses. Bulk harvests are routinely tested for adventitious viruses according to ICH Q5A. A test for MVM is included. No viral contaminants have been found within the cell banks and in the bulk harvest of several batches tested so far.

In summary, virus safety has been demonstrated.

Compliance with TSE-Guideline EMEA 410/01 rev03 has been demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set.

The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Trodelvy is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Trodelvy is considered approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical package submitted contains in total 13 studies on primary and secondary pharmacodynamics pharmacology, 1 study in safety pharmacology, 7 studies in pharmacokinetics and 8 toxicology studies. Primary pharmacology was tested in murine xenograft models bearing human Trop-2 expressing tumors. Pharmacokinetic and toxicity studies were also conducted in mice and / or rabbits to evaluate Trop-2-independent (off-target) PK, biodistribution or toxicity. Cynomolgus monkeys were identified as the only relevant toxicity species due to cross-reactivity of the target, Trop-2 with the hRS7antibody, the binding moiety of sacituzumab govitecan.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Trophoblast cell surface antigen 2 (Trop-2) is a member of the epithelial cell adhesion molecule family, that is expressed on healthy epithelial cells in many organs and described to be overexpressed in a number of carcinomas. Expression of Trop-2 by various human cancer cell lines was demonstrated *in vitro* by flow cytometry analysis. Across the different cell lines analysed, Trop-2 expression levels varied but did not correlate with the tumour type. Relevant to the present marketing authorisation application, Trop-2 was expressed by different human breast cancer lines, including triple-negative breast cancer.

In binding affinity studies ([RR 01-15-10], [RR 01-17-14]) Sacituzumab govitecan was shown to bind to human Trop-2-expressing tumour cells (K_D 0.658 ± 0.14 nM) and to recombinant human Trop-2 (K_D 0.26 ± 0.14 nM). The binding affinity of the ADC was comparable to that of mAb hRS7, indicating that conjugation with SN-38 did not impair binding to the target antigen Trop-2 (study RR 05-07-12). In addition, sacituzumab govitecan was shown to be cytotoxic for Trop-2 positive tumour cells *in vitro* while the un-conjugated mAb hRS7 did not inhibit tumour cell growth (RR 01-15-10; Cardillo et al., 2011).

Across the different cancer cell lines evaluated, the EC50 for cytotoxicity induced by sacituzumab govitecan (based on SN-38 equivalents) ranged from 1.95 nM to 23.14 nM. It is noted that the EC50 did not strictly correlate with the Trop-2 expression level of the target cells. When compared to free SN-38, the ADC was slightly less active (1.4 - 2.8x).

Table 1 Susceptibility of cancer cell lines to sacituzumab govitecan (Cardillo et al., 2011)

	Trop-2 Expression		Cytotoxicity Results				
Cell Line	**Median Fluorescence (Background)**	**Percent Positive**	**SN-38 IC_{50} (nM)**	**95% C.I. IC_{50} (nM)**	**hRS7-SN38* IC_{50} (nM)**	**95% C.I. IC_{50} (nM)**	**ADC/Free SN-38 Ratio**
Calu-3	282.2 (4.7)	99.6%	7.19	5.77 - 8.95	9.97	8.12 - 12.25	1.39
COLO 205	141.5 (4.5)	99.5%	1.02	0.66 - 1.57	1.95	1.26 - 3.01	1.91
Capan-1	100.0 (5.0)	94.2%	3.50	2.17 - 5.65	6.99	5.02 - 9.72	2.00
PC-3	46.2 (5.5)	73.6%	1.86	1.16 - 2.99	4.24	2.99 - 6.01	2.28
SK-MES-1	44.0 (3.5)	91.2%	8.61	6.30 - 11.76	23.14	17.98 - 29.78	2.69
BxPC-3	26.4 (3.1)	98.3%	1.44	1.04 - 2.00	4.03	3.25 - 4.98	2.80
*IC_{50}-value is shown as SN-38 equivalents of sacituzumab govitecan							

Treatment of Trop-2-positive tumour cells with sacituzumab govitecan resulted in an increase of DNA double-strand breaks as evidenced by the increase in phosphorylated histone H2AX. Induction of DNA double-strand breaks due to inhibition of topoisomerase I is a known mode of action for SN-38, the active metabolite of irinotecan. Furthermore, the apoptotic pathway induced by sacituzumab govitecan was consistent with that of free SN-38 (Goldenberg et al., 2015).

In vivo pharmacology of sacituzumab govitecan was evaluated in murine xenograft models of human lung, colorectal, pancreatic cancers and gastric cancers. In these studies, treatment with sacituzumab govitecan either stopped tumour growth or resulted in reduction of tumour volume. In general, the ADC was more efficacious in tumour growth inhibition than irinotecan at the same SN-38 dose (Cardillo et al., 2011; 2015).

More relevant to the present MAA, sacituzumab govitecan also showed anti-tumour activity in mice bearing TNBC xenografts (**study 022714-218)**. Four IV doses of sacituzumab govitecan at 7.5 and 12.5 mg/kg given over a 2-week period led to a clear reduction in growth of TNBC cells. At the lower sacituzumab govitecan dose, a cumulative dose of 9.6 µg SN-38-equivalents were administered. In contrast, irinotecan treatment, resulting in a cumulative dose of 600 µg SN-38, did not achieve a persistent reduction in tumour volume. In this group, tumour progression was observed earlier than in the sacituzumab govitecan-treated groups.

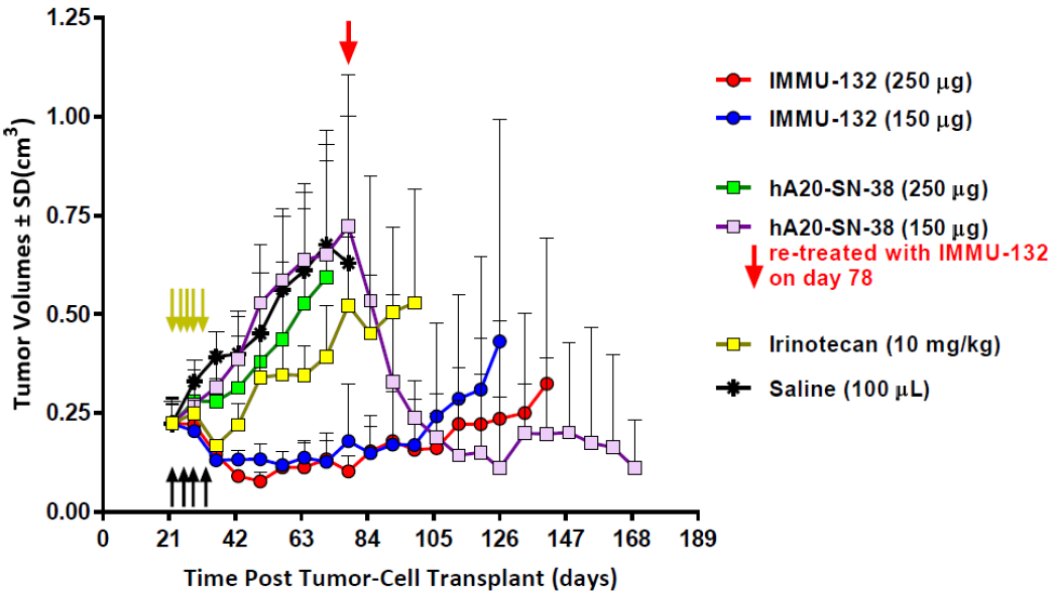


Figure 3 Therapeutic efficacy of sacituzumab govitecan (IMMU-132) in a TNBC xenograft model (study 022714-218).

Together the xenograft studies provide evidence that specific targeting of SN-38 to the tumour is more effective than a larger dose of the untargeted toxin.

In study 120415-337 the efficacy of sacituzumab govitecan produced from two sources (clones 8F6 used in phase I/II studies vs clone 80-36-35 used in Phase 3 studies) was compared in a human TNBC xenograft model. The anti-tumour effects induced by sacituzumab govitecan from the two sources were not significantly different with regard to inhibition of tumour growth and survival

Species cross-reactivity

Reactivity of mAb hRS7 with Trop-2 from non-clinical species was evaluated by ELISA. Despite approx. 80% sequence homology at the protein level between human and rodent Trop-2, hRS7 did not bind to mouse and rat Trop-2. In contrast, mAb hRS7 and also the ADC sacituzumab govitecan bound with comparable affinity to human and rhesus monkey Trop-2. Given that rhesus and cynomolgus Trop-2 have an identical amino acid sequence, these data support the use of cynomolgus monkeys for the non-clinical safety assessment of hRS7 and sacituzumab govitecan (studies rr-08-27-13; rr-01-apr-2019; rr-25-nov-2020**)**.

Tissue cross-reactivity of hRS7 was evaluated with cynomolgus and human tissues in GLP studies IM1735 and DMP 0411. In both studies hRS7 stained epithelial cells in a number of different tissues; staining was mostly cytoplasmic but membrane staining was also observed for selected tissues. It is noted that more tissues stained positive in cynomolgus than in humans while staining of liver bile ducts and pituitary gland was observed in human but not in cynomolgus tissues. The cynomolgus study also identified hRS7 staining in tissue elements that were not previously reported to express Trop-2 (few epithelial cell types, myoepithelium, mesothelium and decidual cells). To what extent this staining represents previously unreported sites of Trop-2 expression or cross-reactivity with another closely related epitope(s) is not known.

Secondary pharmacodynamic studies

The ability of the non-conjugated mAb hRS7 to induce cytotoxic activity against Trop-2-expressing cancer cells was evaluated *in vitro* in study RR-06-10-11. Incubation of cancer cells with hRS7 (0.078 to 2 µg/ml) did not result in any signs of growth inhibition against any of the cell lines tested. The addition of a cross-linking antibody did not cause any observable growth inhibition in these lines either.

Evaluation of other secondary pharmacologic effects is performed as part of the primary pharmacology studies.

These studies assessed the Fc functionality of sacituzumab govitecan and the binding to FcRn.

As an IgG1 molecule, sacituzumab govitecan can interact with Fcγ receptors and may induce Fc-dependent effector functions. Thus, the potential of hRS7 and sacituzumab govitecan to induce ADCC and CDC was assessed *in vitro* in studies TR-PD-IMMU-132-17-017 and TR-PD-IMMU-132-17-018. The non-conjugated mAb hRS7 induced ADCC against Trop-2 expressing tumour cell lines with a specific lysis up to approx. 30%. The % specific lysis mediated by sacituzumab govitecan was lower. Neither hRS7 nor sacituzumab govitecan induced CDC. Together these data suggest that Fc-dependent effector functions to not contribute significantly to the anti-tumour activity of sacituzumab govitecan.

Binding affinity of sacituzumab govitecan to FcRn at pH 6.0 ranged from 138.2 to 228.8 nM, and was 1.5-2.6 times lower than affinity of the non-conjugated mAb hRS7. This lower affinity may contribute to the short half-life of sacituzumab govitecan in cancer patients (study RR 05-07-12).

Safety pharmacology programme

An *in vitro* human ether-à-go-go related gene (hERG) assay was not conducted with sacituzumab govitecan. This is acceptable since hERG testing is not typically required for biologicals with large molecular weight.

Based on the results from evaluation of safety pharmacology parameters in the two repeat-dose toxicity studies in cynomolgus monkeys (12.5, 25, 50 mg/kg (study SNBL.160.25); 60, 120 mg/kg (study SNBL.160.03), there were no apparent adverse effects on the CNS, the cardiovascular system including assessment of QT or corrected QT (QTc) interval or respiratory function following intravenous dosing of sacituzumab govitecan in cynomolgus monkeys at doses up to 120 mg/kg.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies of sacituzumab govitecan have not been performed.

2.3.3. Pharmacokinetics

Pharmacokinetic studies of sacituzumab govitecan comprised the *in vitro* assessment of its stability in human and cynomolgus serum, a study in mice comparing PK of sacituzumab govitecan and hRS7, a study in rabbits, comparing the PK of hRS7 manufactured according different processes and two toxicokinetic studies

in cynomolgus monkeys. In addition, studies in tumour-bearing mice evaluated biodistribution of radio-labelled sacituzumab govitecan vs. hRS7 and kinetics of sacituzumab govitecan vs. irinotecan.

Bioanalytical methods

Two sets of bioanalytical methods were used, research methods and GLP-compliant methods. The pivotal, 3-months-repeat-dose GLP-compliant toxicity study in monkeys utilised validated, GLP-compliant LC-MS/MS and electroluminescence assays for the PK and immunogenicity assessments. All other studies used non-GLP bioanalytical methods.

Four analytes were measured to characterize the pharmacokinetics of the ADC: 1) total antibody (hRS7-SN-38, DAR ≥ 0), 2) free SN-38 (cytotoxic payload), 3) SN-38 glucuronide (SN-38G, metabolite of SN-38) and total SN38 (free SN-38 + hRS7-SN-38). Additional quantification of the ADC (rather than total Ab) would have been welcomed. However, it is acknowledged that an assay that detects only the ADC (based on capture with anti-SN-38 and detection with anti-hRS7) would not provide evidence on the number of SN-38 molecules linked the ADC. Given the hydrolysable linker, the drug antibody ratio will be highly variable *in vivo* over time for individual sacituzumab govitecan molecules. Thus, total SN-38 better reflects exposure to the payload.

Absorption:

Stability of sacituzumab govitecan in human and monkey serum was determined *in vitro* in study RD-CH-20-1020-01. The half-life of SN-38 release from sacituzumab govitecan *in vitro* (at 37°C, 5% CO_2) was 30.82 hrs in cynomolgus serum and 44.1 hrs in human serum. Results from this study are roughly in line with results published by Goldenberg et al. (2015), which reported a half-life of 22.9 hrs in monkey serum and of 23.98 hrs in human serum. In murine serum, the half-life of SN-38 release from sacituzumab govitecan at 37°C *in vitro* was calculated to be 17.5 hrs. Together these data demonstrate that SN-38 is released from the ADC even without up-take into a Trop-2-expressing target cell which is an intended property of sacituzumab govitecan.

In study SNBL.160.24 pharmacokinetics of sacituzumab govitecan and hRS7 after a single IV administration (200 µg/dose; 10 mg/kg) were compared in SW mice. Since hRS7 does not bind to Trop-2 from these species, the study provides information on target-independent kinetics only. When serum concentrations were determined based on the Ab moiety, the PK of the unconjugated hRS7 and sacituzumab govitecan were comparable with a β-elimination half-life of approx. 200 hrs and a MRT of approx. 300 hrs. In contrast, clearance of the intact ADC was much faster (approx. 8x). This finding indicates that the toxin moiety is cleaved from the ADC *in vivo* even in the absence of Trop-2 binding and is consistent with the data on serum stability of sacituzumab govitecan *in vitro*.

Toxicokinetics of sacituzumab govitecan and its metabolites after repeat dosing were assessed in cynomolgus monkeys in study SNBL.160.03. Since hRS7 binds to cynomolgus Trop-2, these studies reflect both target-dependent and -independent kinetics. After 2 IV doses of sacituzumab govitecan given 3 days apart, kinetics of total Ab were typical for a mAb; Cmax was reached shortly after the second IV administration; the elimination half-life was 5.2 days. With regard to the toxin moiety, exposure (C_{max}, AUC_{inf}) to total SN-38 was greater than exposure to free SN-38 while the half-life of free SN-38 was approx. 2x as long as the half-life of total SN-38.

In study SNBL.160.25, cynomolgus monkeys were treated with sacituzumab govitecan at 12.5, 25 and 50 mg/kg IV in 4 treatment cycles of 21 days with treatment on days 1 and 8 of the cycle. Exposure to total Ab,

total SN-38 and SN-38 was dose-proportional. After the last dose, exposure (based on AUC) was approx. 1.5x of the exposure after the first dose for total Ab and up to 1.2x for total SN-38 and free SN-38. Thus, accumulation was minimal. On average, the exposure to free SN-38 was approximately 2.3 % of total SN-38 based on AUC. SN-38G was detected in serum with a Tmax ranging from 4 to 12 hrs after the 1st dose and from 2 to 11 hrs after the last dose.

ADA were detected in all sacituzumab govitecan treated groups and appeared to affect primarily the exposure in the low dose group, as exposures to total Ab, total SN-38 and free SN-38 were lower on after last dose compared to the first dose.

Distribution and PK in tumour bearing mice

The distribution of radio-labelled hRS7 and sacituzumab govitecan was studied in mice bearing human squamous cell lung carcinoma xenograft in study 031210-156. The radio-label was attached to the antibody, not SN-38, therefore, the data reflect uptake of the mAb component of the ADC. Since sacituzumab govitecan does not bind to mouse Trop-2, the target-mediated distribution in this study is limited to the Trop-2 expressing tumor. In blood the ADC appeared to clear faster than the equivalent amount of unconjugated hRS7 mAb, however, this did not appear to affect tumour targeting. In addition to tumour, both hRS7 and sacituzumab govitecan distributed to normal tissues, primarily to liver, spleen, kidney and lungs among the normal tissues analysed. A preferential distribution of sacituzumab govitecan to the tumour compared to liver was only observed at 72 and 168 hrs.

Metabolism and excretion:

Studies on the metabolism and excretion of sacituzumab govitecan in non-clinical species were not performed based on the rationale that the Ab moiety of sacituzumab govitecan can be expected to be catabolised to amino acids in line with ICHS6(R1) which states that "omission of metabolism and excretion studies for the Ab moiety is accepted".

With regard to metabolism and excretion of the toxin moiety, the applicant refers to literature on metabolism of irinotecan in humans (Mathijssen et al., 2001; Slatter et al., 2000. Given the knowledge on SN-38 metabolism and excretion in humans, additional studies to evaluate SN-38 metabolism/excretion in cynomolgus monkey were not done.

Metabolism of MES

Study BBIA-0004-DV-CB/BBIA-0005-DV-CB evaluated the involvement of human cytochrome P450 enzymes (CYPs) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 in MES metabolism using human recombinant enzymes and human liver microsomes. During 120 min incubation of the test systems with 5 µM MES, no CYP-mediated metabolism was detected. There was no indication of metabolism of MES by the major human cytochrome P450 enzymes under the conditions of the study.

Study BBIA-0002-DV-TB investigated inhibition potential of the novel excipient MES for CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 in human liver microsomes. Inhibitory activity of MES was observed only at very high concentrations. IC50 values exceeded 8 mM, which is more than 30-fold of the expected MES clinical Cmax of 0.054 mg/mL (0.256 mM). Therefore, inhibition potential of MES towards CYPs appears not clinically relevant.

Study BBIA-0003-DV-DA aimed at assessing induction potential of MES with respect to CYP3A4, CYP1A2 and CYP2B6. The experiments were performed using single-donor hepatocytes from three individual donors. No

induction of these CYP enzymes at mRNA and enzyme activity level was detected at MES concentrations of 3 and 30 mM.

Study 3277-002, non-GLP Routes and rates of MES excretion were evaluated in a radioactivity mass balance study in male SD rats. After IV administration, Cmax was observed at 5 min post-dose and serum concentrations declined rapidly. Radioactivity was primarily excreted via urine within 24 hrs post-dose; while hepatobiliary excretion was limited

PK drug interactions

Pharmacokinetic drug interactions have not been performed; the applicant refers to literature on drug interactions for SN-38 released from irinotecan and concludes that inhibitors of UGT1A1 may prolong the half-life of unconjugated SN-38.

PK in tumour-bearing mice

Three studies were submitted (Table below) in nude mice bearing 2 different human tumour xenografts (Capan-1 and NCI-N87) to assess potential differences between the biodistribution of SN-38 and SN-38G in tissues of animals administered irinotecan (40 mg/kg, IV) or sacituzumab govitecan (1 mg/kg, IV) (studies 012014-275 and 062714-291 and study published by Sharkey, R. M., et al., 2015).

Table 2 Examination of SN-38 concentrations in tissues of nude mice bearing human cancer xenografts.

Study	Tumor	Intervals *(N=3 animals/interval)*	Tissues examined	IMMU-132 (SN-38 equivalents)[a]	Irinotecan (SN-38 equivalents)[a]
012014-275 ('Study 1')	Capan-1	**Irinotecan** 5 min, 1, 2, 6, and 24 h **IMMU-132** 1, 6, 24, 48, 72 h	Tumor, serum, liver, small intestine contents	1.0 mg (16 µg)	773 µg (448 µg)
Sharkey, 2015 ('Study 2')	Capan-1	**Irinotecan** 1 and 6 h **IMMU-132** 1, 6, and 24 h	Tumor, serum, liver, small and large intestine contents	1.0 mg (16 µg)	808 µg (468 µg)
062714-291 ('Study 3')	NCI-N87	**Irinotecan** 5 min, 1, 2, 6, and 8 h **IMMU-132** 1, 6, 24, 48, 72 h	Tumor, serum	1.0 mg (16 µg)	840 µg (486 µg)

[a] SN-38 equivalents for IMMU-132 based on spectrophotometric determinations of protein and SN-38 concentrations. SN-38 equivalents for irinotecan based on mass, with SN-38 representing approximately 58% of irinotecan's mass.

Within the liver of these mice bearing human xenograft tumours, the majority of SN-38 detected was in the intact form (total SN-38), whereas free SN-38 was not detected in the liver. Conversely, only free SN-38 was detected in the intestine indicating that intact conjugate was not transported from the liver to the intestine.

2.3.4. Toxicology

The toxicity of sacituzumab govitecan was assessed in Swiss Webster (SW) mice and cynomolgus monkeys, taking into account ICH guidelines S6(R1) and S9. In mice, sacituzumab govitecan does not recognise the target antigen Trop-2, thus these studies provide information on target-independent toxicity. Target-dependent toxicity was assessed in cynomolgus monkeys. The genotoxic potential of SN-38 was assessed *in vitro*. In addition, the cytotoxicity of the novel excipient 2-(N-morpholino) ethanesulfonic acid (MES) was assessed *in vitro*.

Single dose toxicity

Single-dose toxicity studies with sacituzumab govitecan were not performed. Evaluation of acute toxicity after two high doses is reported in the repeat-dose toxicity section

Repeat dose toxicity

Studies 100209-143 and 122109-151 (non-GLP): Acute toxicity of high doses of sacituzumab govitecan was evaluated in Swiss Webster mice. These studies evaluate target-independent toxicity of sacituzumab govitecan since hRS7 does not recognise murine Trop-2. Two IP doses at up to 750 mg/kg/dose were given 3 days apart. All animals survived to the end of study (up to day 18 or day 39). In both studies, transient reductions in body weight (up to 9%) and transient increases in liver enzymes (AST and ALT) were observed sacituzumab govitecan-treated animals. There were no treatment-related changes in haematology and histopathology. Exposure to exposure to sacituzumab govitecan and/or free SN-38 was not determined.

Study SNBL.160.03 (GLP): Cynomolgus monkeys were treated with two doses of sacituzumab govitecan at 60 or 120 mg/kg IV three days apart. Treatment with the high-dose was associated with mortality. One male animal was found dead 3 days after the second dose. Cause of death was considered to be related to sacituzumab govitecan-related bone marrow suppression and gastrointestinal complications. In animals that survived to their scheduled necropsy, two types of responses were evident in both males and females. 1) decreased cellularity of all haematopoietic organs with decreases in counts of all blood cell types; 2) inflammation, haemorrhage and degeneration of various structures and regions within the gastrointestinal tract. In addition, pathological changes to the reproductive organs were observed in females: increased numbers of atretic follicles and fewer matured follicles in the ovaries, and mild to moderate haemorrhage of the endometrium and atrophy of endometrial glands. By day 32 the sacituzumab govitecan-related responses showed a trend towards or a complete recovery. In the absence of a NOAEL, the HNSTD in this study was 60 mg/kg/dose.

Study SNBL.160.25 (GLP): In the second study, cynomolgus were treated with lower doses of sacituzumab govitecan (up to 50 mg/kg/dose), in a treatment regimen representative of the clinical regimen, i.e. 4 cycles of 21 days duration with treatment on days 1 and 8 of the cycle. In this study sacituzumab govitecan was better tolerated, as there was no mortality. Sacituzumab govitecan-related findings in this study concerned the skin, with abnormal discoloration, alopecia and degeneration of hair follicles and sebaceous glands, in animals treated at 25 and 50 mg/kg. Further histopathological findings that were considered potentially

related to treatment are decreased in lymphoid cellularity in the thymus in individual animals and 1 case of mild renal periarteritis.

A comparison of the exposure in cynomolgus at the NOAEL/HNSTD (50 mg/kg) and in humans at the proposed clinical dose (10 mg/kg) was made. The exposure margin was 6.4x for total antibody, 4.6x for total SN-38 and 3.1x for free SN-38.

Genotoxicity

CTP1595_R1b (GLP): The mutagenic potential of SN-38 was evaluated in a bacterial reverse mutation assay. SN-38 (up to 158 µg/plate) was tested using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 uvrA pKM101 in the presence and absence of Aroclor-induced rat liver S9 enzymes. Under the condition of the study, SN-38 was found to be negative in the bacterial reverse mutation assay.

CYP1595_R1a (GLP) The mutagenic potential SN-38 was evaluated in the *in vitro* mammalian cell micronucleus test using the CHO-K1 cell line. SN-38 (0.02 to 2 µg/ml) were tested in the absence and presence of Aroclor-induced rat liver S9 enzymes. Under the condition of the study, SN-38 was found to be positive for micronuclei formation under the experimental conditions of the study.

The linker, also referred to as CL2A, was evaluated in silico using two quantitative structure activity relationship ((Q)SAR) methodologies to predict for bacterial mutagenicity in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M7(R1). The expert rules-based methodology was Derek Nexus version 2.3.1 Knowledge Base 2020.1.0 and the statistical-based methodology was Leadscope Model Applier version 3.0.2-4. The Derek Nexus prediction was negative with no misclassified or unclassified features. The Leadscope Model Applier prediction was within the domain of applicability and the result was a negative prediction and therefore not considered genotoxic.

Carcinogenicity

No assessment of carcinogenicity has been conducted in accordance with ICH S9 according to which carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

Reproduction Toxicity

Reproductive and developmental toxicity studies have not been performed. Since the GLP-compliant genotoxicity studies as well as the general toxicity studies in cynomolgus monkeys demonstrated that SN-38, once released from the ADC, targets rapidly dividing cells, embryo-fetal development and reproductive toxicity studies are not needed to support a marketing authorisation application submission for the proposed indication as per ICH S9. The target patient population with Trop-2 expressing cancers are typically adults, therefore toxicity studies in juvenile animals were not conducted.

Local Tolerance

Local tolerance was assessed within the repeat-dose toxicity studies in cynomolgus monkeys. In study SNBL.160.03, changes at the injection sites consisting of mild to moderate perivascular haemorrhage, moderate haemorrhage in the dermis and subcutis, and minimal to mild perivascular mixed cell infiltration were observed at the terminal necropsy. The applicant considers these changes to be due to mechanical stimulation or stimulation by leaked test article.

In study SNBL.160.25, injection site changes were observed during macroscopic or microscopic examination in both treated animals and the controls. The study pathologist attributed these changes to mechanical trauma associated with the dosing procedure and not to the test article

Other toxicity studies

Toxicity of MES

MES (2 (N morpholino) ethanesulfonic acid) is a buffer used as an excipient in the formulation of the drug product for sacituzumab govitecan (IMMU-132) and considered a novel excipient. At the recommended dose of 10 mg/kg (1 mL/kg), patients receive a dose of 4.88 mg/kg MES with each injection. Based on its intended use in patients with advanced cancer, the non-clinical assessment of MES followed ICH S9 guidance with consideration of the Guidance for Industry entitled, "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients".

***In vitro* cytotoxicity of MES [RR-24-OCT-2019; RR-05-NOV-2019]**

Study RR-24-oct-2019 evaluated if MES mediates any type of cytotoxic effect on two different human cancer cell lines, HCC18606 (TNBC) and T24 (urinary bladder transitional cell carcinoma). The MES concentrations evaluated ranged from 3.08 x 10^{-6}M to 1.2 M. In this study, MES did have a growth-inhibitory effect, with an IC50 of 430 mM and 340 mM respectively.

The plasma Cmax for MES was estimated as 0.6 mM, if sacituzumab govitecan was administered to an 80 kg patient as a single bolus IV injection. MES concentration of 0.6 mM was not cytotoxic *in vitro*, at a 10-fold higher concentration (6 mM), a modest growth inhibition was observed.

The applicant indicates that the growth inhibition noted for MES was observed after a 96-h continuous exposure in tissue culture and considers that this is not likely to happen clinically since MES would be cleared from the plasma resulting in diminishing concentrations over time.

Study RR-05-NVO-2019 evaluated, if MES affects the cytotoxic dose-response induced by sacituzumab govitecan *in vitro*. Possible changes to the sacituzumab govitecan-induced cytotoxicity in the presence of MES (0.6 mM and 6 mM) were assessed using HCC1806 and T24 cells.

MES alone at 0.6 mM resulted in minimal growth inhibition (≤ 3.5%), at 6.0 mM growth inhibition was ≤12.4%. At both concentrations, MES did not significantly alter the cytotoxicity profile of sacituzumab govitecan in either of the cell lines used in this assay. No significant differences in the sacituzumab govitecan IC50 were observed in the presence of MES (0.6 and 6.0 mM).

Study 3277-001, GLP The applicant has evaluated the toxicity of MES in a 1 month study in SD rats. Rats received MES IV at up to 1000 mg/kg Q1W for a total of 4 doses. Parameters of observed were adequate for a general toxicity study. No MES-related effects were observed; in principle the NOEL of 1000 mg/kg can be agreed.

Genotoxicity of MES

The genotoxic potential of MES was evaluated in 2 *in vitro* assays (Ames bacterial reverse mutation and *in vitro* chromosomal aberration assay 01551002, GLP) and *in vivo* in a rat micronucleus assay 3277-003, GLP. MES was found to be non-genotoxic in a bacterial mutation assay (01551001, GLP) and a mammalian chromosome aberration test *in vitro*. Furthermore, MES was found to be negative for clastogenic activity *in vivo* in a rat bone marrow micronucleus test.

In addition to the studies submitted, the applicant refers to studies published by the European Chemicals Agency (ECHA) assessing the genotoxicity of MES. MES was found to be non-genotoxic in a bacterial mutagenicity assay (OCED TG 471) and in a micronucleus test (OCED TG 487). In addition, MES was not mutagenic in an *in vitro* mammalian cell mutation test in CHO V79 cells (OECD TG 476).

Carcinogenicity of MES

A literature search was performed to identify any other potential risks of MES (CAS#s 4432-31-9 and 145224-94-8) including carcinogenicity. Data bases searched included Toxplanet and Toxline, VITIC version 2020.1, Google, and the EPA Comptox Dashboard. This most recent search identified two additional studies with MES relevant to safety assessment. In all studies, no safety concern was identified.

Reproductive and developmental toxicity

With regard to reproductive and developmental toxicity of MES, the applicant refers to a study published by the European Chemicals Agency (ECHA) [ECHA 2021a]. According to the ECHA report, MES (hydrate form) did not adversely affect the reproductive performance in parental males and females; also development of F1 off-spring (until PND 13) was not impaired at doses of up to 1000 mg/kg body weight per day. This corresponds to 930 mg/kg body weight/day of MES anhydrous form.

Phototoxicity of MES

In study RR10Jul2020 a solution of 25 mM MES at pH 6.5 did not absorb light in the range of 290 to 700 nm. In line with ICH S10, MES is not sufficiently photoreactive to result in direct phototoxicity.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant notes, that the Ab part of the active ingredient is unlikely to result in a significant risk to the environment as proteins of biological origin are abundant in the biosphere and are, if present in a soluble form in the environment, rapidly inactivated and degraded in the wastewater treatment facility.

For SN-38, the applicant notes that it will be hydrolysed by endogenous esterases from the linker CL2A and that CL2A will remain covalently bound to the Ab and concludes that it is unlikely that SN-38 bound to the linker (SN-38-CL2A) will enter the environment at any meaningful concentration and therefore considers an environmental risk assessment for SN-38-CL2A not to be appropriate.

The applicant supplies literature on fate and effects for some of the CL2A linker building blocks and concludes, that the building blocks and consequentially the linker do not pose a risk to the environment.

The applicant concludes that SN-38 is considered as the relevant part of the active ingredient to base the assessment on.

Screening for persistence, bioaccumulation and toxicity (PBT)

Information on the partition coefficient for SN-38 (predicted and experimentally determined) was retrieved from relevant databases and the literature. A partition coefficient (log P) of 2.65 for SN-38 was reported by Fang et al, 2018. Wu et al, 2019 reported the same partition coefficient for SN-38 which was experimentally determined using the shake flask method. All predicted log P values and log D values (at pH 5.5 and 7.4) were similar to or lower than the experimentally determined values.

In summary, the octanol-water partition coefficient for SN-38 is below the trigger value (log Kow/log P >4.5). Therefore, no further screening for persistence, bioaccumulation and toxicity is warranted.

Calculation of the predicted environmental concentration in surface water (PEC_{sw})

Refinement of the Fpen value
Taking into consideration the treatment schedule of twice every three weeks, the number of treatment days per year is 34.67 days. Thus, the Fpen (0.01) was refined by a factor of 0.095 (34.67 days/365 days). The refined Fpen (0.00095) was used for the calculation of the PECsw.

PEC_{sw} for SN-38
As described above the PEC value is calculated for SN-38. At a maximum daily dose of sacituzumab govitecan of 10 mg/kg (or 600 mg for a 60 kg patient) the maximum daily dose of SN-38 is 12 mg. Using the refined Fpen this gives:

$$PEC_{SW} = \frac{12 \text{ mg x } 0.00095}{200 \text{ L x } 10} = 0.0000057 \text{ mg/L} = 0.0057 \text{ µg/L}$$

The calculated PECsw for SN-38 is approximately 2-fold below the action limit of 0.01 µg/L. No further investigations on the environmental fate and effects detailed in Phase II Tier A of the European Medicines Agency (EMA) guidance document are required.

2.3.6. Discussion on non-clinical aspects

The non-clinical studies were, in general, performed in accordance with legal requirements and available guidelines including ICH S6 and ICH S9. Scientific advice on non-clinical developmental aspects has been received and the CHMP advice concerning the extent of the toxicology studies have been followed.

The applicant has presented adequate non-clinical data which characterise the pharmacodynamic properties of sacituzumab govitecan. These data were presented in research study reports and in form of publications from the group in scientific journals. The ADC inhibits growth of Trop-2-positive tumour cells, including TNBC cells, *in vitro* as well as in xenograft transplant models in mice. In general, sacituzumab govitecan was more efficacious in tumour growth inhibition than irinotecan at the same SN-38 dose. Results from secondary PD studies indicate that the contribution of Fc effector functions to the anti-tumour activity of sacituzumab govitecan may be limited.

In line with ICH S6 (R1), the safety pharmacology studies *in vivo* were incorporated into the two repeat-dose GLP-compliant toxicity studies in monkeys using the IV route of administration, consistent with that used

clinically. Overall, there were no apparent safety signals from the core battery of studies in major organ systems of cynomolgus monkeys at the highest dose tested (120 mg/kg, IV).

Pharmacokinetic studies of sacituzumab govitecan comprised the *in vitro* assessment of its stability in human and cynomolgus serum, a study in mice comparing PK of sacituzumab govitecan and hRS7, a study in rabbits, comparing the PK of hRS7 manufactured according different processes and two toxicokinetic studies in cynomolgus monkeys. In addition, studies in tumour-bearing mice evaluated biodistribution of radio-labelled sacituzumab govitecan vs. hRS7 and kinetics of sacituzumab govitecan vs. irinotecan. Studies on metabolism and excretion were not performed for sacituzumab govitecan. , instead the applicant refers to literature on the metabolism of irinotecan in humans which is accepted.). Irinotecan is reported to act as a prodrug to SN-38 which is formed via carboxylesterase cleavage and has a 100 to 1000-fold higher cytotoxic effect than the parent drug or any of the other identified metabolites. This is however not verified by original data in the references provided. As irinotecan is a known substance approved and used in the treatment of advanced cancer and as the plasma exposure and distribution of the active metabolite SN-38 is evaluated in the non-clinical pharmacokinetic studies, and the plasma exposure of SN-38 is monitored in the non-clinical toxicology studies, the lack of further metabolic studies is considered acceptable and in line with ICH S9. In humans, SN-38 is metabolised in liver by uridine diphosphate glucuronosyltransferase (UGT1A1) to the inactive compound SN-38G while cytochrome P450 enzymes do not appear to be involved in biotransformation of SN-38. According to literature, cynomolgus UGT1A1 was shown to glucuronidate SN-38 *in vitro* with similar kinetics as the human enzyme [Hanioka et al, 2010], supporting the use of cynomolgus for the safety assessment of sacituzumab govitecan. In humans, SN-38 is excreted intact, lactone-hydrolysed or as glucuronide metabolite SN-38G [Slatter et al., 2000]. Fecal excretions represent the major elimination pathway

The submitted studies and published literature are considered sufficient to characterise the ADME of sacituzumab govitecan and its metabolite.

Omission of non-clinical PD drug interaction studies is accepted, based on the understanding of SN-38 metabolism derived from literature on irinotecan metabolism in humans.

The toxicity of sacituzumab govitecan was assessed in mice (acute toxicity) and in cynomolgus monkeys (long-term toxicity). Overall the programme is in line with ICH guidelines S6(R1) and S9. In mice, sacituzumab govitecan does not recognise the target antigen Trop-2, thus these studies provide information on target-independent toxicity. Target-dependent toxicity was assessed in cynomolgus monkeys. General toxicity studies with the toxin moiety SN-38 were not conducted. This is acceptable, in line with ICH S9 and taking into account published literature on the toxicity of irinotecan and its active metabolite SN-38. The repeat-dose studies in cynomolgus identified gastrointestinal tract, lymphoid organs, bone marrow, bone marrow (and concomitant reductions in blood cells), skin and kidney as target organs of toxicity. Findings in the gastrointestinal tract and reductions in white blood cells are known toxicities of irinotecan-derived SN-38. Findings in skin may represent Trop-2-dependent toxicity. A comparison of the exposure in cynomolgus at the NOAEL/HNSTD (50 mg/kg) and in humans at the proposed clinical dose (10 mg/kg) was made. The exposure margin was 6.4x for total antibody, 4.6x for total SN-38 and 3.1x for free SN-38.

Genotoxic potential of SN-38 was assessed *in vitro*. In a bacterial mutation assay SN-38 was not genotoxic, but was identified as clastogenic in a micronucleus test in mammalian cells, which is consistent with the genotoxicity of irinotecan. The linker structure CL2A was not considered genotoxic based on in silico structural analysis.

Based on the evidence for teratogenicity of irinotecan, sacituzumab govitecan has the potential for teratogenicity and/or embryofetal toxicity. This is reflected in the SmPC.

Additional non-clinical studies were performed to characterise MES as a novel excipient.

Metabolism studies *in vitro* showed that MES is not metabolised by human cytochrome P450 enzymes; in a radioactivity mass balance study in rats MES was rapidly eliminated via urinary excretion. According to literature on irinotecan metabolism [Mathijssen et al, 2001], SN-38 is generated from irinotecan by carboxy esterases. SN-38 is subsequently converted to a glucuronide derivative (SN-38G) by uridine diphosphate glucuronosyltransferase (UGT1A) while cytochrome P450 enzymes do not appear to be involved in biotransformation of SN-38. In the responses to questions the applicant clarified that there is no evidence that CYP3A4 contributes to SN-38 metabolism. Consequently, only the effect of UGT1A1 inhibitors or inducers is addressed in the SmPC

The safety of MES was evaluated in a GLP-compliant repeat-dose toxicity study in rats. In this study, the NOEL was 1000 mg/kg, the maximum feasible dose. However, the final study report, including bioanalysis and TK evaluation is still lacking.

Exposure to MES is not demonstrated yet. The applicant confirmed that the final study report including bioanalysis and TK will be provided for review once available at the end of Q1 2022.

Additional studies evaluated the genotoxic and phototoxic potential of MES. For reproductive and developmental toxicity the applicant refers to a study published by the European Chemicals Agency. These studies did not identify any safety concerns and are considered adequate to support the use of MES as excipient in the formulation of sacituzumab govitecan.

2.3.7. Conclusion on the non-clinical aspects

Marketing authorisation for Trodelvy can be approvable from a non-clinical point of view. The CHMP recommended the following measures necessary to address the non-clinical issues:

- The applicant committed to provide the final study report including bioanalysis and TK for the repeat-dose toxicity study with MES (study 3277-001) by Q1 2022.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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 3 Clinical Studies for Sacituzumab govitecan in TNBC

Trial No. NCT No.	NCT No. EudraCT No.	Trial Design	Regimen, Schedule, and Route	Trial Endpoints	Treatment Duration/ Follow-up	No. Pts Enrolled	Trial Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
IMMU-132-05	02574455 2017-003019-21	Phase 3, MC, R, OL, C	• SG 10 mg/kg IV infusion on Days 1 and 8 of a 21-day treatment cycle OR • TPC (ie, 1 of the following single-agent treatments): – Eribulin 1.4 mg/m^2 at North American sites and 1.23 mg/m^2 at European sites[1] IV on Days 1 and 8 of a 21-day cycle – Capecitabine 1,000 to 1,250 mg/m^2 orally BID for 2 weeks followed by 1-week rest period – Gemcitabine 800-1,200 mg/m^2 IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle – Vinorelbine 25 mg/m^2 weekly IV injection over 6-10 minutes	Primary: PFS by IRC in BM-ve Population Secondary: OS, ORR, DOR, and CBR in BM-ve and ITT Populations	Until PD or unacceptable toxicity	Total: 529 SG: 267 TPC: 262	Patients with either locally-advanced or metastatic TNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens	85 centers Belgium, Canada, France, Germany, Spain, United Kingdom, and US
Uncontrolled Study to Support Efficacy and Safety								
IMMU-132-01	01631552 Not applicable	Phase 1/2, dose escalation (3+3 design), dose expansion, multicohort	SG 10 mg/kg IV infusion on Days 1 and 8 of a 21-day treatment cycle, with treatment continued until disease progression or unacceptable toxicity	Primary: ORR Secondary: DOR, CBR, PFS, and OS	Until PD or unacceptable toxicity	Total: 495[2] TNBC: 108[3]	Patients with advanced epithelial cancer that was relapsed or refractory to ≥1 standard therapy for their disease	13 centers US

[1]Eribulin mesylate 1.4 mg/m^2 equivalent to eribulin 1.23 mg/m^2.
[2]Included ovarian, endometrial, cervical, TNBC, HR+/HER2- mBC, castration-resistant prostate cancer, colorectal cancer, NSCLC, SCLC, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and mUC. Patients with GBM were also eligible, but were not required to have metastatic disease.
[3]A total of 144 patients with TNBC were enrolled in the study and received at least 1 dose of SG. Of these 144 patients, 108 were treated with SG at a starting dose of 10 mg/kg; these patients were included in the efficacy analyses and are referred to throughout as the TNBC Target Population.
BID=twice daily; C=controlled; F=female; DOR=duration of response; GBM=glioblastoma multiforme; HER2- =human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; IV=intravenous; mBC=metastatic breast cancer; MC=multicenter; mUC=metastatic urothelial cancer; NSCLC=non-small cell lung cancer; OL=open-label; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; R=randomized; SCLC=small cell lung cancer; SG=sacituzumab govitecan; TNBC=triple-negative breast cancer; TPC=treatment of physician's choice; US=United States

2.4.2. Pharmacokinetics

The table below summarises the studies involving the investigation of pharmacokinetics properties of SG.

Table 4 Studies involving the Examination of the pharmacokinetic properties of SG

Study Number	Phase	Study Design	Population	PK Sampling Scheme(s)
IMMU-132-01 final Section 16.1.13	1/2	Multicenter, open-label, single-arm, dose escalation (3+3 design), dose expansion, multicohort	Adult subjects with metastatic epithelial cancer[1] (except for GBM) who had either relapsed or were refractory after at least one standard therapeutic regimen for their tumor type	Cycle 1 at the following times relative to Day 1: preinfusion, 30 min and 3-4 hours postinfusion, 1 day, 2 days, 3 days, and 7 days postinfusion (ie, Day 8 preinfusion)
IMMU-132-05 Section 16.1.13.1 and Section 16.1.13.2	3	Randomized, multicenter, open-label, randomized, controlled study (ie, single-agent chemotherapy with either eribulin, gemcitabine, capecitabine, or vinorelbine)	Adult subjects with either locally-advanced or mTNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens	Cycle 1 at the following times relative to Day 1: preinfusion, 30 min and 3-4 hours post infusion, 1 day, 2 days, 3 days and 7 days post infusion (ie, Day 8 preinfusion) PK in overall population and effect of UGT1A1 genotype on PK were examined
IMMU-132-05 Module 5.3.3.5 CSR IMMX-PMX-SN38-2457	Substudy	PK/QTc substudy to assess the effects of SG on cardiac repolarization (QTc interval) and other ECG parameters	29 patients from the SG group of Study IMMU-132-05	Cycle 1 Day 1 at the following times: pre-infusion, 30 min, 3-4, 24, 48, and 72 hours after the end of infusion together with ECGs. Peak and trough values were measured on Cycle 1 Day 8 and thereafter on Days 1 and 8 of even cycles

[1]Included ovarian, endometrial, cervical, TNBC, HR+/HER2- mBC, castration-resistant prostate cancer, colorectal cancer, NSCLC, SCLC, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), mUC, and GBM.
ECG=electrocardiogram; GBM=glioblastoma multiforme; HER2- =human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; mBC=metastatic breast cancer; mTNBC=triple-negative breast cancer; mUC=metastatic urothelial cancer; NSCLC=non-small cell lung cancer; PK=pharmacokinetics; QTc=corrected QT interval; SCLC=small cell lung cancer; SG=sacituzumab govitecan; UC=urothelial cancer; UGT1A1=uridine diphosphate-glucuronosyl transferase 1A1

The clinical pharmacology package for SG comprises noncompartmental PK analyses for Studies IMMU-132-01 and IMMU-132-05, population PK analyses to examine the effects of intrinsic factors on PK variability, and analyses of exposure-efficacy and exposure-safety relationships. The recommended dose and regimen for SG is 10 mg/kg as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity.

Bioanalytical assays

PK assays

Four analytes were measured to characterize the PK of SG:

1) total antibody (hRS7 + hRS7-SN-38)

2) free SN-38 (the cytotoxic payload, not covalently bound to SG)

3) SN-38G (an inactive metabolite of SN-38, not covalently bound to SG)

4) total SN-38 (free SN-38 + hRS7-SN-38)

An LC-MS/MS method was developed for the quantification of free SN-38, SN-38G and total SN-38. Validation exercise comprised the analysis of selectivity, carry-over, sensitivity, linearity, accuracy, precision, stability and recovery. A further bioanalytical method based on an electrochemiluminescence assay (ECL) was developed for the determination of total antibody (hRS7-IgG + hRS7-SN38) in human serum. Validation parameters included accuracy, precision, selectivity, specificity, dilutional linearity, and matrix interference.

No validated assay is currently available which is capable of distinguishing naked (unconjugated; DAR 0) hRS7-IgG from SN-38-conjugated SG (DAR 1-8). Therefore, the amount of SG in serum was calculated using the concentrations of measured total SN-38, free SN-38, and free SN-38G (see Equation 1 below).

Equation 1. Calculation of Estimated Circulating IMMU-132 in Serum

$$\frac{(8 * 392\ AMU)}{161{,}000\ AMU} = \frac{Concentration\ of\ Bound\ SN\text{-}38}{X}$$

Where (8*392 atomic mass units [AMU]) refers to the molecular weight of SN-38 (392 AMU) multiplied by the fixed DAR of 8; 161,000 AMU refers to the molecular weight of the 8-loaded ADC. Concentration of Bound SN-38 (ng/mL) is calculated by subtracting the concentrations of measured free SN-38 and free SN-38G from measured total SN-38, and X is the estimated SG concentration (ng/mL).

This calculated value may both under-estimate and over-estimate the actual amount of the ADC at various times post dose, since a fixed DAR of 8 is assumed in the equation, although it is known that the DAR of the ADC in circulation changes over time.

Immunogenicity assays

For the detection of anti-drug antibodies against SG a standard 3-tier approach comprising a screening (tier I) and a subsequent confirmatory assay (tier II), followed by the analysis of ADA titer (tier III) was applied. Validation results demonstrated that the assay performs with adequate precision and high sensitivity (≤3.9 ng/mL). The drug tolerance level of the assay was 5 µg/ml hRS7-SN38 at 50 ng/mL ADA and 25 µg/mL hRS7-SN38 at 500 ng/mL ADA. A new ADA assay with several improvements to the immunogenicity assay and drug tolerance was developed and summarised below (method validation report for the revised ADA assay V1101906E1).

Table 5 Method validation report for the revised ADA assay V1101906E1

Validation Reference Number	V1101906E1
KCAS Method ID	TP70641
Positive Control (PC)	WU; Rat anti-hRS7-SN38 monoclonal antibody (Anti GS-0132 Antibody)
Control Samples	Negative Control (NC): 0.00 ng/mL Low Positive Control (LPC): 10.0 ng/mL Mid Positive Control (MPC) 120 ng/mL High Positive Control (HPC) 1200 ng/mL
Analyte	Anti-hRS7-SN38 antibodies (Anti GS-0132 antibodies)
Species	Human
Matrix	Serum
Required Sample Volume	20-µL aliquot per each tier
Sample Storage Temperature	-80°C
Minimum Required Dilution (MRD)	Samples added neat
Screening Cut Point (SCP), 5% FPR	Normal Serum: 1.48 (S/N) TNBC Serum: 1.79 (S/N) Urothelial Serum: 1.28 (S/N)
Confirmatory Cut Point (CCP), 1% FPR	Normal Serum (Tier II CCP): 31.5% (%Inhibition, NC Normalized) Normal Serum (Tier IIb CCP): 39.3% (%Inhibition, NC Normalized) TNBC Serum (Tier II CCP): 73.5% (%Inhibition, NC Normalized) TNBC Serum (Tier IIb CCP): 62.0% (%Inhibition, NC Normalized) Urothelial Serum (Tier II CCP): 33.3% (%Inhibition, NC Normalized) Urothelial Serum (Tier IIb CCP): 34.1% (%Inhibition, NC Normalized)

Titer Cut Point (TCP), 0.1% FPR	Normal Serum: 2.36 (S/N) TNBC Serum: 2.83 (S/N) Urothelial Serum: 1.64 (S/N)			
Sensitivity	Tier I: 7.81 ng/mL of anti-hRS7-SN38 Ab Tier II: 104 ng/mL of anti-hRS7-SN38 Ab			
Intra-assay Precision (%CV)		**Tier I**	**Tier II**	**Tier IIb**
	LPC1 (10.0 ng/mL)	3.4 to 23.5%	2.3 to 40.6%	8.0 to 29.7%
	LPC2 (5.00 ng/mL)	3.4 to 38.8%	31.0 to 181.7%	8.3 to 92.6%
	MPC (120 ng/mL)	1.7 to 22.0%	0.8 to 31.3%	1.7 to 22.5%
	HPC (1200 ng/mL)	2.3 to 23.3%	0.6 to 18.3%	0.5 to 29.4%
Inter-assay Precision (%CV)		**Tier I**	**Tier II**	**Tier IIb**
	LPC1 (10.0 ng/mL)	7.3%	16.7%	9.5%
	LPC2 (5.00 ng/mL)	23.1%	64.9%	42.9%
	MPC (120 ng/mL)	15.6%	13.2%	11.0%
	HPC (1200 ng/mL)	13.3%	5.6%	12.2%
Titer Precision	HPC: 1:1024 LPC: 1:8			
Drug (hRS7-SN38) Tolerance (Tier I) 1200 ng/mL of PC: 100 ng/mL of PC: 10 ng/mL of PC:	 Tolerant up to at least 1000 µg/mL of hRS7-SN38 Tolerant up to at least 1000 µg/mL of hRS7-SN38 Tolerant up to at least 0.00 µg/mL of hRS7-SN38			
Drug (hRS7 IgG) Tolerance (Tier I) 1200 ng/mL of PC: 100 ng/mL of PC: 10 ng/mL of PC:	 Tolerant up to at least 1000 µg/mL of hRS7 IgG Tolerant up to at least 1000 µg/mL of hRS7 IgG Tolerant up to at least 0.00 µg/mL of hRS7 IgG			
Selectivity (Tier I)	No matrix effect observed. Selectivity for at least 80% of the 10 lots of Normal, TNBC and Urothelial Cancer Human Serum were within acceptance criteria at both HPC and LPC levels.			
Selectivity (Tier II)	No matrix effect observed. Selectivity for at least 80% of the 10 lots of TNBC and Urothelial Cancer Human Serum were within acceptance criteria. Selectivity at the HPC for at least 80% of the 10 lots of Normal Human Serum were within acceptance criteria. The LPC did not meet acceptance criteria for Normal Human Serum.			
Hemolysis (Tier I and Tier II)	No apparent effect from hemolysis on the detection of anti-hRS7-SN38 Ab			
Lipemia (Tier I and Tier II)	No apparent effect from lipemia on the detection of anti-hRS7-SN38 Ab			
Hook (Prozone) effect (Tier I and Tier II)	No apparent hook effect observed at concentrations up to 25,000 ng/mL hRS7-SN38			
Bench-top Stability (Tier I and Tier II)	19 hours 30 minutes at room temperature			

Noncompartmental PK analysis

PK parameters were determined using noncompartmental analyses (NCA) in validated Phoenix® WinNonlin (Pharsight, Cary, NC) version 8.2 or higher and third-party reporting tools, including R version 3.6.3 or higher, and Microsoft® Office Word and Excel 2016. The results (not shown here) were characterised by standard PK parameters, including area under the serum concentration-time curve (AUC), maximum observed serum concentration (Cmax), trough concentration (Ctrough), and terminal elimination half-life (t1/2), if feasible, and summarised using descriptive statistics ((number of subjects [n], mean, geometric mean, geometric coefficient of variation, coefficient of variation, median, minimum, and maximum). Area

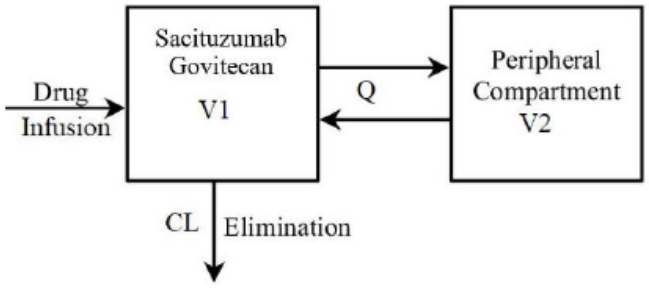
under the serum concentration-time curve (AUC) values were estimated using the linear trapezoidal rule. A minimum of 3 descending concentration-time points, excluding the Cmax, above the lower limit of quantification (LLOQ) were used in the estimation of the terminal elimination rate constant (λz) for the determination of t1/2. λz was reported wherever the adjusted coefficient of determination (R2) value is >0.8. The $AUC_{0\text{-}inf}$, total volume of distribution during the terminal phase (Vz), and total body clearance (CL) values were reported in tables and figures only when extrapolation % for estimation of $AUC_{0\text{-}inf}$ ≤20%.

Population PK analysis

Population pharmacokinetic (PK) modelling for the 5 analytes of sacituzumab govitecan (serum-free SN-38, serum total SN-38, serum SN-38G, total antibody, and serum sacituzumab govitecan) was developed to evaluate the effects of covariates on the variability of the PK of the 5 analytes; and to characterize the exposure-response (E-R) relationships of the 5 analytes in terms of efficacy and safety.
Pop PK data set used for the derivation of final pop PK models of different entities was pooled over three different indications and studies. Analysis of exposure and the effects of covariates were evaluated for only the relevant study, Study 05 and combined Study 05 and 01, while models were informed by PK data collected from three studies.

The final selected model for SG was a 2-compartment model with first-order elimination. Weight effects were included on CL, V1, V2, and inter-compartmental clearance (Q) using fixed allometric exponents of 0.75 for the CL related terms and 1 for the volume of distribution (V) related terms. Baseline albumin was added to the V1 as a covariate. Between-subject variability was included on central CL and, V1, and a combined error model was used to characterize variability.

Figure 4 Diagram of the Final Population PK Model



Abbreviations: CL=central clearance; PK=pharmacokinetic; Q=inter-compartmental clearance; V1=central compartment volume of distribution; V2=first peripheral compartment volume of distribution.

Table 6 Parameter Estimates for the Final Model of Sacituzumab Govitecan

Parameter	Parameter Description	Estimates	% RSE
θ1	Central CL, (L/h)	0.14	1.2
θ2	V1, L	2.96	0.9
θ3	V2, L	1.22	4.9
θ4	Q, (L/h)	0.01	3.1
Vp ~ Baseline albumin	Baseline albumin effect on V2	-0.26	26.4
ωCL	IIV on CL, (L/h)	0.21	4.4
ωV1	IIV on V1, (L)	0.21	3.6
ωV2	IIV on V2, (L)	0.20	21.2
θ5	Residual Additive error (ng/mL)	70.02	11.0
θ6	Residual Proportional error	0.12	1.5

Abbreviations: CL=clearance; IIV=inter-individual variability; Q=inter-compartmental clearance; RSE=relative standard error; V1=central compartment volume of distribution; V2=first peripheral compartment volume of distribution.

The final selected model for free SN-38 was a 2-compartment model with first-order elimination. Between-subject variability was included central CL and V as well as on V2. Baseline weight effects were included on CL, V1, V2, and Q using fixed allometric exponents of 0.75 for the CL related terms and 1 for the distribution related terms. Between-subject variability was included on CL, V1, and V2, and a combined error model was used to characterize variability. No covariate effect was retained in the model.

Table 7 Parameter Estimates for the Final Model of free SN-38

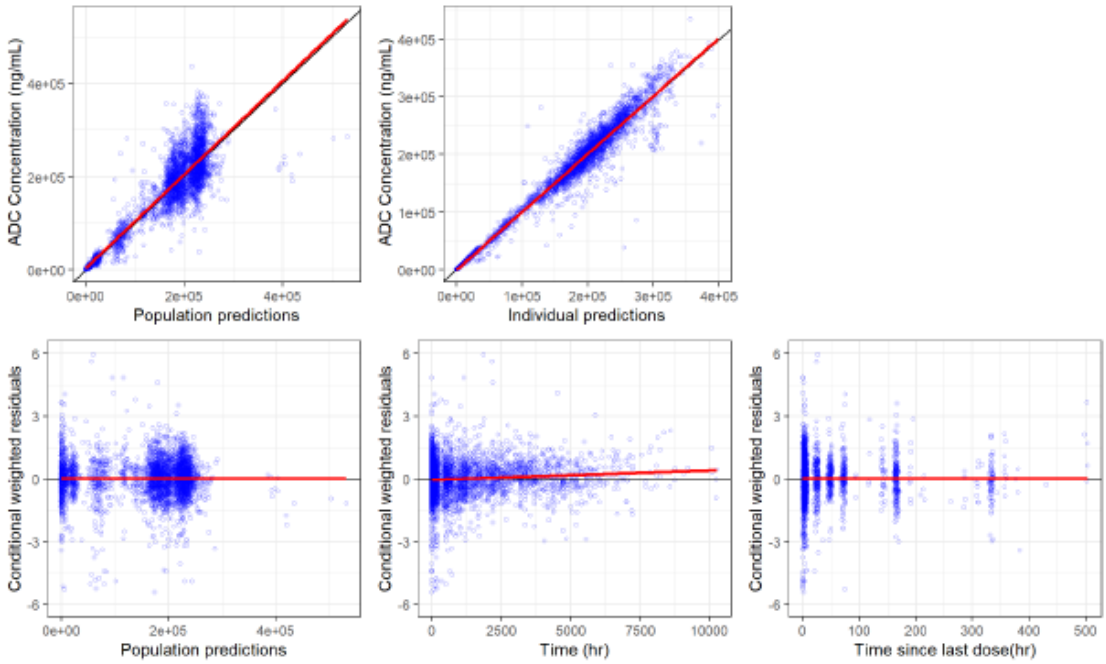
Parameter	Parameter Description	Estimates	% RSE
θ1	Central CL, 1/hr	292.70	0.5
θ2	V1, L	7383.00	0.3
θ3	V2, L	54780.00	2.2
θ4	Q,1/hr	14.38	1.4
θ5	Residual Additive error (ng/L)	0.69	0.6
θ6	Residual proportional error	0.42	2.6
ωCL	IIV on CL, 1/hr	0.71	0.4
ωV1	IIV on V1, L	0.50	0.3
ωV2	IIV on V2, L	1.35	2.3

Abbreviations: CL=clearance; IIV=inter-individual variability; RSE=relative standard error V1=central compartment volume of distribution, V2=first peripheral compartment volume of distribution, Q=inter-compartmental clearance.

Overall, derived final pop PK models were able to predict the observed median and p5 and p95 of observed concentrations acceptably well. The median concentration was fully captured throughout the profiles over time since last dose. However, the overall range of variability in exposure is over-predicted as shown by p5 and p95 percentiles observed vs predicted. Observed p95 and especially p5 were not well captured by predicted bands for segments of the time course.

The final PK models were evaluated by goodness-of-fit (GOF) plots and VPCs.

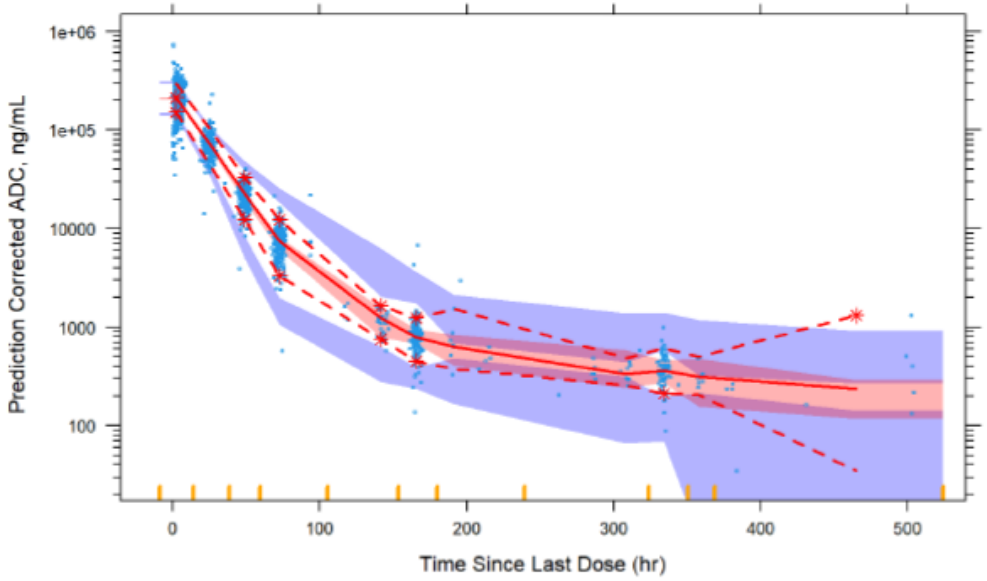
Figure 5 **GOF Plots for the Final Model of Sacituzumab Govitecan**



Abbreviations: ADC=antibody-drug conjugate; CWRES=conditional weighted residual; GOF=goodness-of-fit; LOESS=locally estimated scatterplot smoothing.

Notes: Dots are individual data points, and solid lines are smoothed LOESS lines. In the 2 plots in the first row, dashed lines are lines of identity, while in the 2 plots in the second row, dashed lines show the boundaries of the CWRES ±5 interval.

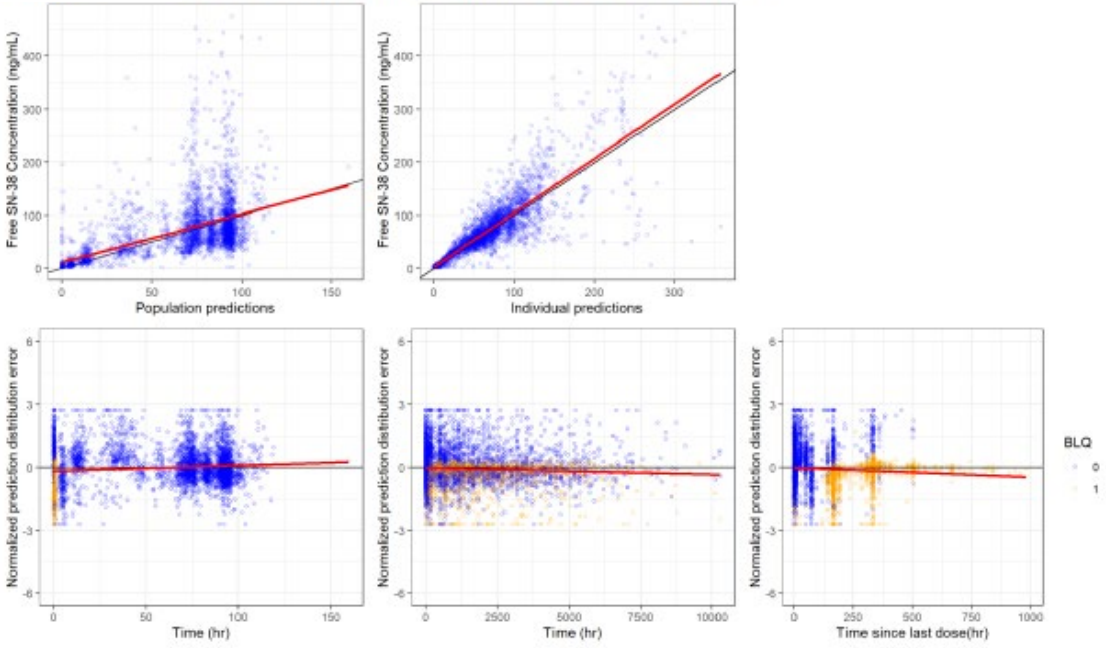
Figure 6 VPC for the Final PK Model of Sacituzumab Govitecan



Notes: Blue dots are observed data points; the red solid line is the observed median; red dashed lines are observed p5 and p95. The pink area is the 95% PI of the simulated median, and purple areas are the 95% PI of the simulated p5 and p95.
Abbreviations: p5=5th percentile; p95=95th percentile; PI=prediction interval; PK=pharmacokinetic; VPC=visual predictive check.

SN-38

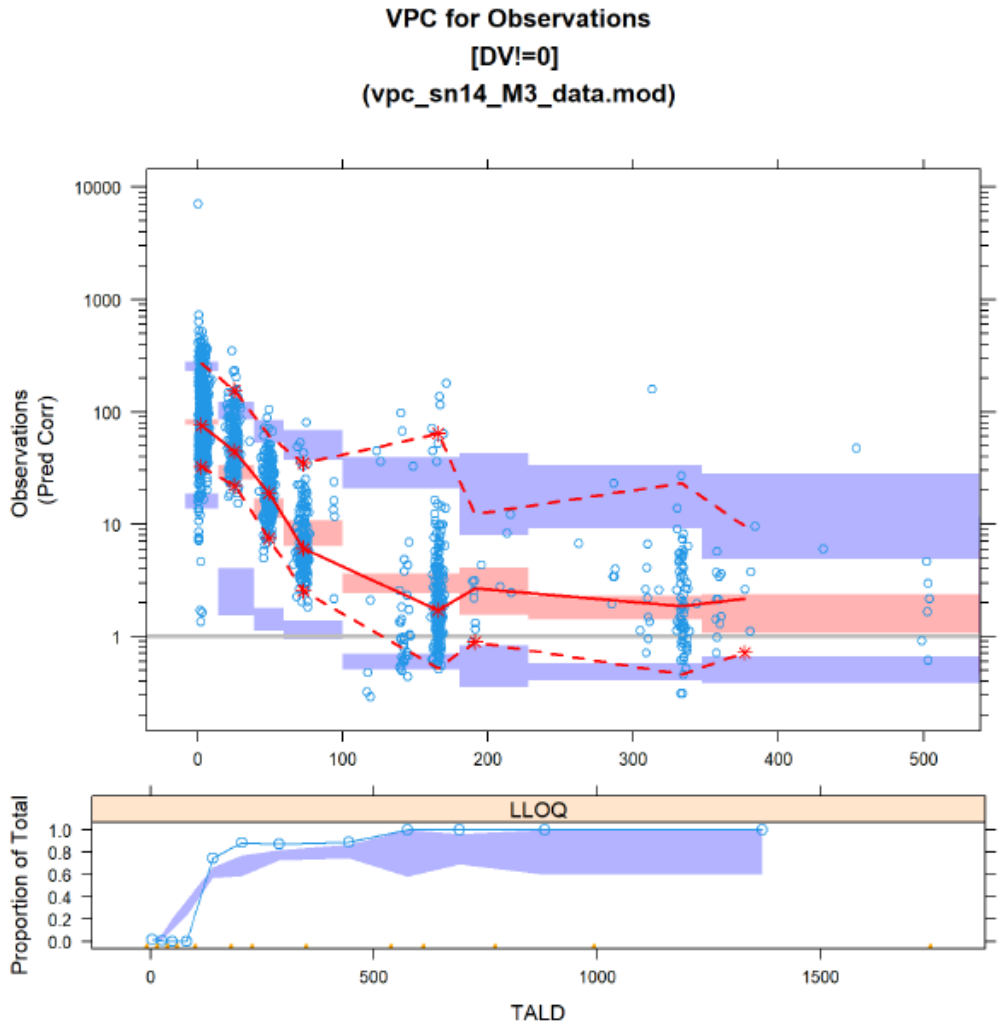
Figure 7 GOF Plots of the Final Model for Free SN-38



Abbreviations: CWRES=conditional weighted residual; GOF=goodness-of-fit; LOESS=locally estimated scatterplot smoothing.
Notes: Dots are individual data points and solid lines are smoothed LOESS lines. In the 2 plots in the first

row, dashed lines are lines of identity, while in the 2 plots in the second row, dashed lines show the boundaries of the CWRES ±5 interval.

Figure 8 VPC for the Final PK Model of Free SN-38



Abbreviations: DV=dependent variable; LLOQ=lower limit of quantification; p5=5th percentile; p95=95th percentile; PI=prediction interval; PK=pharmacokinetic; TALD=time after last dose; VPC=visual predictive check.

Notes: Blue dots are observed data points; the red solid line is the observed median; red dashed lines are observed p5 and p95. The pink area is the 95% PI of the simulated median, and purple areas are the 95% PI of the simulated p5 and p95.

Exposure-response-analyses

Exposure-response analyses were conducted to examine the relationship between PK and efficacy and safety in the Phase 3 Study IMMU-132-05. Exposure-safety analyses were also conducted for a pooled dataset that included data from the mTNBC cohort in Study IMMU-132-01 (N=22) and Study IMMU-132-05 (N=250); this pool is referred to as the Overall Target TNBC pool.

Each exposure-response analysis consisted of the following steps:

1. Univariate exposure-response analyses: For each analyte, area under the concentration-time curve at steady state (AUC_{ss}), maximum concentration at steady state (C_{maxss}) and average concentration at steady state (C_{avgss}) were tested as univariate predictors of response. Only the exposure measure with the lowest

univariate Akaike information criterion (AIC) was carried forward for subsequent exposure-response analyses.

2. Combined main effect exposure-response model: The univariate exposure measures selected for each analyte and all covariates were combined into a single linear model (Full Model) exposure-response model. A backward elimination procedure was then performed using the step AIC function until no terms remain in the model whose removal would result in an improvement (decrease) in AIC.

3. Testing of bivariate interaction terms: Once backward elimination was completed, bivariate interaction terms of the selected exposure measure in step 1 and all the remaining covariates from step 2 were evaluated. The initial model included all these possible bivariate terms. This model was again subjected to backward elimination using the step AIC function. The final model was comprised of main effect and interaction terms remaining after the second backward elimination procedure.

Exposures that were shown to be significantly different from zero at the α=0.05 level (ie, $p<0.05$) with a confidence interval of odds ratio (OR)/hazards ratio (HR) that did not include 1 (null effect) were deemed significant. The number of patients with exposure data for free SN-38 and SG were 235 and 245, respectively.

The pharmacokinetic parameters of sacituzumab govitecan and free SN-38 are presented in the Table below.

Exposure parameters (C_{max} and AUC_{0-168}) were higher for SG than free SN-38.

Table 8 Summary of Mean PK Parameters (CV%) of sacituzumab govitecan and Free SN-38

	IMMU-132-01		IMMU-132-05	
	SG	Free SN-38	SG	Free SN-38
T_{max}	3.3 (65.1%)	3.85 (36.5%)	3.3	3.78 (32.0%)
C_{max} (ng/mL)	227000 (23.8%)	120 (81.7%)	240000 (22.2%)	90.6 (65.0%)
AU_{0-168} (ng*h/mL)	5190000 (24.0%)	3620 (71.9%)	5340000 (23.7%)	2730 (41.1%)

AUC_{0-168}=area under the serum concentration-time curve from time 0 to 168 hours; C_{max}=maximum serum concentration; CV=coefficient of variation; T_{max}=time of maximum concentration

Absorption

SG is administered by IV infusion; there are no studies characterizing absorption by other routes of administration and thus, drug absorption is not applicable.

Distribution

Vss for SG derived by noncompartmental analysis in studies IMMU-132-01 and IMMU-132-05 was 2.82 L and 2.45 L, respectively. Population PK results predicted V1, V2, and Q of SG to be 2.96 L, 1.22 L and 0.01 L/hr, respectively. For free SN-38, V1, V2, and Q were predicted to be 7383.00 L, 54780.00 L and 14.38 L/hr, respectively.

Elimination

The mean terminal t½ of SG is approximately 15 hours.

Table 9 **Mean (CV%) Half-Life**

	IMMU-132-01		IMMU-132-05	
	SG	Free SN-38	SG	Free SN-38
$t_{½}$ (h)	15.2 (18.4%)	17.4 (19.8%)	15.3 (23.7%)	19.7 (36.3%)

$t_{1/2}$=terminal elimination half-life

In study IMMU-132-01, CL of SG is listed with 149 L/h for the 10 mg/kg dose. In study IMMU-132-05, the estimated CL for sacituzumab govitecan was 0.138 L/hr in subjects with TNBC. In the population PK analysis, CL of sacituzumab govitecan was estimated to be 0.14 L/hr, while CL of free SN-38 was estimated to be 292.70 L/hr.

Studies of the excretion of the SG have not been conducted. SN-38 and SN-38 G are reported to be primarily excreted through the hepatobiliary route, with lesser amounts detected in the urine [Slatter et al, 2000; Matthijssen et al, 2001; Camptosar Prescribing Information].

No metabolism studies of SG have been conducted. The metabolism of SG is mediated by both catabolism of the antibody into individual amino acids and metabolism of SN-38 (the small molecule moiety of SG) by UGT1A1 in the liver to form the inactive metabolite, SN-38 glucuronide (SN-38G).

PK of SN-38G

Following IV administration of sacituzumab govitecan, the mean plasma concentrations of SN-38G did not increase significantly in a dose-dependent manner, there was no obvious non-linear or saturable clearance (data not shown).

According to the population PK analysis, CL and V of SN-38G were 64.2 L/hr, and 160.8 L respectively.

The model-predicted geometric mean (CV%) of AUC, C_{max}, and C_{avg} across all subjects can be found in the Table below.

Table 10 **Simulated Exposure Metrics of SN-38G After 1 Cycle of Treatment**

Parameter	GM (CV%)
AUC (ng*h/mL)	1610 (44.7%)
Cmax	22.5 (45.2%)
Cavg	3.19 (44.7%)

Abbreviations: AUC=area under the serum concentration-time curve; Cavg=average serum concentration; Cmax=maximum observed serum concentration; CV=coefficient of variation; GM=geometric mean.

Since SN-38 glucuronidation occurs via UGT1A1 in the liver, a possible effect of UGT1A1 on the concentration and safety/adverse effect endpoints (Diarrhoea, Neutropenia, Vomiting) of Free SN-38, Total SN-38 and SN-38G was analysed in study IMMU-132-05.

Summary of UGT1A1 Genotype (1/1, 1/28, 28/28, and Rest) by Adverse Effects

Table 11 *Summary of Adverse Effects by UGT1A1 Genotype, N = 258*

	UGT1A1 Genotype			
Adverse Effect	*1/1*	*1/28*	*28/28*	*Rest*
Diarrhea (No)	43 (38.1%)	35 (36.8%)	8 (23.5%)	4 (25%)
Diarrhea (Yes)	70 (61.9%)	60 (63.2%)	26 (76.5%)	12 (75%)
Neutropenia (No)	65 (57.5%)	54 (56.8%)	14 (41.2%)	9 (56.2%)
Neutropenia (Yes)	48 (42.5%)	41 (43.2%)	20 (58.8%)	7 (43.8%)
Vomiting (No)	73 (64.6%)	65 (68.4%)	22 (64.7%)	12 (75%)
Vomiting (Yes)	40 (35.4%)	30 (31.6%)	12 (35.3%)	4 (25%)

Population PK analysis further indicated that UGT1A1 genotype is not a significant covariate for free SN-38 or SN-38G exposure.

Dose proportionality and time dependencies

Dose proportionality

A nonlinear power model was used to assess the multiple-dose proportionality of sacituzumab govitecan, total SN-38, free SN-38, total antibody, and SN-38G if data permitted based on all subject exposures (C_{max} and area under the serum concentration-time curve from time 0 to 24 hours [AUC_{0-24}]) on Days 1 and 8 of Cycle 1 using Phoenix WinNonlin. If the 90% CI for the slope (B) includes 1.0, then the relationship was considered to be dose proportional. Geometric means of C_{max} and AUC_{0-24} on Days 1 and 8 of Cycle 1 were tabulated by dose level.

Parameters derived with the power model for sacituzumab govitecan are presented in Tables below, and the relationship between the exposure parameters of sacituzumab govitecan exposure and the dose of sacituzumab govitecan are shown in Figure 4 and Figure 5.

Table 12 Dose-Proportionality Assessment of Sacituzumab Govitecan for Day 1

Day 1				
Dependent	**Coefficient/Constant**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**
AUC0-24	Ln(A)	7.65	6.58	8.72
	B	0.22	-0.26	0.70
C_{max}	Ln(A)	4.04	3.22	4.85
	B	0.60	0.24	0.96

CI=confidence interval; CV=coefficient of variation; GM=geometric mean; PK=pharmacokinetic.

Table 13 Dose-Proportionality Assessment of Sacituzumab Govitecan for Day 8

Day 8				
Dependent	**Coefficient/Constant**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**
AUC0-24	Ln(A)	5.42	2.54	8.30
	B	1.33	-0.04	2.69
Cmax	Ln(A)	4.02	1.70	6.34
	B	0.63	-0.47	1.73

Figure 9 Relationship Between Sacituzumab Govitecan Exposure Parameters Cmax and Sacituzumab Govitecan Dose for Day 1

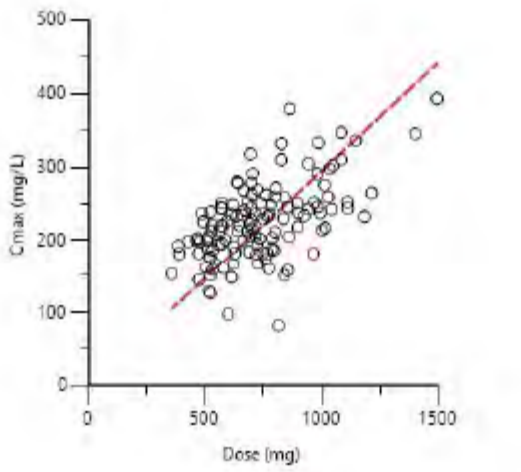
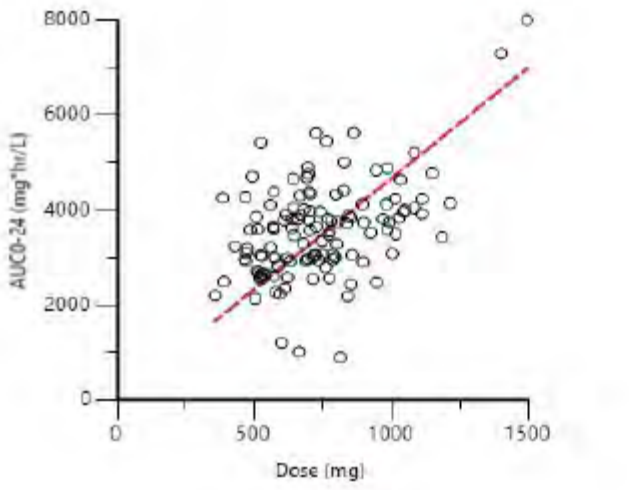


Figure 10 Relationship Between Sacituzumab Govitecan Exposure Parameters AUC0-24 and Sacituzumab Govitecan Dose for Day 1



Parameters derived with the power model for free SN-38 are presented in tables below, and the relationship between the exposure parameters of Free SN-38 exposure and the dose of sacituzumab govitecan are shown in Figures below.

Table 14 Dose-Proportionality Assessment of Free SN-38 for Day 1

Day 1				
Dependent	**Coefficient/Constant**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**
AUC0-24	Ln(A)	0.00	0.00	0.00
	B	1.00	1.00	1.00
Cmax	Ln(A)	-2.81	-2.85	-2.77
	B	0.89	0.84	0.94

CI=confidence interval; CV=coefficient of variation; GM=geometric mean; PK=pharmacokinetic.

Table 15 Dose-Proportionality Assessment of Free SN-38 for Day 8

Day 8				
Dependent	**Coefficient/Constant**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**
AUC0-24	Ln(A)	0.00	0.00	0.00
	B	1.00	1.00	1.00
Cmax	Ln(A)	-2.95	-3.05	-2.85
	B	0.91	0.78	1.04

CI=confidence interval; CV=coefficient of variation; GM=geometric mean; PK=pharmacokinetic.

Figure 11 **Relationship Between Free SN-38 Exposure Parameters Cmax and Sacituzumab Govitecan Dose (mg)**

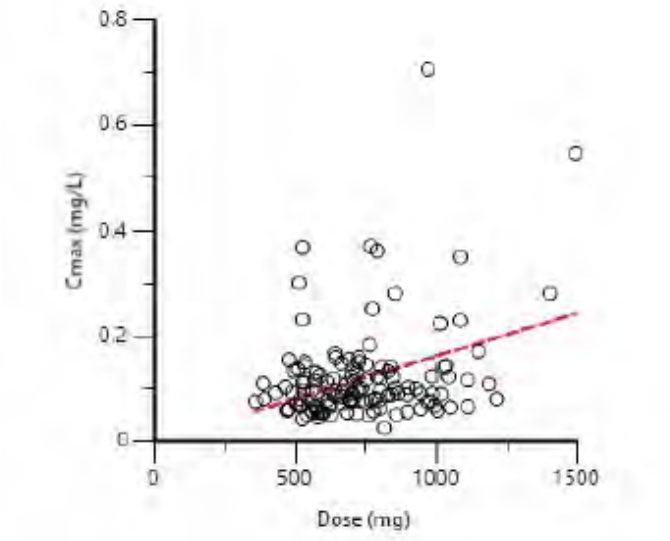
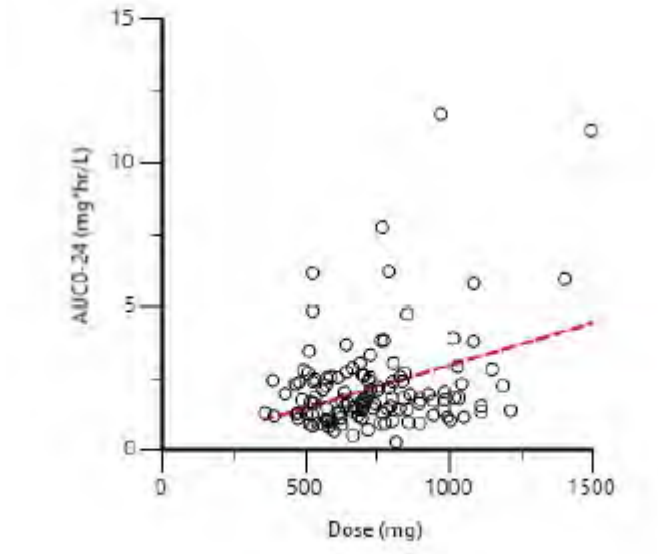


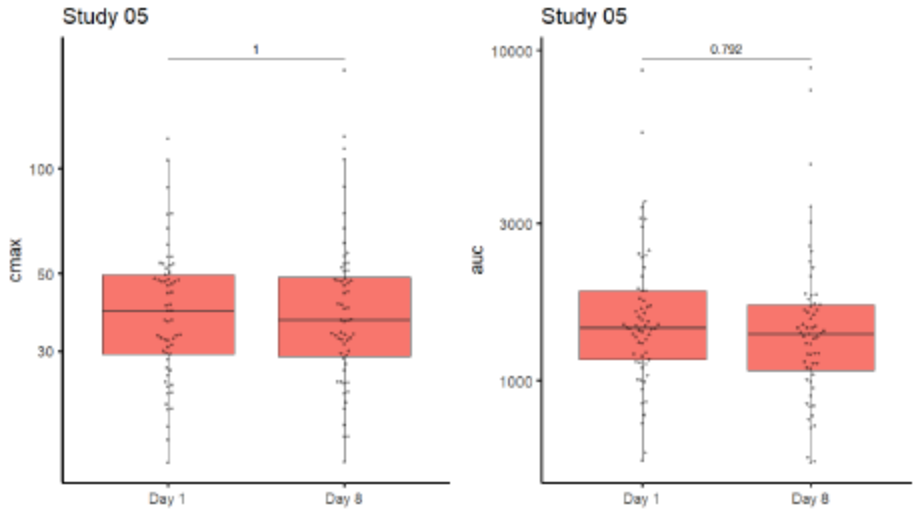
Figure 12 **Relationship Between Free SN-38 Exposure Parameters AUC0-24 and Sacituzumab Govitecan Dose (mg)**



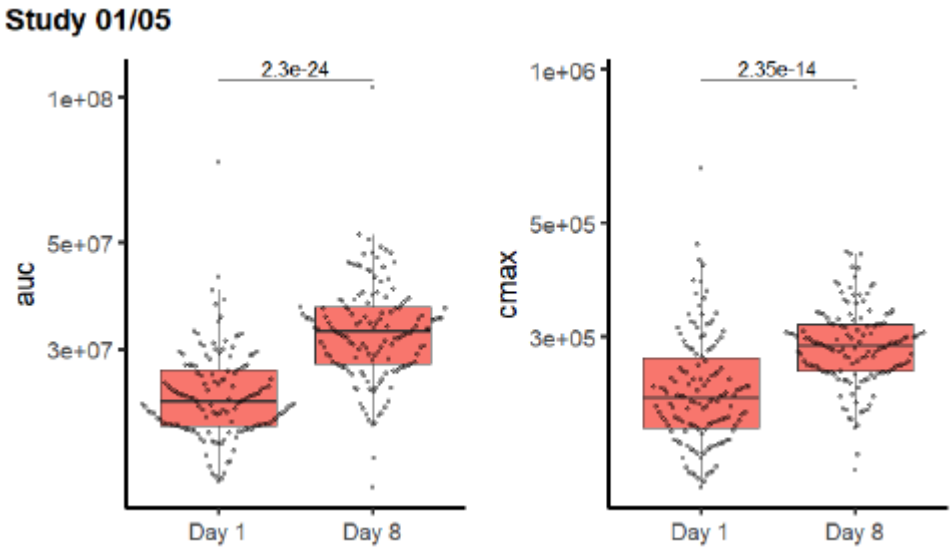
Time dependency

Referring to the population PK analysis, there was no accumulation of SG when Day 1 and Day 8 ($p > 0.05$) were compared for AUC and Cmax (Figure below).

Figure 13 **Comparing Trough Levels on Day 1 and Day 8 of SG Exposure (AUC and C_{max}) in Study IMMU-132-05**

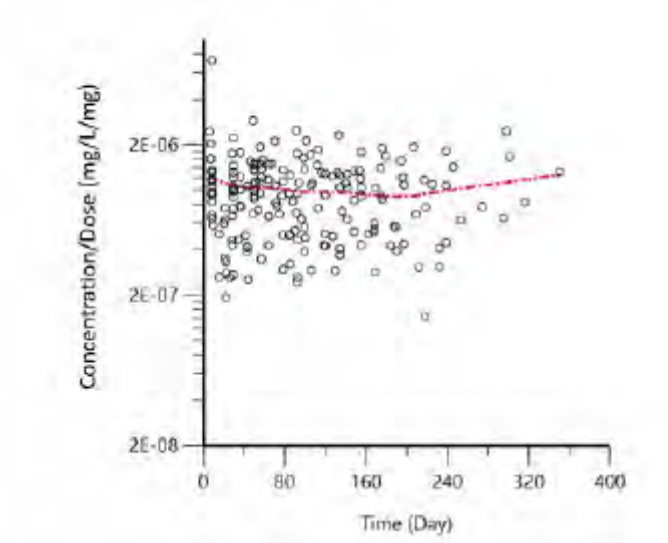


Accumulation was however observed for total antibody:



In study IMMU-132-01, C_{trough} values of sacituzumab govitecan by dose levels, as presented in the figure below, do not suggest accumulation of the drug.

Figure 14 Sacituzumab Govitecan Ctrough Levels by Dose Level – Semi-Log Scale



Pharmacokinetic interaction studies

No drug-drug interaction studies were conducted with either SG or its components.

Exposure relevant for safety evaluation

AUC_{0-24} Comparison of Irinotecan SN-38 and Irinotecan

A comparison between AUC_{0-24} of free SN-38 and SN-38 after administration of irinotecan based on data in the United States prescribing information (USPI) with free SN-38 and SN-38 values obtained after administration of sacituzumab govitecan was made (see Table below for results from study IMMU-132-05).

Table 20 Comparison of Free SN-38 Exposure Parameters After Administration of Sacituzumab Govitecan or Irinotecan

Dose (mg/m²)	Irinotecan SN-38		Dose	Free SN-38	
	Cmax (ng/mL)	AUC0-24 (ng·h/mL)	(mg/kg)	Cmax (ng/mL)	AUC0-24 (ng·h/mL)
125 (N=64)	26.3±11.9	229±108	10 (N=27)	90.6±58.9	1440±773
340 (N=64)	56.0±28.2	474±245			

AUC0-24=area under the serum concentration-time curve from time 0 to 24 hours; Cmax=maximum observed serum concentration; N=number of subjects.

2.4.3. Pharmacodynamics

Mechanism of action

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate with the small molecule SN-38, a topoisomerase I inhibitor, covalently attached to the antibody by a hydrolysable linker. The mode of action as proposed for sacituzumab govitecan is as follows: Upon binding to Trop-2 sacituzumab govitecan is internalised with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks which if unrepaired, progress to double-stranded DNA breaks. The resulting DNA damage leads to activation of several signalling pathways leading to apoptosis and cell death. Due to the hydrolysable linker, SN-38 can also be released extracellularly from the ADC by hydrolysis in the tumour environment. Since free SN-38 is membrane permeable it can diffuse into nearby cancer cells in the tumour microenvironment resulting in cell death of Trop-2 negative tumour cells.

Primary and Secondary pharmacology

Throughout the clinical studies, no specific pharmacodynamic endpoints were investigated. Pharmacodynamic effects of SN-38 have been described for the small molecule drug irinotecan and are therefore well known.

Immunogenicity

An ADA assay is currently under development and any samples from IMMU-132-01 analysed using this assay will be reported. In addition, an assay for the detection of neutralising anti-SG antibodies is in validation. Samples from Study IMMU-132-05 will be analysed once the new assays are available and fully validated. See also section 2.4.5.

Cardiac electrophysiology

Study IMMU-132-01

QT prolongation was present in 15 of 420 patients (3.6%) during treatment. These patients were identified in one or more of three ways: they had an abnormal ECG that was determined by the site investigator to be clinically significant (search criterion: A); they were found to have prolonged QTcF values as determined by search of ECG numerical values in the ECG database (search criterion: B); a cardiac-related serious adverse event was recorded (search criterion: C).

In all, QT prolongation was judged to be possibly related to SG in 4 of those 15 cases in which it was present (27% of cases, 0.95% of patients), probably unrelated in 8 cases and unrelated in the remaining 4.

Using the threshold of >500 msec that was used by Porta-Sanchez to define clinically significant QTc prolongation, there were 8 cases (1.4% of all patients) in our study.

In most patients in this study alternative explanations for QT prolongation and other cardiac adverse effects were present. QT prolongation was not judged to be definitely related to SG in any case and was thought to be possibly related in only 4 cases (0.95% of all enrolled subjects). None of the other cardiac adverse effects were judged to be related, probably related or possibly related to SG.

PR interval prolongation rates in oncology trials have not been reported on. The average PR increase over baseline in this trial was modest (4.65 msec). Though this could have been related to SG, there are many alternate explanations, as for QT prolongation, during cancer therapy. There were no adverse effects related to PR prolongation, and there were no reported second- or third-degree block events.

This analysis is limited by the unavailability of numerical ECG data in many patients. The reliability of the available data is limited by the non-centralised nature of ECG acquisition and interpretation, and the fact that baseline ECGs were collected up to a month before initiation of treatment, without synchronisation of the time of day of ECG acquisition. Thus, firm conclusions are not possible, but it is reasonable to conclude that the nature and frequency of QT prolongation observed in this study are typical of oncology trials in general and that evidence is insufficient to conclude that SG is an independent cause of QT prolongation.

Study IMMU-132-05

Concentration-QTc modelling was performed using data collected from the QT sub-study of IMMU-132-05 clinical study, to evaluate the relationship between serum free SN-38, serum total SN-38, serum serum total antibody, and serum sacituzumab govitecan concentration and QTc interval at clinical doses in oncology patients.

The serum free SN-38, serum total SN-38, serum SN-38-glucuronide (SN-38G), serum total antibody, and serum sacituzumab govitecan were evaluated in the concentration-QTc analysis and deemed to have clinically significant QTc prolongation if the upper bound of the two—sided 90% condence interval [CI] of the predicted mean baseline-adjusted QTc at clinically relevant concentrations is 10 ms.

Model Prediction for Free SN-38

The final C-QTc model was used to predict the mean and 90% Cls of mean ΔQTcF for the range of concentrations in the data. The mean reaches the 10 ms boundary at 122 ng/mL. The slope parameter of the model had a p-value of 0.09 indicating lack of statistically significant correlation between ΔQTcF and free SN-38 concentrations. Overall, the data available does not suggest a significant impact of concentration on ΔQTcF.

Concentration-QTc modelling for total SN-38, SN-38G, total antibody and sacituzumab govitecan revealed a statistically significant correlation of serum concentrations and QTc prolongation. Based on the estimated slope parameters and sacituzumab govitecan exposures at the 10 mg/kg dose level, QT prolongation exceeding the 10 ms threshold at higher concentrations cannot be excluded, however, QT prolongation exceeding 20 ms seems unlikely based on the totality of the data.

Exposure-response analyses

Exposure-efficacy-analyses

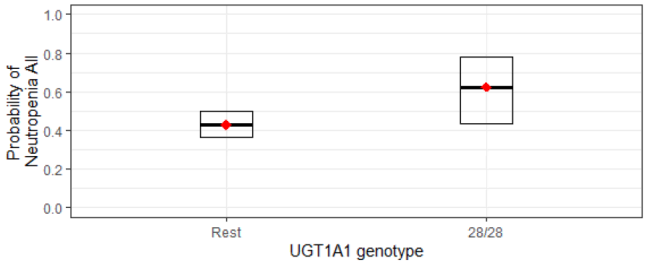
There was no significant relationship for either AUC or Cmax and PFS or OS) for SG and free SN-38 (data not shown).

Exposure-safety-analyses

Univariate exposure-safety analyses identified significant relationship of SG exposure (especially Cmax) and probability of vomiting or diarrhoea (not for free SN-38). Odds ratio > 1 indicates that baseline weight is associated with higher odds of occurrence of diarrhoea or vomiting. Further, Odds ratio > 1 indicates that baseline weight is also associated with the higher odds of occurrence of dose reduction and dose delay.

In addition, there was a trend in higher probability of neutropenia with increase in SG AUC and SG Cmax observed in Study IMMU-132-05. Odds ratio >1 indicates that UGT1A128/28 is associated with a higher odds of occurrence of Neutropenia.

Figure 15 VPCs for Final Logistic Regression Model



Abbreviations: AUC=area under the serum concentration-time curve; PI=prediction interval; UGT1A1=UDP glucuronosyltransferase family 1 member A1; VPC=visual predictive check.
Notes: The red diamonds represent the observed proportion of subjects with Neutropenia All. The boxes bound the 2.5th and 97.5th percentiles (95% PI) of the simulated proportions, and the crossbars within the boxes represent the median of the simulated proportions. VPCs were generated for the logistic regression model using 1000 replicates of the subjects in the analysis dataset.

There was no significant relationship for either AUC, Cmax, or Cavg with nausea, vomiting, diarrhoea, neutropenia, or hypersensitivity for both SG and free SN-38 (final full combined effect model).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The clinical pharmacology package of sacituzumab govitecan so far comprised two clinical studies (study IMMU-132-01 and study IMMU-132-05) contributing to the characterisation of PK of the 5 analytes SG, free SN-38, total SN-38, SN-38G, and total antibody. In study IMMU-132-01, doses of 4.5 to 18 mg/kg IV were investigated.

The proposed standard dose of SG is 10 mg/kg administered IV once weekly on Days 1 and 8 of 21-day treatment cycles.

SG contains a hydrolysable linker (CL2A), which links the humanised monoclonal antibody to SN-38. The applicant describes that the linker is still attached to the IgG molecule after release of SN-38 and that free linker is not present in the circulation.

Analytical methods

Free SN-38, SN-38G and total SN-38 (after application of a hydrolysis step) were quantified after solid phase extraction by a validated LC-MS/MS method. During validation, all investigated parameters met the

acceptance criteria of the relevant EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). Long-term frozen stability of free SN-38/SN-38G, total SN-38, and total antibody at -80°C has been shown for 832, 792, and 994 days. This period sufficiently covers the maximum storage time between sample collection and analysis of samples from clinical study IMMU-132-05 for each of the analytes. Only for study IMMU-132-01, the analysis is pending and will continue into 2023 in order to cover the study sample storage duration. The applicant committed to provide long-term stability data for study sample storage duration in Study IMMU-132-01 as a post-authorisation measure by Q4 2023.

For quantification of total antibody (hRS7-IgG and hRS7-SN38), an electrochemiluminescence assay (ECL) was developed and adequately validated.

No assay capable of distinguishing naked (unconjugated; DAR 0) hRS7-IgG from SN-38-conjugated SG (DAR 1-8) was available. The amount of SG in serum was therefore calculated by applying a fixed DAR of 8 and using the concentrations of measured total SN-38, free SN-38, and free SN-38G. It has to be recognised that this calculated value may both under-estimate and over-estimate the actual amount of the ADC since the DAR of the ADC in circulation changes over time.

However, no bioanalytical study reports on ADA have been provided. The applicant committed to provide the bioanalytical study reports for antidrug-antibody (ADA) and neutralizing antibody (NAb) determination for both Studies IMMU-132-01 and IMMU-132-05 as well as the NAb assay method validation report as a post-authorisation measure by Q3 2022.

PK parameters were determined using noncompartmental analyses (NCA) in validated reporting tools. Population pharmacokinetic (pop PK) modelling for the 5 analytes of sacituzumab govitecan (serum-free SN-38, serum total SN-38, serum SN-38G, total antibody, and serum sacituzumab govitecan) was conducted to evaluate the effects of covariates on the variability of the PK of the 5 analytes; and to characterize the exposure-response (E-R) relationships of the 5 analytes in terms of efficacy and safety.

During evaluation of final pop PK analyses for different entities, cancer type was found a statistically significant covariate on PK. Data did not indicate a significant effect of gender on the exposure of both SG and free SN-38. Forest plot analyses involved UGT1A1 polymorphism, that also did not indicate to have a significant effect on exposure (AUC, Cmax) of SG and free SN-38. Pairwise distribution of continuous and categorical covariates were provided and corrected, indicating strong correlations between covariates tumor type, sex, UGT1A1, race and GFRCAT.

Overall, derived final pop PK models were able to predict the observed median and p5 and p95 of observed concentrations acceptably well. The median concentration was fully captured throughout the profiles over time since last dose. However, the overall range of variability in exposure is over-predicted as shown by p5 and p95 percentiles observed vs predicted. Observed p95 and especially p5 were not well captured by predicted bands for segments of the time course.

ADME

SG is administered as IV infusion and is therefore 100% bioavailable. Tmax of SG and free SN-38 ranged between 3 – 4 hours. Cmax of SG and free SN-38 in study -01 was 227,000 ng/ml and 120 ng/ml, respectively. In study -05, Cmax of SG and free SN-38 was 240,000 ng/ml and 90.6 ng/ml.

Volume of distribution of SG (2.5 – 3 L) is similar to typical values described for monoclonal antibodies, indicating that distribution is mainly restricted to the systemic circulation. An error in calculation of Vss for SG by NCA in study IMMU-132-05 was corrected in the eCTD submission 0001 and finally in section 5.2 of the

SmPC for Trodelvy. Values for volume of distribution of free SN-38 should be considered as apparent values, since kinetics of SN-38 is limited by its release from the antibody.

Clearance of SG was estimated to be 0.14 L/h in the population PK analysis. Similar results were obtained by noncompartmental analysis. The typical plasma clearance of unconjugated mAbs has been described to range between 0.2 – 0.4 L/day for a 70 kg adult. Thus, CL of SG is significantly higher as compared to a typical mAb, which is further reflected by a shorter half-life of only approx. 15 hours as compared to the half-life of 14 – 21 days, which is typically observed for unconjugated mAbs. Half-life of total antibody was approx. 3-4 fold higher as compared to SG, free SN-38, total SN-38 or SN-38G.

As to the linker molecule, it is expected that it will be degraded through enzymatic degradation while attached to the antibody.

Dose proportionality and time dependency

Dose proportionality of PK of SG and free SN-38 at steady state was confirmed.

Referring to the rather short half-life of 15 – 20 hours determined for SG and free SN-38, no accumulation is expected for the proposed dosing regimen (once weekly on Days 1 and 8 of 21-day treatment cycles). This is supported by population PK analysis revealing no difference of SG AUC or Cmax comparing Day 1 and Day 8. Similar results were obtained for free SN-38, SN-38G, and total SN-38. Significant accumulation between Day 1 and Day 8 was however observed for AUC and Cmax of total antibody, which is in line with the described longer t1/2 (approx. 50 – 60 h) of total antibody. Referring to pop PK analyses, the exposure of total antibody was observed to reach steady state by Cycle 8. Time-dependent clearance is not expected based on the assessment of the pop PK conditional weighted residuals where there were no apparent trends or biases over time.

PK in the target population

Values derived by NCA analysis were overall comparable between study -01 and study -05. In general, SG concentrations must be considered imprecise, given that there is no validated assay for quantification of SG in plasma. SG concentrations were calculated assuming a fixed DAR of 8, however, the DAR of the ADC in circulation changes over time and SG concentrations may be over- or under-estimated.

In the population PK analysis, Results are similar to NCA analyses. Impact of concomitant medication on SN-38 PK was not evaluated in the current population PK analyses. A trend towards increased incidence of neutropenia and diarrhoea was seen in patients with UGT1A1*28/28 genotype. However, Cmax of free SN-38 was even lower in patients with UGT1A1 genotype 28/28 as compared to patients with wildtype or heterozygous UGT1A1.The applicant plans to evaluate the impact of concomitant medications including UGT1A1 inhibitors/inducers on SN-38 PK in future pop PK model refinement when data from new studies are available. The applicant commits to provide these data post-approval.

Steady state PK parameters were provided that confirm no accumulation of SG and free SN-38 after repeated dosing (3-week cycles with dosing on Day 1 and Day 8). Accumulation was however seen for total antibody, which is anticipated due to the longer half-life observed for total antibody (study -01: 67.2 h, study-05: 54.5 h, popPK estimate: 134 h). The population PK derived estimates for elimination half-life of SG are higher (median [min, max]: 79.4 h [35.5, 128]) than the NCA-derived values (mean of approx. 15 h). Similarly, the estimate for elimination half-life of total antibody is higher in the population PK analysis. In the SmPC, half-life of SG is described with 15.3 hours as derived by NCA in study -05. The applicant clarified that the estimated half-life based on NCA was primarily driven by the distribution phase half-life, since limited PK sampling was conducted in the true terminal elimination phase. It was argued that the distribution phase

covers most of the AUC based on the measurable concentrations and therefore the half-life determined by NCA approximates better the effective half-life and is considered to be a more reliable estimate for the half-life of SG and the total antibody. This is also supported by limited accumulation observed for SG and total antibody over time. An analysis of distribution half-life (alpha phase; α half-life) and elimination half-life (beta phase; β half-life) conducted by population PK resulted in values of 13.5 h and 91.7 h for alpha and beta half-life, respectively. Conclusively, the popPK-derived value for alpha half-life is similar to the NCA-derived estimate.

PK in special populations

The effect of the intrinsic factors weight, age, UGT1A1, GFR, hepatic impairment, albumin concentration, alkaline phosphatase and race on SG and free SN-38 exposure was examined using the population PK model. No impact of mild renal or hepatic impairment on the exposure of SG or free SN-38 was observed. No data are available for patients with moderate to severe renal or hepatic impairment. Gender effects were analysed in study IMMU-132-01, where female patients presented with reduced dose-normalised AUC of SG and increased SG CL as compared to male patients. As per population PK analysis, higher body weight was associated with a (non-significant) increase of SG exposure, which is assumed to be driven by weight-adjusted SG dosing. For the subject exhibiting the lowest exposure, it seems to be due to a combination of low weight-based dose and high clearance. Race did not significantly influence the exposure of SG or free SN-38. No significant differences in exposure of SG or free SN-38 were seen in the elderly. No data in children are available.

Interactions

No drug-drug interaction studies were conducted with either SG or its components which is acceptable.

Systemic exposure to SN-38 may be increased due to concomitant administration of SG with inhibitors of UGT1A1, which may further increase the incidence of adverse reactions. In contrast, in patients concomitantly receiving UGT1A enzyme inducers, exposure of SN-38 may be reduced, which may impact efficacy of SG. Therefore, UGT1A1 inhibitors or inducers should not be administered with SG. This is adequately reflected in section 4.5 of the SmPC.

Exposure relevant for safety evaluation

In comparison to irinotecan at a dose level of 350 mg/m², the total amount of SN-38 administered with SG is reduced by approximately factor 30. However, it is noted that exposure of free SN-38 after administration of SG is higher than the exposure of SN-38 after administration of irinotecan at the dose level of 350 mg/m²: Cmax of SN-38 is described to be 90.6 ng/ml for SG as compared to 56 ng/mL for irinotecan, AUC(0-24h) is described to be 1440 ngxh/mL for SG as compared to 474 ngxh/mL for irinotecan. Considering that SG is a targeted therapy which is intended to deliver the toxic moiety directly to the tumour/site of action, it appears unexpected that such high plasma concentrations of SN-38 are necessary. However, despite an approximately 2- to 3-fold higher AUC of SN-38 observed with SG in comparison to irinotecan, the safety profiles (e.g. incidences of neutropenia) of irinotecan and SG were suggested to be similar.

Pharmacodynamics

Throughout the clinical studies, no specific pharmacodynamic endpoints were investigated. Pharmacodynamic effects of SN-38 have been described for the small molecule drug irinotecan and are therefore well known.

Immunogenicity

Only a subset of available samples collected in study IMMU-132-01 were analysed. Referring to the results presented in bioanalytical study report BIMME1715E1/BIMME1717E1, and the majority of these were reported as ADA negative. Complete ADA and NAb results from study -01 and -05, including the analysis of the impact of ADA status on PK, efficacy and safety within an integrated summary of immunogenicity, will be provided as post authorisation measure (REC) by Q3/2022 at the latest.

Cardiac electrophysiology / QT prolongation

In study IMMU-132-01, clinically significant QTc prolongation was only seen in 1.4% of all patients and thought to be possibly related in only 4 cases (0.95% of all enrolled subjects). ECG analyses and interpretation had several limitations, e.g. numerical ECG data was unavailable in many patients, ECG acquisition and interpretation was performed non-centralised, and baseline ECGs were collected up to one month before treatment without any synchronisation. Altogether, QT prolongation was not judged to be definitely related to IMMU-132 in any case, which is agreed.

Concentration-QTc modelling for total SN-38, SN-38G, total antibody and sacituzumab govitecan revealed a statistically significant correlation of serum concentrations and QTc prolongation. Based on the estimated slope parameters and sacituzumab govitecan exposures at the 10 mg/kg dose level, QT prolongation exceeding the 10 ms threshold at higher concentrations cannot be excluded, however, QT prolongation exceeding 20 ms seems unlikely based on the totality of the data. Importantly, statistical significance was not reached in concentration-QTc modelling for free SN-38. Overall, it may therefore be agreed that no evidence for significant or clinically relevant QTc prolongation was seen for SG and other analytes in the PK-QTc substudy of Study IMMU-132-05.

In addition, irinotecan itself has not been reported as a typical drug with a risk of QTc prolongation in the past.

Exposure-response analyses

No exposure-efficacy relationship was identified for SG or free SN-38 with regard to ORR, PFS, and OS, neither in the analysis of subjects with mTNBC in study IMMU-132-05 only nor in the analysis of subjects with mTNBC in both study IMMU-132-01 and study IMMU-132-05. In part, the highest exposure quartile(s) even showed a tendency towards lower efficacy.

Univariate exposure-safety analyses identified significant relationship of SG exposure (especially Cmax) and probability of vomiting or diarrhoea (not for free SN-38). An odds ratio > 1 indicates that baseline weight is associated with higher odds of occurrence of diarrhoea or vomiting. Further, an odds ratio > 1 indicates that baseline weight is also associated with the higher odds of occurrence of dose reduction and dose delay.

In addition, there was a trend in higher probability of neutropenia with increase in SG AUC and SG Cmax observed in Study IMMU-132-05. Odds ratio >1 indicates that UGT1A128/28 is associated with a higher odds of occurrence of neutropenia.

However, the final full combined main effect model did not reveal that AUC, Cmax or Cav of SG or free SN-38 were significant covariates predicting toxicity (except for dose delay, which correlated with AUC and weight of all analytes except for SN-38G).

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics of SG and its relevant analytes have been analysed in both clinical studies (IMMU-132-01 and IMMU-132-05) pertinent to the claimed indication TNBC. In general, PK of SG and the relevant analytes was as expected for an ADC. Data on steady state exposure revealed no accumulation of SG and free SN-38. Overall, derived final pop PK models were able to predict the observed median and p5 and p95 of observed concentrations acceptably well but indicate high variability.

Impact of concomitant medication on SN-38 PK was not evaluated in the current population PK analyses. No results on immunogenicity of SG have been presented. Long-term stability data for study sample storage duration are also missing in Study IMMU-132-01.

Therefore the CHMP recommended to the following measures necessary to address the issues related to pharmacology:

- provide bioanalytical study reports for antidrug-antibody (ADA) and neutralizing antibody (NAb) determination for both Studies IMMU-132-01 and IMMU-132-05, the NAb assay method validation report as well as an integrated summary of immunogenicity by Q3 2022.
- Provide data on the impact of concomitant medications including UGT1A1 inhibitors/inducers on SN-38 PK based on the future PopPK model refinement by Q3 2022
- Provide long-term stability data for study sample storage duration in Study IMMU-132-01 by Q4 2023

2.5. Clinical efficacy

The primary support for the efficacy of SG as monotherapy "for the treatment of adult patients with unresectable or metastatic TNBC who have received two or more prior therapies, including at least one of them for advanced disease", is provided by the controlled Phase 3 study, **IMMU-132-05**. Supportive efficacy data are available from a cohort of 108 mTNBC patients with relapsed/refractory mTNBC who received a starting dose of 10 mg/kg SG in the uncontrolled, open-label study, **IMMU-132-01**.

2.5.1. Dose response study

Study IMMU-132-01

Study IMMU-132-01 is an uncontrolled, Phase 1/2 basket study in which SG monotherapy was evaluated in previously-treated metastatic epithelial cancers. Please see also section "supportive study".

Phase 1 was a dose escalation, 3+3 design in which SG doses of 8, 10, 12, and 18 mg/kg were administered. The primary objectives of Phase 1 were to evaluate the safety and tolerability of SG as a single agent administered in 3-week treatment cycles, to determine a maximum acceptable dose and select cancer types for a continued expanded study in Phase 2.

Dose selection:

SG 12 mg/kg was determined as the MTD in Phase 1; however, this dose was associated with dose reductions and dose delays in many subjects. Therefore, a maximum acceptable dose, defined as the highest dose at which ≥2 of 6 treated subjects tolerated a 3-week treatment cycle without the need for either a dose

delay or dose reduction and without experiencing any AE ≥grade 3, was defined. Both 8 mg/kg and 10 mg/kg met the criteria for a maximum acceptable dose.

Subjects in Phase 2 were enrolled in a sequential manner to the 8 mg/kg dose and subsequently to the 10 mg/kg dose. An interim analysis was performed when 81 and 97 patients with different tumor types had been treated at the 2 dose levels, respectively. The duration of treatment at the 2 dose levels was similar and no important differences in safety were seen. However, the 10 mg/kg dose compared with the 8 mg/kg dose was associated with a higher ORR (22% and 10%, respectively) and clinical benefit rate (CBR) [Ocean et al, Cancer 2017]. Based on these data, 10 mg/kg SG was selected as the dose for this study.

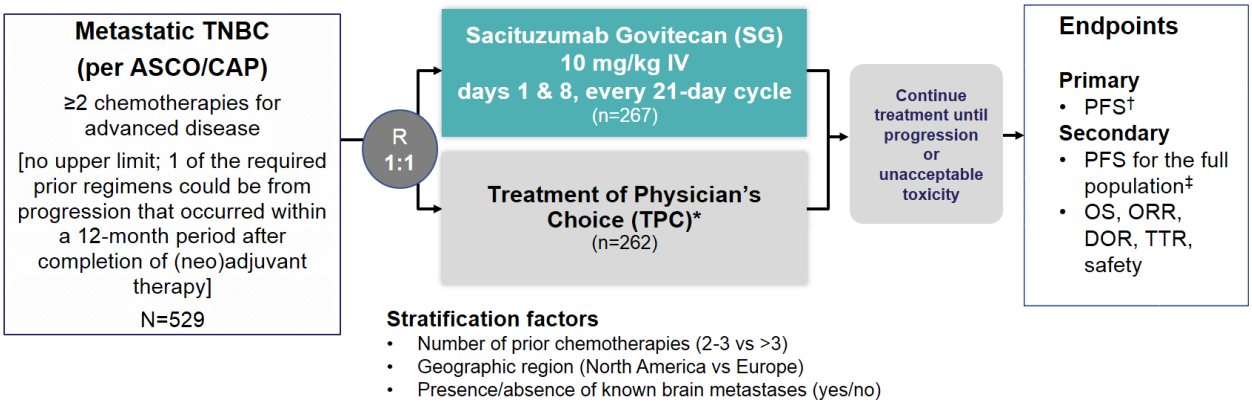
2.5.2. Main study

Title of study

Study IMMU-132-05 (ASCENT) An international, multicenter, open-label, randomised, phase 3 trial of sacituzumab govitecan versus treatment of physician' choice in patients with metastatic triple-negative breast cancer (mTNBC) who received at least two prior treatments

Methods

Figure 16 Study design of IMMU-132-05



*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
(Figure from presentation at presubmission meeting)

Study Participants

Inclusion criteria (excerpt)

1. Female or male, ≥18 years of age, who were able to understand and provide written informed consent

2. Histologically- or cytologically-confirmed TNBC (estrogen receptor negative [ER-], progesterone receptor negative [PR-], and HER2 negative [HER2-]) per American Society of Clinical Oncologists (ASCO)/College of American Pathologists (CAP) criteria on the most recent biopsy or other pathology specimen
    - Triple negative was defined as <1% expression for the ER and PR and HER2- by in-situ hybridisation.
3. Either metastatic or locally-advanced disease (Patients with locally advanced TNBC were allowed to be enrolled with protocol amendment 4 (May 2018)).
4. Measurable disease by either computed tomography (CT) or magnetic resonance imaging (MRI) as per RECIST 1.1. Bone-only disease was not considered measurable and was not permitted.
5. Brain MRI done for patients with brain metastasis; patient must have had stable central nervous system disease for at least 4 weeks, with stable defined as follows:
    - Prior local treatment by radiation, surgery, or stereotactic surgery
    - Imaging – stable or decreasing size after such local treatment
    - Clinically stable signs and symptoms (Definition of stable CNS disease was added with amendment 4 (May 2018).)
    - ≥ 2 weeks from discontinuation of anti-seizure medication
    - Corticosteroid (if needed) – dose was either stable or decreasing for at least 2 weeks before randomisation. Steroid dose was ≤20 mg of prednisone/prednisolone daily or equivalent for a different steroid.
6. At least 2 weeks after high-dose systemic corticosteroids (low dose corticosteroids ≤20 mg prednisone or equivalent daily were permitted provided the dose was stable for 4 weeks;
7. Refractory to or relapsed after at least 2 prior therapies, including a taxane in any setting. Patients who had either a contraindication or were intolerant to taxanes were eligible for Study IMMU-132-05. Earlier adjuvant or neoadjuvant therapy for more limited disease qualified as one of the required prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy.
8. Eligible for 1 of the chemotherapy options for TPC (eribulin, capecitabine, gemcitabine, or vinorelbine) as per investigator assessment
9. Eastern Cooperative Oncology Group (ECOG) status ≤1; A life expectancy of ≥3 months
10. Adequate haematology without transfusional support (hemoglobin >9 g/dL, absolute neutrophil count >1,500 cells/µL; platelets >100,000 cells/µL).
11. Adequate renal and hepatic function defined as
    - Creatinine clearance of >60 mL/min
    - Bilirubin ≤1.5 X ULN
    - Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤2.5X ULN or ≤5X ULN if known liver metastases
    - Serum albumin ≥3 g/dL

12. All toxicity at study entry ≤ grade 1 by Common Terminology Criteria for Adverse Events (CTCAE) v4.0, except for alopecia and ≤grade 2 peripheral neuropathy
13. Completed all prior cancer treatments at least 2 weeks prior to randomisation. Prior antibody treatment for cancer must have been completed at least 3 weeks prior to randomisation.
14. Prior investigational agents were permitted, provided completion to the timeframes above.
15. A life expectancy of 3 months or greater in the opinion of the investigator

Exclusion criteria (excerpt)

- Women who were pregnant or lactating
- Women of childbearing potential or fertile men unwilling to use highly effective contraception during study and up to 3 months after treatment discontinuation in women of child-bearing potential and 6 months in males post last study drug
- Gilbert´s disease
- Patients with prior malignancies must have had at least a 3-year disease-free interval (non-melanoma skin cancer or carcinoma in situ of the cervix were eligible).
- HIV positive; Hepatitis B or hepatitis C positive infection
- History of any of the following:
    - Previously received irinotecan (*Note*: introduced with amendment 4)
    - Unstable angina, myocardial infarction, or congestive heart failure present within 6 months of randomisation or a clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy
    - Clinically significant active chronic obstructive pulmonary disease or other moderate-to-severe chronic respiratory illness present within 6 months of randomisation
    - Clinically significant bleeding, intestinal obstruction, or gastrointestinal perforation within 6 months of randomisation
- Infection requiring IV antibiotic use within 1 week of randomisation
- Active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- Received a live vaccine within 30 days of randomisation (amendment 4)
- Rapid deterioration during screening prior to randomisation (eg, significant change in performance status, ≥20% decrease in serum albumin levels, unstable pain symptoms requiring modifications in analgesic management) (amendment 4)
- Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, were likely to confound study interpretation or prevent completion of study procedures and follow-up examinations

Treatments

Prophylactic antiemetic drugs for both treatment arms

Prior to the administration of either SG or TPC, patients were administered a 2- or 3-drug combination regimen (eg, dexamethasone with either a 5-HT3 receptor antagonist or a NK1 receptor antagonist and other drugs as indicated) for prevention and treatment of chemotherapy-induced nausea and vomiting.

All patients were given additional medications for prevention and treatment of nausea, vomiting, and diarrhoea for use at home.

SG arm

Premedication to prevent infusion reactions with sacituzumab govitecan (SG), including antipyretics, H1 and H2 blockers, or corticosteroids (50 mg hydrocortisone or equivalent orally or intravenously [IV]), was strongly recommended.

SG 10 mg/kg was administered on Days 1 and 8 of a 21-day treatment cycle as a slow IV infusion either by gravity or with an infusion pump.

The initial infusion was administered slowly and incrementally advanced if vital signs were stable and in the absence of infusion reactions. If infusion reactions or vital sign changes occurred, the infusion rate was either slowed, interrupted, or terminated.

Table 21 **Infusion Rate Guidelines for Sacituzumab Govitecan**

Infusion Rate	Infusion #1	Subsequent Infusions
Initial rate (first 15 min)	50 mg/hr or less	100 to 200 mg/hr
Incremental rate (advance every 15-30 min)	50 mg/hr	100 to 200 mg/hr
Maximum recommended rate	500 mg/hr	1,000 mg/hr

During the course of the study (in April 2019) the pharmacy manual of study IMMU-132-05 was updated with simplified administration instructions (first infusion over 3 hours and subsequent infusions over 1 to 2 hours if tolerated), which is also reflected in the SmPC.

TPC arm

- Eribulin 1.4 mg/m² at North American sites and 1.23 mg/m² at European sites IV over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle
    - Lower doses were administered on the same schedule to patients with moderate hepatic impairment (ie, Child-Pugh B; 0.7 mg/m^2 and 0.67 mg/m^2 for NA and EU sites, respectively).
- Capecitabine 1,000 to 1,250 mg/m² orally BID for 2 weeks followed by 1 week rest period
- Gemcitabine 800-1,200 mg/m² IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle
- Vinorelbine 25 mg/m² weekly IV injection over 6-10 minutes

Dose Reduction, Treatment Interruption, or Termination

Sacituzumab Govitecan

Dose reductions, treatment interruptions, or permanent discontinuations of SG were allowed in the event of toxicity.

The first dose of SG on Day 1 of Cycle 1 was not administered if a patient had ≥grade 2 neutropenia or ≥grade 2 GI toxicity (either disease related or from prior therapy); treatment was withheld until resolution to grade 1 or lower. If recovery to ≤grade 1 required more than a 3-week delay, the patient was withdrawn from the study.

Treatment was permanently discontinued if a patient had any ≥grade 3 infusion reactions that occurred after premedication with antihistamines, H2 blockers, and steroids.

If ≥grade 3 toxicity was present on a scheduled treatment day, SG was not administered. If recovery to ≤grade 1 delayed the next dose by only 1, 2, or 3 weeks, SG treatment was resumed (see Table below). If recovery to ≤grade 1 required more than a 3-week delay, treatment was permanently discontinued.

The development of grade 4 neutropenia ≥7 days, grade 3 febrile neutropenia, and grade 3 or grade 4 non-haematologic toxicity (Table below), despite medical treatment, required permanent dose reduction for that patient by 25% of the assigned dose for first occurrence, 50% of the initial assigned dose for the second occurrence, and, treatment discontinuation for the third occurrence. The SG dose was not re-escalated after reduction.

Table 22 **Sacituzumab Govitecan Dose Reduction and Discontinuation**

Dose	10 mg/kg IV on day 1 and 8 of a 21-day cycle			
Dose reduction	Infusion reaction	Grade 2: stopped for 15 min or until resolution then resumed at a slower rate Grade 1: slow infusion rate		
		Any infusion reaction must have resolved to <grade 1 before the next scheduled infusion		
	Hematologic toxicity-used growth factors at any time as clinically indicated, including prophylactically	If a patient had ≥grade 2 neutropenia on Cycle 1 Day 1, treatment was withheld until ≤grade 1. If delayed more than 3 weeks, the patient was discontinued from the study.		
		If a patient had ≥grade 3 neutropenia in subsequent treatment cycles, treatment was withheld until ≤grade 1 and growth factors were administered as clinically indicated. Patients were assessed weekly for grade 3 and bi-weekly for grade 4. If delayed more than 3 weeks, the patient was discontinued from the study.		
		In the event of ≥grade 3 neutropenia on the scheduled treatment day: Resumed treatment without dose reduction if delay was 1 week only Resumed treatment without dose reduction with addition of growth factors if delay was 2 or 3 weeks (also recommended for delays greater than 1 week) Resumed treatment with a dose reduction if patient was already receiving growth factors		
		Dose reduction scheme		
		Grade 4 neutropenia ≥7 days, grade 3 febrile neutropenia	First occurrence	Added growth factors
			Second occurrence	25% reduction
			Third occurrence	50% reduction
			Fourth occurrence	Discontinued
	GI toxicity	If a patient experienced ≥grade 2 GI toxicity on Cycle 1 Day 1, treatment was withheld until ≤grade 1. If delayed more than 3 weeks, the patient was discontinued from the study.		
		If a patient experienced ≥grade 3 GI toxicity in subsequent treatment cycles, treatment was withheld until ≤grade 1. Patient was assessed weekly for grade 3 and bi-weekly for grade 4. If delayed more than 3 weeks, the patient was discontinued from the study.		
		In the event of GI toxicity >grade 3 on the time of scheduled treatment day: Resumed treatment without dose reduction if delay was 1 week only Resumed treatment without dose reduction if delay was 2 or 3 weeks		
	Non-hematologic toxicity	**Dose reduction scheme**		
		-Grade 4 non-hematological toxicity of any duration -Any >grade 3 nausea, vomiting or diarrhea not controlled by antiemetics and antidiarrheal agents ->Grade 3 non-hematologic toxicity >48 h despite optimal medical treatment -Grade 3 non-hematologic toxicity that delayed dose by 2-3 weeks for recovery to <Grade 1	First occurrence	25% reduction
			Second occurrence	50% reduction
			Third occurrence	Discontinued
Discontinuation	Grade 3-4 infusion reaction and any delay more than 3 weeks			

GI=gastrointestinal; h=hours; IV=intravenous

Treatment of Physician's Choice

Specific recommendations for dose reductions, treatment interruptions, or permanent discontinuations in the event of toxicity were provided for all chemotherapeutic agents in the study protocol.

Objectives

Primary objective

The primary objective of the study was to compare the efficacy of SG to the treatment of physician's choice (TPC) as measured by independently-reviewed progression-free survival (PFS) in patients with locally-advanced or metastatic TNBC previously treated with at least 2 systemic chemotherapy regimens for unresectable, locally-advanced or metastatic disease and without brain metastasis at baseline (brain metastasis negative [BM-ve] Population).

Secondary objectives

- PFS for the Intent-to-Treat (ITT) Population
- Overall survival (OS) in both the ITT population and in the subgroup without brain metastasis
- Independently-determined objective response rate (ORR), duration of response (DOR), and time to onset of response (TTR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
- Quality of life (QOL)
- Safety, including adverse events (AEs), safety laboratories and evaluations, incidence of dose delays and dose reductions, and treatment discontinuations due to AEs

Outcomes/endpoints

Primary endpoint:

PFS by Independent Review Committee (IRC) assessment per RECIST v1.1 in patients without brain metastasis at baseline

Secondary endpoints:

Secondary endpoints were analysed in the BM-ve and ITT Populations by IRC assessment (assessment by investigator as supportive sensitivity analyses)

- PFS, time from randomisation until objective tumor progression or death, whichever came first
- OS (overall survival), time from randomisation until death
- ORR (objective response rate), percentage of patients who had either a confirmed CR or PR
- TTR (time to response), time from randomisation or the start of study treatment to the first recorded objective response (ie, CR or PR)
- DOR (duration of response), number of days between the first date showing a documented response of CR or PR and the date of progression or death
- CBR (clinical benefit rate), percentage of patients with either CR, PR, or stable disease (SD) with a duration of ≥6 months
- Quality of life, assessed using the EORTC QLQ-C-30

Sample size

The study was planned to randomize 488 patients. The primary analysis was performed when 425 IRC-PFS events have occurred in the ITT population and 315 or more PFS events in the BM-ve population. Assuming at most 15 % patients have brain metastases and there are 13 % or fewer IRC events compared to investigator review, it would be expected that there are at least 315 IRC events in the BM-ve Population at the time 425 investigator PFS events have been observed amongst all randomised.

The PFS power calculation based on the assumption of a median PFS of 3 months in the control TPC group, a 24 months enrollment period, and that the primary analysis was performed after at least 4 months. If the true hazard ratio was 0.6667 in the IRC review of the BM-ve population, the study have had at least 95% power to detect a statistically significant improvement in PFS, with a two-sided type-1-error of 5%, if data were analysed after 315 IRC PFS.

An interim analysis for OS analyses was planned at the same time as the PFS analysis after, and the final analysis after at least 330 deaths have occurred in the BM-ve population (approx. at 17 months follow up). Further assumptions on the OS power calculation was a median OS time of 10 months in the control arm, and 72 % of the planned number of deaths in BM-ve population have occurred at the time of interim analysis. If the true hazard ratio was 0.7 in the BM-ve population, there is a 89.5% power to detect an improvement in OS in the BM-ve population, with a two-sided 5% type-I-error rate.

Randomisation

Patients were randomised in a 1:1 allocation to receive either sacituzumab govitecan (IMMU-132) at a dose level of 10 mg/kg on days 1 and 8 of a 21-day cycle or Treatment of Physician' Choice (TPC). Randomisation was stratified by means of an interactive web-based response system (IWRS) according to the number of prior treatments (2-3, >3), presence of known brain metastases at study entry (yes/no), and North America vs Rest of the world.

Blinding (masking)

This was an open label study.

Statistical methods

Analysis population:

The primary analysis population for efficacy was planned to be the subset of the ITT population without brain metastases at baseline, called BM-ve Population, defined as all randomised patients. Patients were assigned to the treatment group to which they were randomised.

The ITT population was defined as all patients who have been randomised to the trial. Patients were assigned to the treatment group to which they were randomised. Data was analysed in the ITT population after the primary hypothesis on the BM-ve Population has been tested.

The Safety population was defined as all patients administered at least one dose of IMMU-132 or TPC. Safety endpoints were planned to be analysed using the safety population.

The PK population was defined as a subset of approximately 20 patients randomised to IMMU-132 who received intensive PK serum sampling schedules and deemed to have sufficient PK, safety and efficacy data to enable population PK.

Primary endpoints:

The primary endpoint was defined as Progression-Free Survival (PFS) determined by IRC. Further endpoints under the type-I-error control are OS in the BM-ve population, PFS in the ITT population, and OS in the ITT population. Further secondary endpoints are IR-ORR, duration of response and time to onset of response according to RECIST 1.1 criteria, as well as quality of life and safety.

For the definition of PFS the following censoring rules were applied:

Case	Primary Analysis PFS Definition	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3	Sensitivity Analysis 4 (Based on investigator assessed PFS)
No adequate response assessment after Randomisation					
Died prior to second scheduled assessment	Date of Death	Date of Death	Date of Death	Date of Death	Date of Death
Did not die or died after missing 2 or more scheduled assessments	Censored at Randomisation	Progressed at date of Death if died; or censored at date of randomisation if did not die	Censored at Randomisation	Censored at randomisation if did not die, progressed on the date of 2nd missed scheduled assessment	Censored at Randomisation
Continued scheduled response assessments until objective PD or death					
PD at scheduled assessment, or prior to missing 2 scheduled successive assessments	Date of PD	Date of PD	Date of PD if at scheduled assessment; Date of next scheduled assessment if PD between scheduled assessments or prior to missing 2 scheduled successive assessments. (including PD that occurred at End of	Date of PD	Date of PD if at scheduled assessment; Date of next scheduled assessment if PD between scheduled assessments or prior to missing 2 scheduled successive assessments.

			Treatment/Early Withdrawal visits)		
Clinical PD indicated between scheduled assessments or prior to missing 2 scheduled successive assessments	N/A	N/A	N/A	N/A	Date of next scheduled assessment
Death between scheduled assessments, or prior to missing 2 scheduled successive assessments	Date of Death	Date of Death	Date of Death	Date of Death	Date of Death
PD or death after missing 2 or more scheduled assessments	Censored at Date of last adequate response assessment before missed assessments	Date of PD or Death	Censored at Date of last adequate response assessment before missed assessments	Progressed at 2nd missed scheduled assessment	Censored at Date of last adequate response assessment before missed assessments
Treatment discontinuation for undocumented progression, toxicity or other reason	Included in other scenario	Included in other scenario	Included in other scenario	Progressed at the time of discontinuation	Included in other scenario
Continued scheduled response assessments without objective PD or death					
Initiated other anti-cancer treatment	Censored at Date of last adequate response assessment with documented nonprogression prior to starting other anti-cancer treatment	Date of documented progression or death if occurred	Censored at Date of last adequate response assessment with documented non-progression prior to starting other anticancer treatment	Progressed on the date of start of anticancer treatment	Censored at Date of last adequate response assessment with documented nonprogression prior to starting other anti-cancer treatment
No objective PD or death	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment

Primary analysis:

A stratified log-rank test stratified by randomisation strata was used to compare the treatment groups for the time-to-event endpoints of PFS and Overall Survival Estimates of hazard ratios and 95% confidence intervals of PFS and OS were based on a stratified Cox proportional hazard regression model with treatment arm as the only covariate. Results were illustrated by Kaplan-Meier curves, median PFS and its associated 95% Cis determined by the Brookmeyer and Crowley method with log-log transformation.

Overall survival were planned to be analysed both at the time of the primary PFS analysis and, if not statistically significant at this time, later when a total of 330 deaths have occurred in the primary analysis population of randomised patients without brain metastases.

Unless otherwise specified missing data were not imputed or "carried-forward".

Sensitivity analyses for PFS:

Sensitivity analyses of PFS in the BM-ve Population and ITT Population will be generated following the FDA Guidance of Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018) and Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (April 2015). The differences between the primary analysis PFS definition and comparisons of their censoring rules are illustrated in the table above.

Multiplicity:

The type I error across populations and the two key endpoints of IRC assessed PFS and overall survival (OS) was strictly controlled at a two-sided alpha of 0.05 by a hierarchical testing strategy in the following order:

(1) PFS BM-ve, (2) OS BM-ve, (3) PFS ITT, and (4) OS ITT.

If fewer than 30 patients with brain metastases are recruited, analyses in the ITT population were planned to be removed from the hierarchy.

Interim Analyses:

Up to Version 8 of the statistical analysis plan one interim analysis of overall survival was planned at the time of the final PFS analysis with an appropriate alpha spending approach (Lan-DeMets spending function with O'Brien/Fleming stopping boundaries). The final analysis of PFS events was defined at 315 IRC-PFS events in the BM-ve population when 72% of the planned number of deaths was expected. The final OS analysis was planned when 330 deaths in the BM-ve population have occurred. If the final number of events differs from expected, the final significance level was planned to be adjusted so that the overall alpha is controlled given the significance level applied at the first analysis.

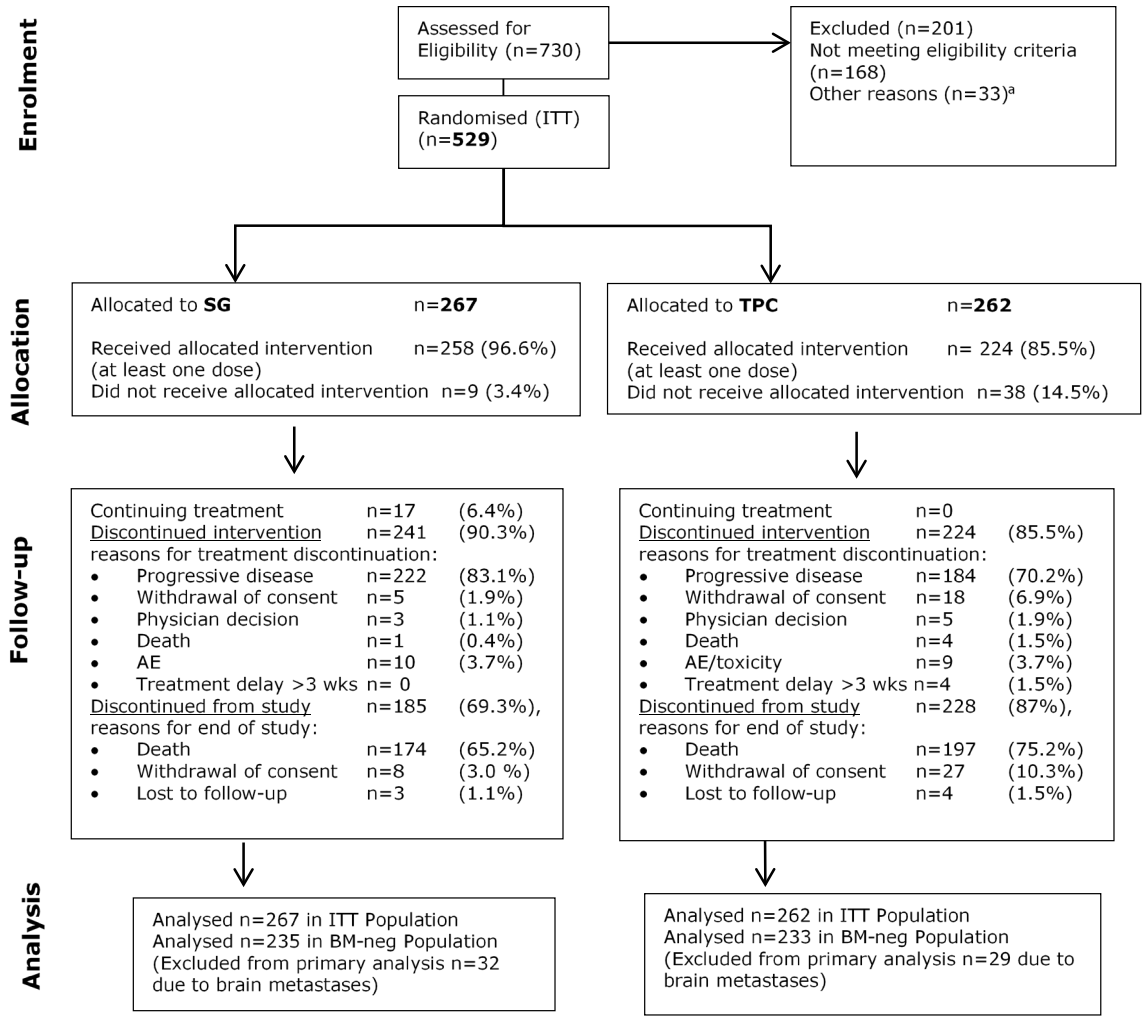
With version 9 of the statistical analysis plan (April 06, 2020), which was implemented one months after the data base cutoff, the primary analysis was changed to only one analysis for OS and PFS at 302 of the 315 (or 96%) targeted PFS events. This analysis should serve as the final analysis for PFS and OS for both the BM-ve and ITT populations. The two-sided significance level for PFS was set to be 0.0443 as well as for the subsequent testing steps.

The number of deaths in the primary BM-ve population was close to reaching full maturity (316 of the 330, or 96% of the deaths the protocol specified in the primary BM-ve population for the final OS analysis), thus this analysis was also served as the final analysis for the secondary endpoint of OS.

Results

Participant flow

Figure 17 Study Participant flow (ITT Population)



Note: The denominator for percentages is the number of patients in the ITT Population for each treatment group

Recruitment

Study IMMU-132-05 recruited patients from 82 sites in North America and Europe. The first patient was enrolled 03 November 2017 and the last participant was randomised 17 September 2019. As of the data cut-off date of 11 March 2020, the median follow-up duration was 10.6 months for participants in the SG arm

compared with 6.3 months the TPC arm (ITT population). A higher percentage of patients in the SG group compared with the TPC group are alive and in survival follow-up (28.5% and 14.9%, respectively).

Screen failures

Of the 730 patients screened for the study, n=201 (27.5%) were not randomised. The most frequent reasons for screening failure (in ≥10 patients) were the lack of stable CNS disease for at least 4 weeks (12.9%), inadequate renal and hepatic function (12.4%), no confirmed TNBC per ASCO/CAP criteria (11.9%), no measurable disease (8.0%), inadequate haematology (6%), and ECOG PS of >1 (5%). Of note, 30% of all patients with brain metastases failed screening due to lack of stable CNS disease for at least 4 weeks;

A total of 61 patients with brain metastases were included in the study: 32 in the SG group and 29

in the TPC group (please see also baseline data). These patients were excluded from the primary analysis population for efficacy. The primary efficacy analysis was performed in the Brain metastasis negative (BM-ve) Population that consisted of 235 patients in the SG group and 233 patients in the TPC group who had no brain metastases at baseline.

Imbalance in withdrawals

A higher percentage of patients in the TPC group compared with the SG group were randomised but not treated (14.5% and 3.4%, respectively). Similarly, a higher proportion of patients discontinued treatment due to withdrawal of consent in the TPC group than in the SG group (6.9% vs. 1.9% in the ITT population, respectively). No further information on the reasons for non-treatment of randomised patients were collected at study enrolment.

Conduct of the study

Protocol amendments

Protocol Amendment Date No. of Patients Enrolled	**Key Changes**
Amendment 1 05 May 2017 no patients	• Added guidelines for infusion reactions, dose delay, dose reduction and treatment discontinuation • Added the inclusion criterion that all patients should have been previously treated with taxane regardless of disease stage (adjuvant, neoadjuvant or advanced) when it was given • Revised the inclusion criterion that patients with treated, non-progressive brain metastases must have stable MRI scans for at least 3 months, including within 4 weeks of study entry • Added collection of *BRCA1* and *BRCA2* mutational status, if known • Removed baseline brain imaging requirement to rule out brain metastases • Removed the CTCAE PRO questionnaire
Amendment 2 31 Jul 2017 246 patients	• Revised the CT/MRI scans from every 6 weeks for 24 weeks to every 6 weeks for 36 weeks

Amendment 3 22 Feb 2018 no patients	• Allowed patients with locally advanced TNBC to be enrolled • Sample size increased from 328 to 488 patients • Defined as <10% expression for ER and PR and negative for human epidermal growth factor receptor 2 HER2 by in-situ hybridization • Added the secondary objective and secondary efficacy endpoint of PFS in the ITT Population • Added that ORR and PFS would also be determined by the investigator • Added PFS and OS in the ITT Population • Added an exploratory analysis of Trop-2 tumor expression and efficacy • Increased the sample size and number of participating sites • Limited the number of patients with brain metastasis at 15% • Added eligibility requirements for patients who had either a contraindication or were intolerant to taxanes • Excluded patients who had received >5 prior standard of care chemotherapies for locally advanced or metastatic disease • Excluded patients with active chronic inflammatory bowel disease (ulcerative colitis, Crohn disease) and patients with a history of bowel obstruction • Excluded patients who had received a live vaccine within 30 days of randomization
Amendment 4 11 May 2018 382 patients	• Removed secondary objective and secondary efficacy endpoint of PFS by investigator assessment • Added inclusion criteria that defined stable CNS disease for patients with brain metastasis • Removed the exclusion of patients who had received >5 prior standard of care chemotherapies for locally advanced or metastatic disease • Excluded patients who had previously received irinotecan • Excluded patients with rapid deterioration during screening • Added a hierarchical testing strategy for efficacy
Amendment 5 14 June 2019 no patients	• Removed assessment of other tumor markers • Clarified that both total and free SN-38 would be assessed • Added that patients who were receiving clinical benefit from SG at the end of the study would be enrolled in a rollover study to ensure continued access to SG • Added that disease progression was not to be reported as an AE • Removed the interim futility analysis for PFS • Added that the significance level for the final analysis of OS in the ITT population would be determined by the Lan-DeMets spending function to ensure alpha was controlled at a 2-sided alpha of 0.05[a]
Amendment 6 26 August 2019 220 patients	• Clarified PK sampling time points

[a]Subsequently changed to a 2-sided alpha of 0.0443 in a SAP amendment since 302 of the prespecified 315 PFS events was used in the final analysis.

* The number of patients enrolled present a count of the participants who were active under each protocol amendment

Changes to the Statistical Analysis Plan

The statistical analysis plan was amended several times. The main changes regarding the statistical analysis plan were the implementation of the BM-ve population in the testing hierarchy, the increase in sample size, and the removal of the planned PFS interim analysis. At the end of the study after the data base cutoff the statistical analysis plan was adapted for declaring the interim OS-analysis to the final analysis.

Protocol deviations

Table 23 Summary of important protocol deviation categories for Study IMMU-132-05 (ITT Population)

Protocol Deviation Category/ Subcategory/ Coded Term	**SG (N = 267)**	**TPC (N = 262)**	**Total (N = 529)**
Participants with at least 1 Important Protocol Deviation	92 (34.5%)	104 (39.7%)	196 (37.1%)
Study Conduct/Procedures	55 (20.6%)	51 (19.5%)	106 (20.0%)
Inclusion/Exclusion Criteria	23 (8.6%)	27 (10.3%)	50 (9.5%)
Dose Formulation/Dose Administration	29 (10.9%)	19 (7.3%)	48 (9.1%)
Screening	5 (1.9%)	7 (2.7%)	12 (2.3%)
Study Assessment	3 (1.1%)	5 (1.9%)	8 (1.5%)
Study Restrictions/Withdrawal Criteria	1 (0.4%)	0	1 (0.2%)
Informed Consent	29 (10.9%)	55 (21.0%)	84 (15.9%)
Investigational Product	16 (6.0%)	1 (0.4%)	17 (3.2%)
Handling/Storage/Retention	12 (4.5%)	1 (0.4%)	13 (2.5%)
Dispensing/Accountability	2 (0.7%)	0	2 (0.4%)
Supply	2 (0.7%)	0	2 (0.4%)
Safety	9 (3.4%)	8 (3.1%)	17 (3.2%)
Other	3 (1.1%)	2 (0.8%)	5 (0.9%)

The denominator for percentages is the number of participants in the ITT population for each treatment group. Participants with multiple categories, subcategories, or coded terms were counted once for each category, subcategory, and coded term.

Baseline data

Table 24 ***Summary of Demographics (ITT Population)***

	IMMU-132 (N = 267)	TPC (N = 262)	Total (N = 529)
Age at Study Entry (years)			
n	267	262	529
Mean (SD)	54.0 (11.34)	54.0 (11.69)	54.0 (11.50)
Median	54.0	53.0	54.0
Minimum	27	27	27
Maximum	82	81	82
Age Group, n (%)			
< 50 years	96 (36.0)	89 (34.0)	185 (35.0)
50-64 years	122 (45.7)	121 (46.2)	243 (45.9)
>= 65 years	49 (18.4)	52 (19.8)	101 (19.1)
Sex, n (%)			
Male	2 (0.7)	0	2 (0.4)
Female	265 (99.3)	262 (100.0)	527 (99.6)
If Female, Childbearing Potential, n (%)			
n	265	262	527
Yes	70 (26.4)	60 (22.9)	130 (24.7)
No	195 (73.6)	202 (77.1)	397 (75.3)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	13 (4.9)	9 (3.4)	22 (4.2)
Black	28 (10.5)	34 (13.0)	62 (11.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	215 (80.5)	203 (77.5)	418 (79.0)
Other	11 (4.1)	16 (6.1)	27 (5.1)
Ethnicity, n (%)			
Hispanic or Latino	20 (7.5)	25 (9.5)	45 (8.5)
Not Hispanic or Latino	234 (87.6)	226 (86.3)	460 (87.0)
Not Reported	7 (2.6)	5 (1.9)	12 (2.3)
Unknown	6 (2.2)	6 (2.3)	12 (2.3)
Body Mass Index (BMI) (kg/m^2) [a]			
n	234	233	467
Mean (SD)	27.00 (6.590)	26.67 (6.104)	26.83 (6.347)
Median	25.74	25.88	25.88
Minimum	15.0	14.6	14.6
Maximum	49.3	48.2	49.3

Note: Denominators for percentages are based on the number of Brain Metastasis Negative patients with non-missing data in each treatment group for the relevant variable.
[a] BMI is calculated as BMI (kg/m^2) = (weight in kg) / (height in m)^2.

Table 25 **Summary of Baseline Disease Characteristics (ITT Population)**

	IMMU-132 (N = 267)	TPC (N = 262)	Total (N = 529)
Number of Prior Chemotherapies for Randomization Stratification, n (%)[a]			
2-3	184 (68.9)	181 (69.1)	365 (69.0)
>3	83 (31.1)	81 (30.9)	164 (31.0)
Presence of Known Brain Metastases at Study Entry for Randomization Stratification, n (%)[a]			
Yes	32 (12.0)	29 (11.1)	61 (11.5)
No	235 (88.0)	233 (88.9)	468 (88.5)
Region for Randomization Stratification, n (%)[a]			
North America	175 (65.5)	172 (65.6)	347 (65.6)
Rest of World	92 (34.5)	90 (34.4)	182 (34.4)
Estrogen Receptor (ER) Less Than 1% of Tumor Cells, n (%)			
Yes	267 (100.0)	262 (100.0)	529 (100.0)
No	0	0	0

Progesterone Receptor (PR) Less Than 1% of Tumor Cells, n (%)			
Yes	267 (100.0)	262 (100.0)	529 (100.0)
No	0	0	0
Diagnosis of HER2 Negativity, n (%)			
IHC 0	145 (54.3)	141 (53.8)	286 (54.1)
IHC 1	45 (16.9)	47 (17.9)	92 (17.4)
FISH	77 (28.8)	74 (28.2)	151 (28.5)
Original Diagnosis Triple Negative Breast Cancer, n (%)			
Yes	192 (71.9)	180 (68.7)	372 (70.3)
No	75 (28.1)	82 (31.3)	157 (29.7)
Time from Diagnosis of Stage 4 to Study Entry (months)[b]			
Mean (SD)	21.74 (21.202)	22.35 (20.353)	22.04 (20.768)
Median	16.82	15.82	16.23
Minimum	0.1	-0.4	-0.4
Maximum	202.9	140.1	202.9
UGT1A1 Genotype (IMMU-132 only), n (%)			
*1/*1	113 (42.3)		
*1/*28	96 (36.0)		
*28/*28	34 (12.7)		
Other	7 (2.6)		
Missing	17 (6.4)		
BRCA 1 Mutational Status, n (%)			
Negative	156 (58.4)	155 (59.2)	311 (58.8)
Positive	16 (6.0)	16 (6.1)	32 (6.0)
Inconclusive	1 (0.4)	0	1 (0.2)
Not Done	94 (35.2)	91 (34.7)	185 (35.0)
BRCA 2 Mutational Status, n (%)			
Negative	164 (61.4)	159 (60.7)	323 (61.1)
Positive	5 (1.9)	8 (3.1)	13 (2.5)
Inconclusive	3 (1.1)	3 (1.1)	6 (1.1)
Not Done	95 (35.6)	92 (35.1)	187 (35.3)
BRCA 1/BRCA 2 Mutational Status, n (%)[c]			
Negative	150 (56.2)	146 (55.7)	296 (56.0)
Positive	20 (7.5)	23 (8.8)	43 (8.1)
Screening ECOG Performance Status, n (%)			
0: Normal Activity	121 (45.3)	108 (41.2)	229 (43.3)
1: Symptoms but Ambulatory	146 (54.7)	154 (58.8)	300 (56.7)
Treatment of Physician Choice, n (%)[d]			
Eribulin	115 (43.1)	139 (53.1)	254 (48.0)
Capecitabine	48 (18.0)	33 (12.6)	81 (15.3)
Gemcitabine	46 (17.2)	38 (14.5)	84 (15.9)
Vinorelbine	58 (21.7)	52 (19.8)	110 (20.8)
Number of Prior Systemic Therapies			
n	267	262	529
Mean (SD)	4.5 (2.05)	4.6 (2.14)	4.5 (2.09)
Median	4.0	4.0	4.0
Minimum	2	2	2
Maximum	17	14	17
Number of Prior Systemic Therapies, n (%)			
2	33 (12.4)	32 (12.2)	65 (12.3)
3	66 (24.7)	60 (22.9)	126 (23.8)
4	59 (22.1)	62 (23.7)	121 (22.9)
5	40 (15.0)	44 (16.8)	84 (15.9)
6	29 (10.9)	24 (9.2)	53 (10.0)
7	19 (7.1)	14 (5.3)	33 (6.2)
8	9 (3.4)	9 (3.4)	18 (3.4)
9	7 (2.6)	8 (3.1)	15 (2.8)
10	2 (0.7)	5 (1.9)	7 (1.3)
11	2 (0.7)	2 (0.8)	4 (0.8)
14	0	2 (0.8)	2 (0.4)
17	1 (0.4)	0	1 (0.2)

Prior PD-1/PD-L1 Therapy, n (%)			
Yes	79 (29.6)	74 (28.2)	153 (28.9)
No	188 (70.4)	188 (71.8)	376 (71.1)
Setting of Prior Systemic Therapies, n (%)			
Adjuvant	161 (60.3)	148 (56.5)	309 (58.4)
Neo-adjuvant	124 (46.4)	125 (47.7)	249 (47.1)
Metastatic	258 (96.6)	260 (99.2)	518 (97.9)
Locally Advanced Disease	10 (3.7)	5 (1.9)	15 (2.8)
Prior Radiotherapy (Non-Brain), n (%)			
Yes	223 (83.5)	206 (78.6)	429 (81.1)
No	44 (16.5)	56 (21.4)	100 (18.9)
Prior Radiotherapy (Brain), n (%)			
Yes	32 (12.0)	31 (11.8)	63 (11.9)
No	235 (88.0)	231 (88.2)	466 (88.1)
Baseline serum bilirubin, n (%)			
Normal (<= ULN)	253 (94.8)	218 (83.2)	471 (89.0)
>1-1.5 ULN (>1 and <= 1.5x ULN)	5 (1.9)	4 (1.5)	9 (1.7)
>1.5 ULN (> 1.5x ULN)	0	1 (0.4)	1 (0.2)

Note: The denominator for percentages is the number of patients in the ITT population for each treatment group.
[a] The randomization strata data are based on IXRS
[b] Time from diagnosis is defined as number of days divided by 30.4375 from date of diagnosis to date of study entry.
[c] Positive denotes patient is either BRCA1 positive or BRCA2 positive. Negative denotes patient is both BRCA1 negative and BRCA2 negative.
[d] As specified by the investigator prior to randomization.

Patients with locally advanced TNBC were allowed to be enrolled with protocol amendment 4 (May 2018), while the initial study protocol required metastatic disease. Only a single participant had unresectable locally advanced cancer at the time of study entry in Study IMMU-132-05.

BRCA mutational status were collected at study entry only if available and testing was not required providing information for 65% of the population. Only 8.1% of study participants (n=43) were tested positive for BRCA1 or BRCA2 mutations. Available efficacy data by BRCA status suggest a similar treatment effect across subgroups, although the results do not allow any firm conclusions due to the small number of patients with BRCA positive status (see subgroup results below).

The most frequent prior systemic therapies in the SG and TPC groups were cyclophosphamide (82.8% and 82.4%), anthracycline (81.3% vs. 83.2%), paclitaxel (76.4% and 80.2%), carboplatin (61.4% and 68.3%) and capecitabine (64% vs 69.8%, respectively in the ITT population). Overall, 29.6% and 28.2% of the patients in the SG and TPC groups, respectively, had received prior PD-1/PD-L1 therapy.

The most frequent sites of metastasis in both groups were the liver, lung, and lymph nodes.

Table 26 **Frequent (≥10% in Either Group) Tumor Locations based on IRC Assessment (ITT) and information about brain metastasis**

	IMMU-132 (N = 267)	TPC (N = 262)	Total (N = 529)
Tumor Locations based on IRC, n (%)[e]			
AXILLARY LYMPH NODE	59 (22.1)	78 (29.8)	137 (25.9)
BONE	62 (23.2)	63 (24.0)	125 (23.6)
BREAST	45 (16.9)	50 (19.1)	95 (18.0)
CHEST WALL	51 (19.1)	68 (26.0)	119 (22.5)
HILAR LYMPH NODE	32 (12.0)	37 (14.1)	69 (13.0)
LIVER	107 (40.1)	114 (43.5)	221 (41.8)

LUNG	131 (49.1)	115 (43.9)	246 (46.5)
MEDIASTINAL LYMPH NODE	61 (22.8)	68 (26.0)	129 (24.4)
BRAIN	15 (5.6)	18 (6.9)	33 (6.2)

Note: The denominator for percentages is the number of patients in the ITT population for each treatment group.

Numbers analysed

Table 27 Analysis Populations

	SG n (%)	TPC n (%)	Total n (%)
Patients Screened			730
Patients Randomized (ITT Population)	267	262	529
Patients Randomized but not Treated	9 (3.4)	38 (14.5)	47 (8.9)
Received at Least One Dose of Study Treatment (Safety Population)	258 (96.6)	224 (85.5)	482 (91.1)
Brain Metastasis Negative Population	235 (88.0)	233 (88.9)	468 (88.5)

Note: The denominator for percentages is the number of patients in the ITT Population for each treatment group.
ITT=Intent-to-Treat; PK=pharmacokinetic; SG=sacituzumab govitecan; TPC=treatment of physician's choice

Outcomes and estimation

- **Primary endpoint**

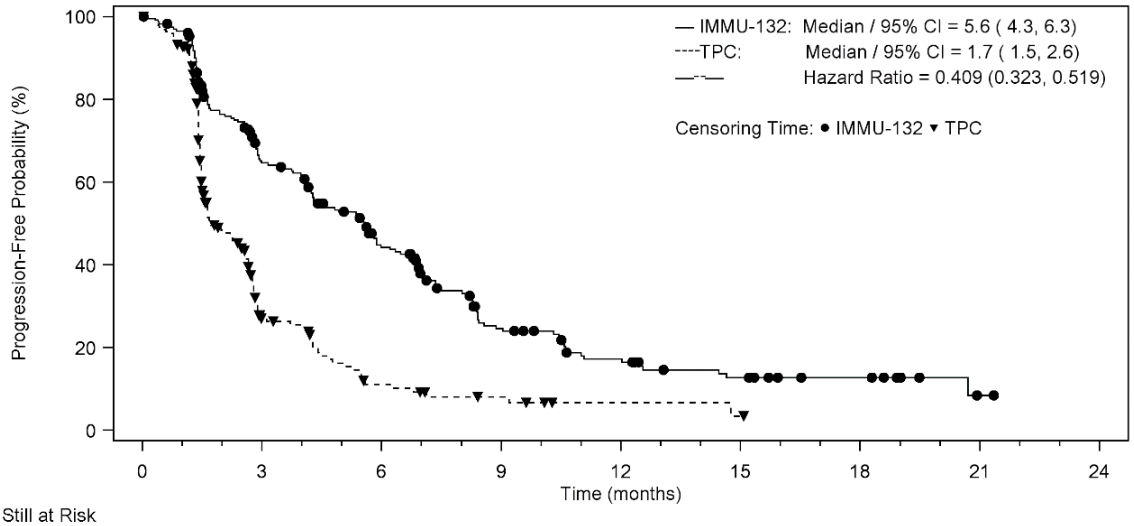
PFS by IRC Assessment in Brain Metastasis negative (**BM-ve**) Population

Table 28 PFS by IRC Assessment per RECIST v1.1 (BM-ve Population)

	SG (N = 235)	TPC (N = 233)	Treatment Comparison
Patients with Events (%)	166 (70.6)	150 (64.4)	
Patients without Events (Censored) (%)	69 (29.4)	83 (35.6)	
Median PFS (months) [a]	5.6	1.7	
95% CI	(4.3, 6.3)	(1.5, 2.6)	
Log-rank p-value (Stratified) [b]			<0.0001
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.409
95% CI for Hazard Ratio			(0.323, 0.519)
PFS Rate (%) at 3 Months (95% CI) [c]	64.6 (57.9, 70.5)	27.0 (20.3, 34.1)	
PFS Rate (%) at 6 Months (95% CI)	44.2 (37.3, 50.9)	11.0 (6.4, 17.1)	
PFS Rate (%) at 9 Months (95% CI)	24.6 (18.5, 31.2)	8.0 (4.0, 13.8)	
PFS Rate (%) at 12 Months (95% CI)	17.2 (11.8, 23.5)	6.7 (3.0, 12.5)	

Note: PFS is defined as the time from the date of randomisation to the date of the first radiological disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases and sensitivity analyses of PFS.
[a] Median PFS is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method.
[b] Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
[c] Estimate and CI for PFS rate at the specified time points are from Kaplan-Meier estimate.
CI=confidence interval; PFS=progression-free survival; SG=sacituzumab govitecan; TPC=treatment of physician's choice
Note: These footnotes are not copied for the following tables if identical

Figure 18 KM Estimates of PFS by IRC Assessment in BM-ve Population in Study IMMU-132-05



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
IMMU-132	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

IMMU-132=SG; TPC=treatment of physician's choice

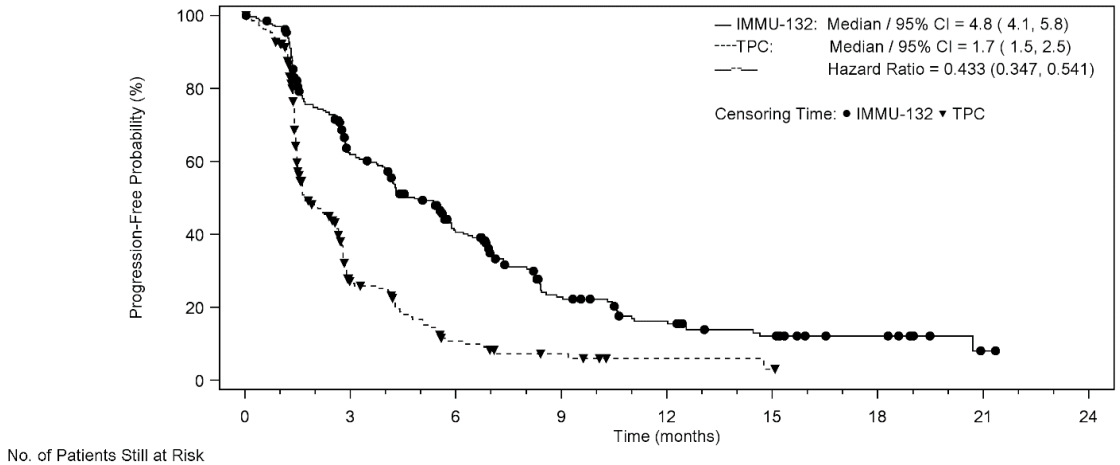
- **Secondary endpoints**

PFS by IRC Assessment in **ITT** Population

Table 29 PFS by IRC Assessment per RECIST v1.1 (ITT Population)

	SG (N = 267)	TPC (N = 262)	Treatment Comparison
Patients with Events (%)	190 (71.2)	171 (65.3)	
Patients without Events (Censored) (%)	77 (28.8)	91 (34.7)	
Median PFS (months) [a]	4.8	1.7	
95% CI	(4.1, 5.8)	(1.5, 2.5)	
Log-rank p-value (Stratified) [b]			<0.0001
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.433
95% CI for Hazard Ratio			(0.347, 0.541)
PFS Rate (%) at 3 Months (95% CI) [c]	61.9 (55.5, 67.6)	27.1 (20.9, 33.8)	
PFS Rate (%) at 6 Months (95% CI)	40.6 (34.2, 46.9)	10.7 (6.4, 16.3)	
PFS Rate (%) at 9 Months (95% CI)	22.8 (17.2, 28.9)	7.2 (3.6, 12.4)	
PFS Rate (%) at 12 Months (95% CI)	16.2 (11.2, 22.0)	6.0 (2.7, 11.2)	

Figure 19 KM Estimates of PFS by IRC Assessment in the ITT Population of Study IMMU-132-05



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
IMMU-132	267	251	184	145	135	110	82	64	55	38	34	25	23	17	16	14	9	8	8	5	3	1	0
TPC	262	199	87	41	37	23	13	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

PFS by **Investigator** Assessment (Sensitivity analyses)

PFS results by investigator assessment were provided for both the BM-ve and ITT Populations: HRs were 0.35 [95% CI: 0.28, 0.44] and 0.38 [95% CI: 0.31, 0.48], in the BM-ve and ITT Population, respectively.

Further sensitivity Analyses of PFS

The pre-specified sensitivity analyses of PFS by IRC and investigator assessment confirm the PFS results for the BM-ve Population and ITT Population (all HRs between 0.33 and 0.55, results not shown).

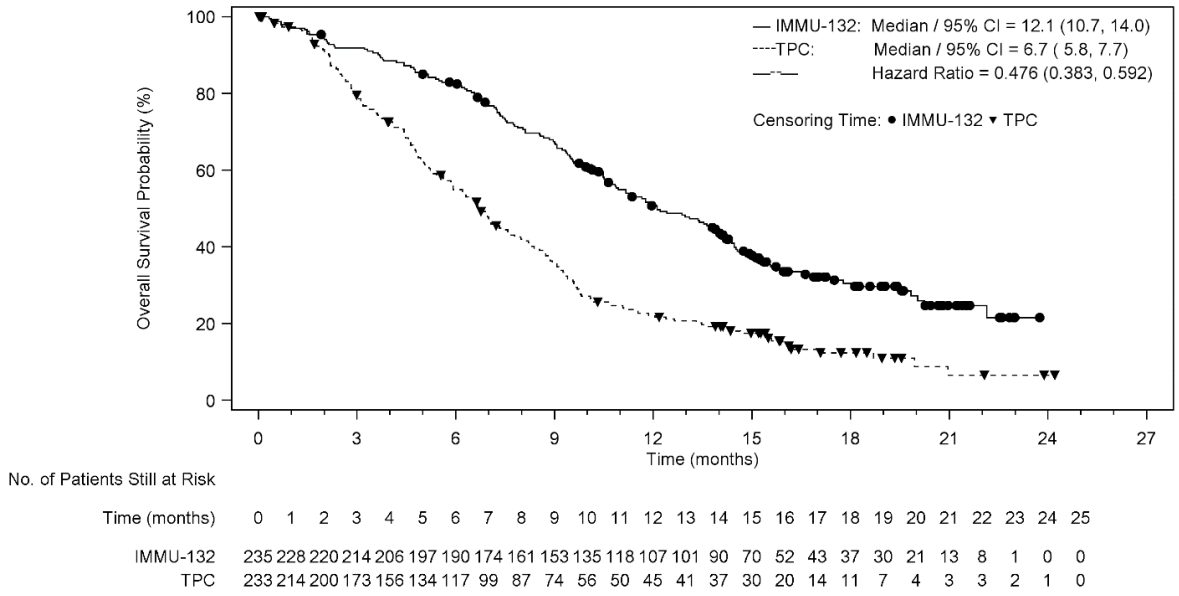
OS in Brain Metastasis negative (**BM-ve**) Population and in **ITT** Population

Table 30 ***Overall Survival (BM-ve and ITT Populations)***

	SG (N = 235)	TPC (N = 233)	Treatment Comparison
BM-ve Population			
Patients with Events (%)	155 (66.0)	185 (79.4)	
Patients without Events (Censored) (%)	80 (34.0)	48 (20.6)	
Median OS (months) [a]	12.1	6.7	
95% CI	(10.7, 14.0)	(5.8, 7.7)	
Log-rank p-value (Stratified) [b]			<0.0001
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.476
95% CI for Hazard Ratio			(0.383, 0.592)
OS Rate (%) at 3 Months (95% CI) [c]	82.4 (76.9, 86.7)	54.9 (48.0, 61.2)	
OS Rate (%) at 6 Months (95% CI)	50.7 (43.9, 57.0)	22.2 (16.8, 28.0)	
OS Rate (%) at 9 Months (95% CI)	30.5 (24.1, 37.1)	12.3 (7.9, 17.7)	
OS Rate (%) at 12 Months (95% CI)	-	6.6 (2.4, 13.6)	
ITT Population			
Patients with Events (%)	179 (67.0)	206 (78.6)	
Patients without Events (Censored) (%)	88 (33.0)	56 (21.4)	
Median OS (months) [a]	11.8	6.9	
95% CI	(10.5, 13.8)	(5.9, 7.7)	
Log-rank p-value (Stratified) [b]			<0.0001
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.508
95% CI for Hazard Ratio			(0.414, 0.624)
OS Rate (%) at 3 Months (95% CI) [c]	79.3 (73.9, 83.7)	55.4 (48.9, 61.4)	
OS Rate (%) at 6 Months (95% CI)	48.8 (42.5, 54.8)	23.0 (17.8, 28.5)	
OS Rate (%) at 9 Months (95% CI)	28.6 (22.6, 34.8)	12.9 (8.7, 18.0)	
OS Rate (%) at 12 Months (95% CI)	-	6.8 (2.8, 13.1)	

Note: OS is defined as the time from date of randomisation to the date of death from any cause. Patients without documentation of death are censored on the date they were last known to be alive.
[a] Median OS is from Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method.
[b] Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies and region.
[c] Estimate and CI for OS rate at the specified time points are from Kaplan-Meier estimate.
BM-ve=brain metastasis negative; CI=confidence interval; ITT=Intent-to-Treat; OS=overall survival; SG=sacituzumab govitecan; TPC=treatment of physician's choice

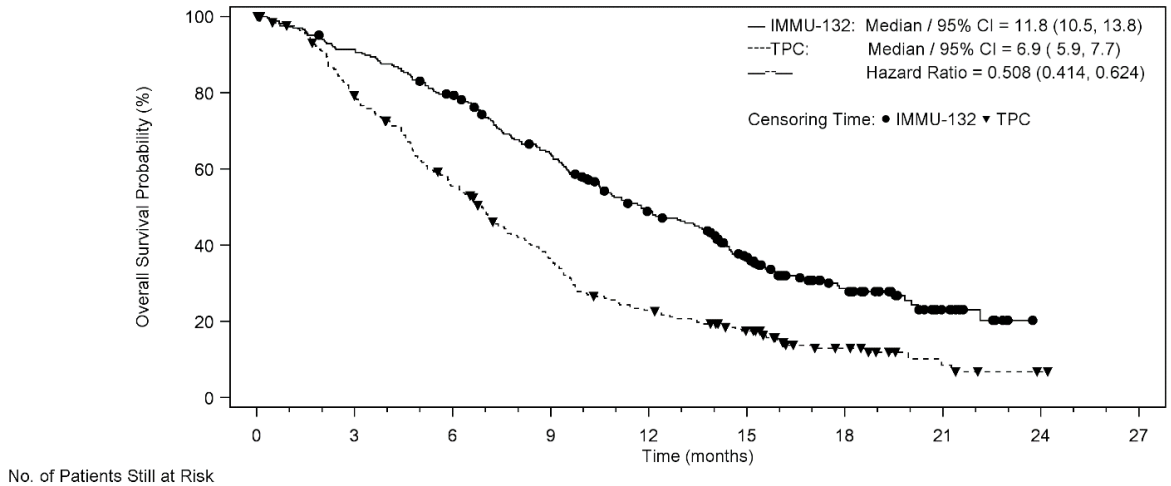
Figure 20 Kaplan-Meier Plot of OS (BM-ve Population)



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
IMMU-132	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Figure 21 Kaplan-Meier Plot of OS (ITT Population)



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
IMMU-132	267	260	250	242	232	219	208	189	174	164	145	127	116	109	98	76	56	46	39	31	21	13	8	1	0	0
TPC	262	239	222	192	174	150	132	113	97	84	64	58	52	46	42	34	24	17	14	9	6	5	3	2	1	0

Objective Response Rate

Table 31 ORR by IRC (BM-ve Population) (confirmed responses)

	SG (N = 235)	TPC (N = 233)	Treatment Comparison
IRC Assessment			
Patients with Measurable Disease at Baseline	230	230	
Objective Response Rate (CR or PR)			
n (%)	82 (34.9)	11 (4.7)	
95% CI (Exact)	(28.8, 41.4)	(2.4, 8.3)	
Odds Ratio			10.859
95% CI			(5.590, 21.095)
p-value			<0.0001
Best Overall Response, n (%)			
Complete Response	10 (4.3)	2 (0.9)	
Partial Response	72 (30.6)	9 (3.9)	
Stable Disease	81 (34.5)	62 (26.6)	
Stable Disease > 6 months	23 (9.8)	9 (3.9)	
Progressive Disease	54 (23.0)	89 (38.2)	
Not Evaluable	18 (7.7)	71 (30.5)	

Note: Denominator for percentages is the number of patients in the Brain Metastasis Negative Population
Note: Exact binomial CI for proportion is based on the Beta distribution. P-value is based on Cochran-Mantel-Haenszel test.
Note: Objective Response is defined as the best confirmed overall response of either CR or PR.
Note: The best overall response is derived based on independent review assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. SD requires a minimum duration of 6 weeks to be classified as SD.
Note: Clinical benefit rate (CBR) is defined as the percentage of patients with a confirmed best overall response of CR or PR and stable disease with a duration of at least 6 months.
CI=confidence interval; CR=complete response; IRC=Independent Review Committee; PR=partial response;

Table 32 ORR in Study IMMU-132-05

	SG	TPC
BM-ve Population	235	233
ITT Population	267	262
ORR by **IRC** assessment in **BM-ve** Population		
Response rate [95% CI exact]	82 (34.9)	11 (4.7)
Odds ratio (95% CI)	10.859 (5.590, 21.095)	
p-value	<0.0001	
ORR by **inv**estigator assessment in **BM-ve** Population		
Response rate [95% CI exact]	80 (34.0) [28.0, 40.5]	15 (6.4) [3.6, 10.4]
Odds ratio (95% CI)	10.859 (5.590, 21.095)	
p-value	<0.0001	
ORR by **IRC** assessment in **ITT** Population		
Response rate [95% CI exact]	83 (31.1) [25.6, 37.0]	11 (4.2) (2.1, 7.4)
Odds ratio (95% CI)	10.994 (5.659, 21.358)	
p-value	<0.0001	
ORR by **inv**estigator assessment in **ITT** Population		
Response rate [95% CI exact]	83 (31.1) [25.6, 37.0]	16 (6.1) [3.5, 9.7]
Odds ratio (95% CI)	7.156 (4.037, 12.685)	
p-value	<0.0001	

Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
BM-ve=brain metastasis negative; CI=confidence interval; DOR=duration of response; IRC=Independent Review Committee; ITT=Intent-to-Treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SG=sacituzumab govitecan; TPC=treatment of physician choice

Participants with non-evaluable response were imputed as nonresponders and sensitivity analyses on efficacy-analysable participants provided confirmed the robustness of the treatment effect of SG. Moreover, supportive sensitivity analyses accounting for a higher percentage of randomised but not treated patients in the TPC group compared with the SG group. (see participant flow above).

Clinical Benefit Rate

CBR was also significantly higher (p<0.0001, p-value nominal) in the SG group than in the TPC group by IRC (40.4% versus 8.0%, respectively; Odds Ratio 8.07) and investigator assessment (43.1% versus 9.9%, respectively; Odds ratio 7.08) in the ITT Population.

Sensitivity Analyses of ORR and CBR

Sensitivity analyses of ORR and CBR in Efficacy Analysable Patients generally confirmed the robustness of results by IRC and investigator review in the BM-ve and ITT populations (see clinical AR for details).

Duration of Response

Table 33 **DOR in Study IMMU-132-05**

	SG	TPC
BM-ve Population	235	233
ITT Population	267	262
DOR by **IRC** assessment in **BM-ve** Population		
Patients with events	49 (59.8)	5 (45.5)
Median (95% CI) [a]	6.3 (5.5, 9.0)	3.6 (2.8, -)
DOR by **inv**estigator assessment in **BM-ve** Population		
Patients with events	58 (72.5)	12 (80.0)
Median (95% CI) [a]	7.0 (5.7, 8.4)	2.9 (2.8, 4.2)
DOR by **IRC** assessment in **ITT** Population		
Patients with events	50 (60.2)	5 (45.5)
Median (95% CI) [a]	6.3 (5.5, 9.0)	3.6 (2.8, -)
DOR by **inv**estigator assessment in **ITT** Population		
Patients with events	61 (73.5)	13 (81.3)
Median (95% CI) [a]	6.9 (5.5, 8.0)	2.9 (2.8, 4.2)

[a] Median DOR is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method.

Time to Response

For patients with a confirmed response, median time to response was similar in the SG and TPC groups by IRC assessment (1.54 months and 1.45 months, respectively).

Updated data based on final database lock (25 February 2021)

The final data cutoff 11 March 2020 was in accordance with the number of events in the prespecified final analysis planned for the study and included any updates to the data after the DMC review. The final database lock (25 February 2021) included further efficacy data collected from the remaining 17 participants after the final data cut for the CSR (study participants pending transition to another clinical study) and confirmed the findings of the final analysis (see Table 3.3.5.14). The only end point with no change from the final CSR was the ORR (independent review).

Table 34 **Summary of Efficacy Data Based on the Original Submission and the Final Database Lock (ITT Population)**

	Original Submission Data (11 March 2020)			Final Data (25 February 2021)		
	SG N = 267	TPC N = 262	Treatment Comparison	SG N = 267	TPC N = 262	Treatment Comparison
OS[a]						
Participants with events (%)	179 (67.0)	206 (78.6)	-	201 (75.3)	222 (84.7)	-
Participants without events, censored (%)	88 (33.0)	56 (21.4)	-	66 (24.7)	40 (15.3)	-
Log-rank *P* Value (stratified)	-	-	<0.0001	-	-	<0.0001
Hazard ratio (relative to TPC)	-	-	0.508	-	-	0.514
95% CI for hazard ratio	-	-	0.414, 0.624	-	-	0.422, 0.625
PFS-independent review[b]						
Participants with events (%)	190 (71.2)	171 (65.3)	-	191 (71.5)	171 (65.3)	-
Patients without events, censored (%)	77 (28.8)	91 (34.7)	-	76 (28.5)	91 (34.7)	-
Log-rank *P* Value (stratified)	-	-	<0.0001	-	-	<0.0001
Hazard ratio (relative to TPC)	-	-	0.433	-	-	0.413
95% CI for hazard ratio	-	-	0.347, 0.541	-	-	0.330, 0.517
PFS-investigator review						
Participants with events (%)	218 (81.6)	193 (73.7)	-	225 (84.3)	193 (73.7)	-
Participants without events, censored (%)	49 (18.4)	69 (26.3)	-	42 (15.7)	69 (26.3)	-
Log-rank *P* Value (stratified)[b]	-	-	<0.0001	-	-	<0.0001
Hazard ratio (relative to TPC)	-	-	0.384	-	-	0.382
95% CI for hazard ratio	-	-	0.311, 0.475	-	-	0.309, 0.473
ORR – independent review[c]						
ORR (CR or PR)	83 (31.1)	11 (4.2)	-	83 (31.1)	11 (4.2)	-
95% CI (exact)	25.6, 37.0	2.1, 7.4	-	25.6, 37.0	2.1, 7.4	-

	Original Submission Data (11 March 2020)			Final Data (25 February 2021)		
	SG N = 267	TPC N = 262	Treatment Comparison	SG N = 267	TPC N = 262	Treatment Comparison
Odds ratio	-	-	10.994	-	-	10.994
95% CI	-	-	5.659, 21.358	-	-	5.659, 21.358
P Value	-	-	<0.0001	-	-	<0.0001
ORR – investigator review[c]						
ORR (CR or PR)	83 (31.1)	16 (6.1)	-	82 (30.7)	16 (6.1)	-
95% CI (exact)	25.6, 37.0	3.5, 9.7	-	25.2, 36.6	3.5, 9.7	-
Odds ratio	-	-	7.156	-	-	6.986
95% CI	-	-	4.037, 12.685	-	-	3.941, 12.385
P Value	-	-	<0.0001	-	-	<0.0001

CI = confidence interval; CR = complete response; ITT = intent to treat; PFS = progression-free survival; PR = partial response; OS = overall survival, ORR = objective response rate; SG = sacituzumab govitecan; TPC = treatment of physician's choice

a. OS is defined as the time from date of randomisation to the date of death from any cause. Patients without documentation of death are censored on the date that they were last known to be alive.

b. PFS is defined as the time from the date of randomisation to the date of the first radiological disease progression or death due to any cause, whichever comes first. See the statistical analysis plan for the handling of censored cases and sensitivity analyses of PFS.

c. ORR is defined as the best confirmed overall response of either CR or PR. The best overall response is derived based on independent or investigator assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. Exact binomial CI for proportion is based on the Beta distribution. *P* Value is based on Cochran-Mantel-Haenszel test.

The denominator for percentages is the number of participants in the ITT Population.
Stratified log-rank test and stratified Cox regression (hazard ratio analyses) adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.

Quality of life

The analysis of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) using a linear mixed effects model for repeated measures (MMRM) analysis was performed to assess the extent of missing quality of life (QoL) data over time and estimate the treatment differences on the change from baseline scores in all functions and symptom domains (data cutoff 11 March 2020).

Table 35 **Linear Mixed Effect Regression Model for Repeated Measures Least Square Mean Changes From Baseline in the EORTC-QLQ-C30 Domains (Study IMMU-132-05 HRQOL-Evaluable Population)**

Domain	SG Mean (95%CI)[a]	TPC Mean (95%CI)[a]	Difference (SG vs TPC) Mean (95%CI)[a]	Noninferiority Margin[b]
Global health status/QoL	0.66 (−2.21, 3.53)	−3.42 (−6.77, −0.08)	4.08 (**0.82**, 7.35)	−4
Physical functioning	1.31 (−1.38, 3.99)	−4.39 (−7.52, −1.26)	5.69 (**2.63**, 8.76)	−5
Role functioning	−2.24 (−6.13, 1.65)	−7.83 (−12.41, −3.25)	5.59 (**1.13**, 10.05)	−6

Emotional functioning	3.34 (0.46, 6.22)	−0.55 (−3.94, 2.84)	3.89 (**0.56**, 7.22)	−3
Cognitive functioning	−1.22 (−4.00, 1.56)	−1.98 (−5.21, 1.24)	0.76 (**−2.36**, 3.89)	−3
Social functioning	−1.51 (−5.47, 2.45)	−5.41 (−10.04, −0.78)	3.90 (**−0.61**, 8.40)	−5
Fatigue	1.97 (−1.20, 5.13)	7.13 (3.40, 10.87)	−5.17 (−8.81, **−1.52**)	+5
Nausea/vomiting	4.30 (1.92, 6.68)	2.50 (−0.23, 5.22)	1.81 (−0.83, 4.44)	+3
Pain	−8.93 (−12.57, −5.30)	−1.89 (−6.18, 2.40)	−7.04 (−11.24, **−2.85**)	+6
Dyspnea	−3.79 (−7.52, −0.06)	3.95 (−0.51, 8.40)	−7.74 (−12.13, **−3.35**)	+4
Insomnia	−4.69 (−8.92, −0.46)	0.34 (−4.64, 5.32)	−5.03 (−9.89, **−0.16**)	+4
Appetite loss	3.52 (−0.47, 7.51)	7.00 (2.31, 11.68)	−3.47 (−8.05, **1.11**)	+5
Constipation	2.16 (−1.76, 6.08)	2.69 (−1.89, 7.27)	−0.53 (−4.97, **3.91**)	+5
Diarrhoea	14.07 (9.94, 18.20)	−1.27 (−6.08, 3.54)	15.34 (10.65, **20.03**)	+3
Financial difficulties	−2.87 (−6.39, 0.65)	0.68 (−3.50, 4.86)	−3.55 (−7.69, **0.59**)	+3

CI = confidence interval; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ESMO = European Society for Medical Oncology; HRQOL = health-related quality of life; LS = least squares; MMRM = mixed effects model for repeated measures; QoL = quality of life; SG = sacituzumab govitecan; TPC = treatment of physician's choice

a Mean (95% CI) of overall LS means from MMRM.

b Noninferiority is demonstrated if the lower or upper bound of 95% CI of the overall LS mean difference (those underscored and bold in the difference column) does not exceed the prespecified noninferiority margin.

Source: IMMU-132-05, Submitted QoL data to ESMO 2021 meeting and data on file

The SG arm was shown to be non-inferior to the TPC arm in all EORTC QLQ-C30 domains, with the exception of nausea/vomiting and diarrhoea, for which the upper bound of the 95% CI of the between-group difference in overall LS mean changes (4.4 and 20.0) exceeded the non-inferiority margin of 3.

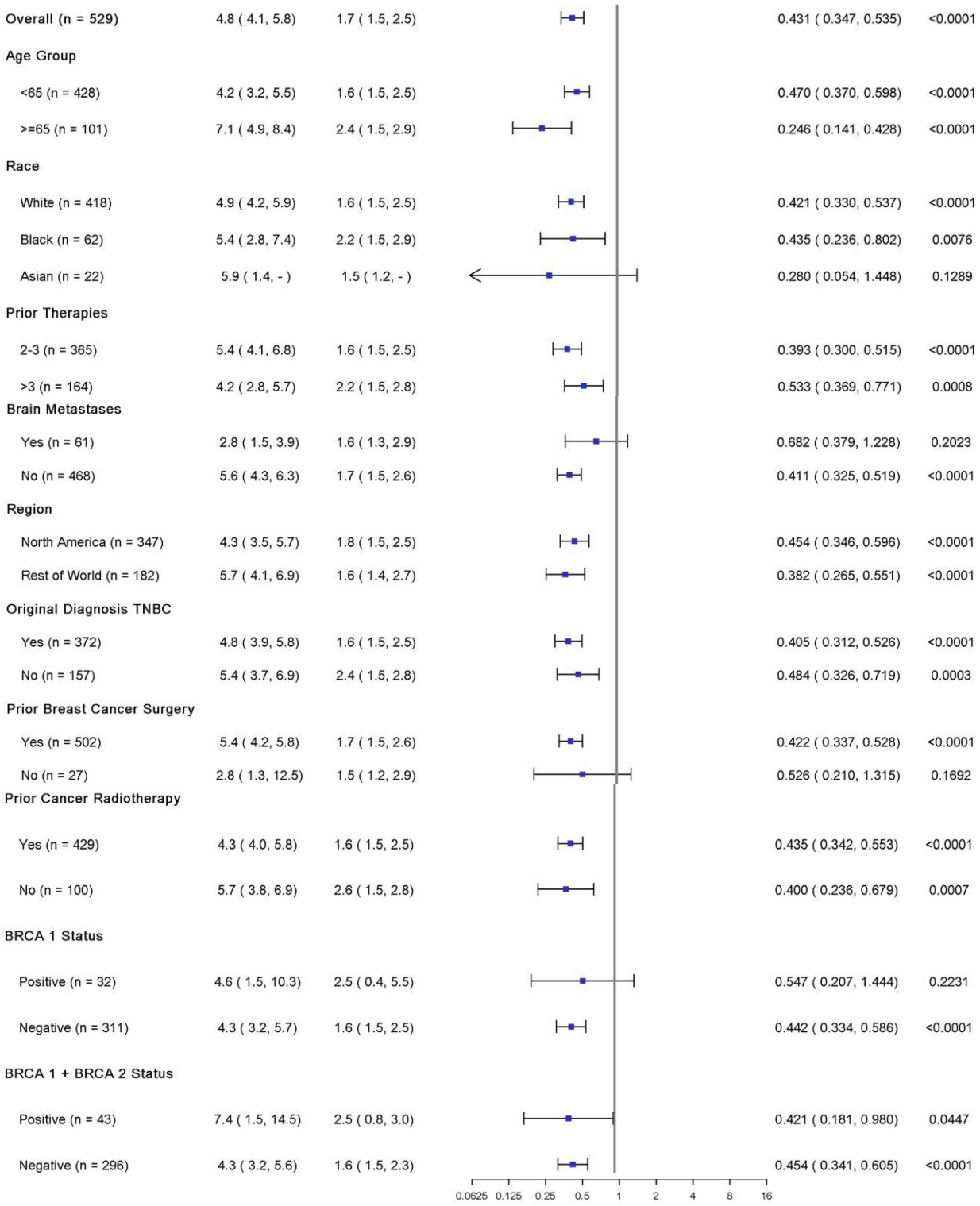
Ancillary analyses

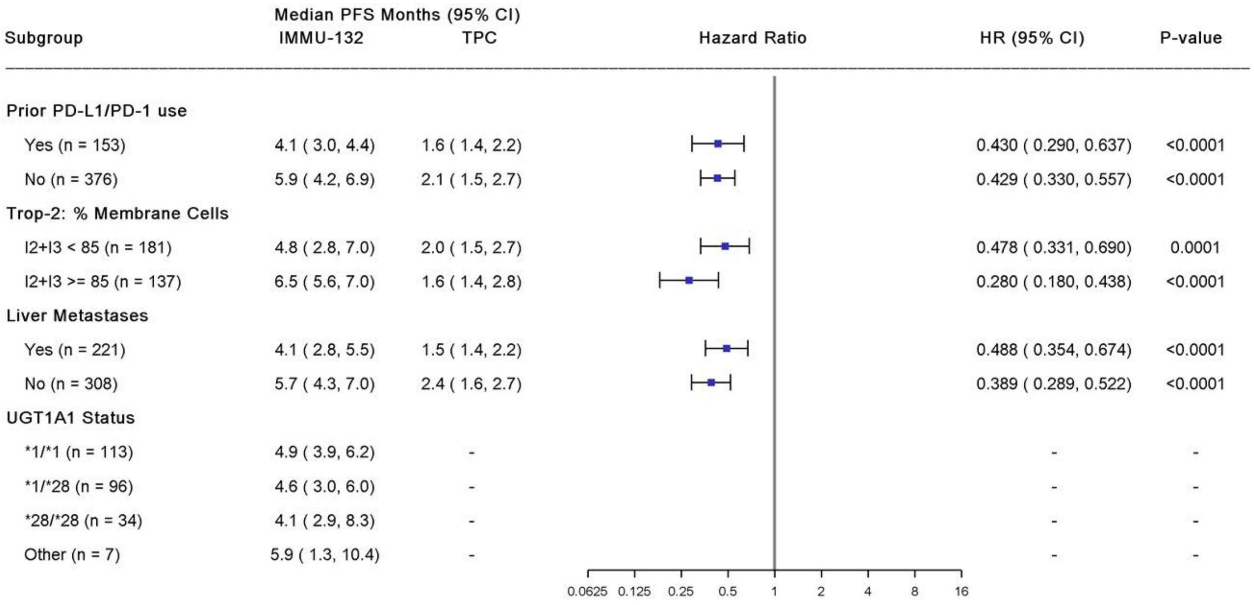
Subgroup analyses (data cutoff 11 March 2020)

Subgroup analyses of **PFS**

Figure 22 Forest Plot of PFS by IRC Assessment in Subgroups (ITT Population)

Subgroup	Median PFS Months (95% CI) IMMU-132	TPC	Hazard Ratio	HR (95% CI)	P-value

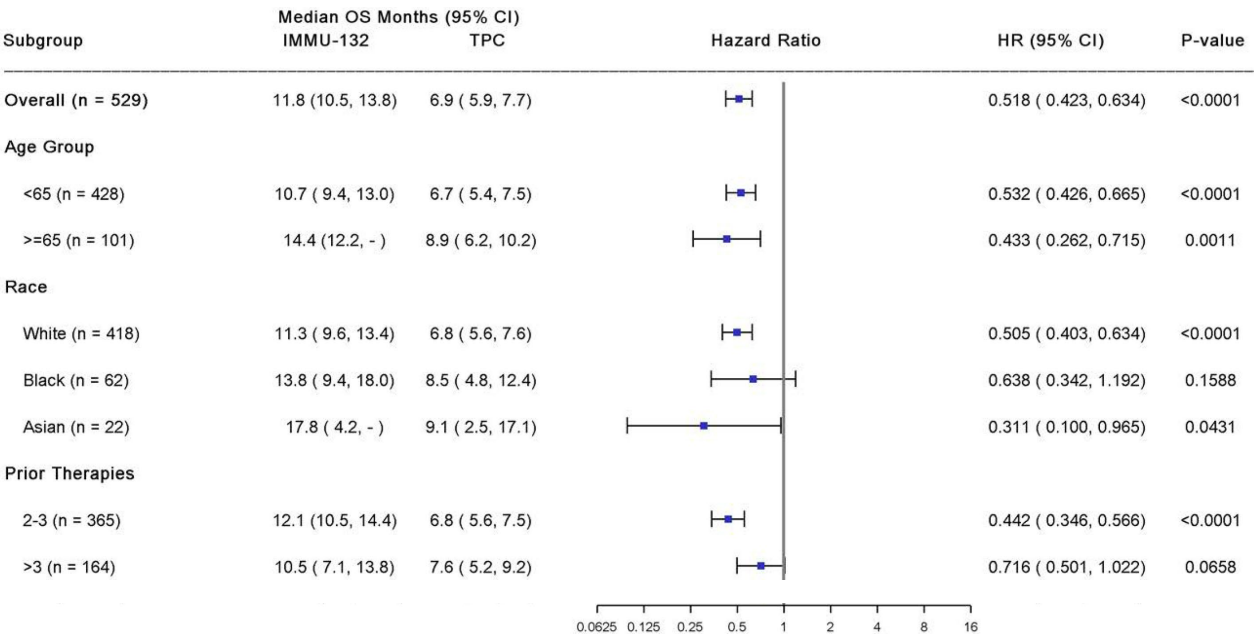

Overall (n = 529) 4.8 (4.1, 5.8) 1.7 (1.5, 2.5) 0.431 (0.347, 0.535) <0.0001
Age Group
<65 (n = 428) 4.2 (3.2, 5.5) 1.6 (1.5, 2.5) 0.470 (0.370, 0.598) <0.0001
>=65 (n = 101) 7.1 (4.9, 8.4) 2.4 (1.5, 2.9) 0.246 (0.141, 0.428) <0.0001
Race
White (n = 418) 4.9 (4.2, 5.9) 1.6 (1.5, 2.5) 0.421 (0.330, 0.537) <0.0001
Black (n = 62) 5.4 (2.8, 7.4) 2.2 (1.5, 2.9) 0.435 (0.236, 0.802) 0.0076
Asian (n = 22) 5.9 (1.4, -) 1.5 (1.2, -) 0.280 (0.054, 1.448) 0.1289
Prior Therapies
2-3 (n = 365) 5.4 (4.1, 6.8) 1.6 (1.5, 2.5) 0.393 (0.300, 0.515) <0.0001
>3 (n = 164) 4.2 (2.8, 5.7) 2.2 (1.5, 2.8) 0.533 (0.369, 0.771) 0.0008
Brain Metastases
Yes (n = 61) 2.8 (1.5, 3.9) 1.6 (1.3, 2.9) 0.682 (0.379, 1.228) 0.2023
No (n = 468) 5.6 (4.3, 6.3) 1.7 (1.5, 2.6) 0.411 (0.325, 0.519) <0.0001
Region
North America (n = 347) 4.3 (3.5, 5.7) 1.8 (1.5, 2.5) 0.454 (0.346, 0.596) <0.0001
Rest of World (n = 182) 5.7 (4.1, 6.9) 1.6 (1.4, 2.7) 0.382 (0.265, 0.551) <0.0001
Original Diagnosis TNBC
Yes (n = 372) 4.8 (3.9, 5.8) 1.6 (1.5, 2.5) 0.405 (0.312, 0.526) <0.0001
No (n = 157) 5.4 (3.7, 6.9) 2.4 (1.5, 2.8) 0.484 (0.326, 0.719) 0.0003
Prior Breast Cancer Surgery
Yes (n = 502) 5.4 (4.2, 5.8) 1.7 (1.5, 2.6) 0.422 (0.337, 0.528) <0.0001
No (n = 27) 2.8 (1.3, 12.5) 1.5 (1.2, 2.9) 0.526 (0.210, 1.315) 0.1692
Prior Cancer Radiotherapy
Yes (n = 429) 4.3 (4.0, 5.8) 1.6 (1.5, 2.5) 0.435 (0.342, 0.553) <0.0001
No (n = 100) 5.7 (3.8, 6.9) 2.6 (1.5, 2.8) 0.400 (0.236, 0.679) 0.0007
BRCA 1 Status
Positive (n = 32) 4.6 (1.5, 10.3) 2.5 (0.4, 5.5) 0.547 (0.207, 1.444) 0.2231
Negative (n = 311) 4.3 (3.2, 5.7) 1.6 (1.5, 2.5) 0.442 (0.334, 0.586) <0.0001
BRCA 1 + BRCA 2 Status
Positive (n = 43) 7.4 (1.5, 14.5) 2.5 (0.8, 3.0) 0.421 (0.181, 0.980) 0.0447
Negative (n = 296) 4.3 (3.2, 5.6) 1.6 (1.5, 2.3) 0.454 (0.341, 0.605) <0.0001
0.0625 0.125 0.25 0.5 1 2 4 8 16

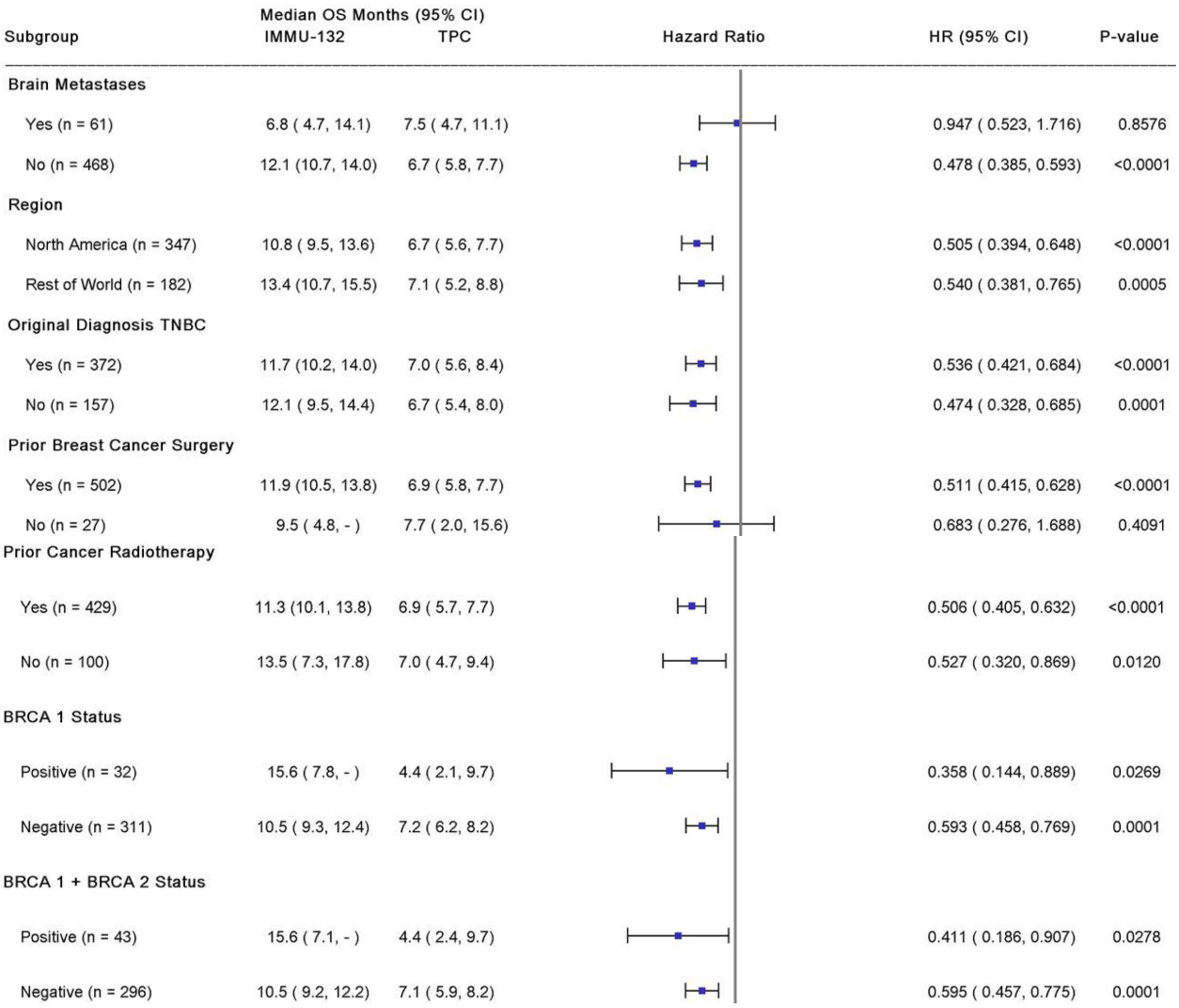


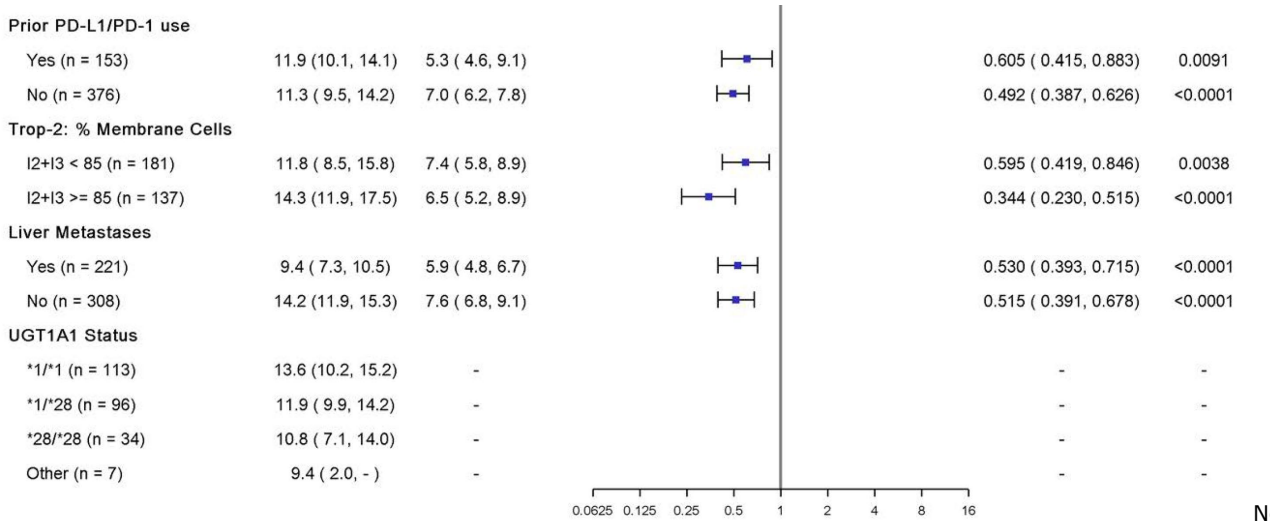
Note: Hazard ratio and p-value are from an unstratified Cox regression analysis; BRCA=breast cancer susceptibility gene; CI=confidence interval; IMMU-132=sacituzumab govitecan; TPC=treatment of physician's choice; UGT1A1=uridine diphosphate-glucuronosyl transferase 1A1

Subgroup analyses of **OS**

Figure 23 **Forest Plot of OS in Subgroups (ITT Population)**




Median OS Months (95% CI)
Subgroup
IMMU-132
TPC
Hazard Ratio
HR (95% CI)
P-value
Brain Metastases
Yes (n = 61) 6.8 (4.7, 14.1) 7.5 (4.7, 11.1) 0.947 (0.523, 1.716) 0.8576
No (n = 468) 12.1 (10.7, 14.0) 6.7 (5.8, 7.7) 0.478 (0.385, 0.593) <0.0001
Region
North America (n = 347) 10.8 (9.5, 13.6) 6.7 (5.6, 7.7) 0.505 (0.394, 0.648) <0.0001
Rest of World (n = 182) 13.4 (10.7, 15.5) 7.1 (5.2, 8.8) 0.540 (0.381, 0.765) 0.0005
Original Diagnosis TNBC
Yes (n = 372) 11.7 (10.2, 14.0) 7.0 (5.6, 8.4) 0.536 (0.421, 0.684) <0.0001
No (n = 157) 12.1 (9.5, 14.4) 6.7 (5.4, 8.0) 0.474 (0.328, 0.685) 0.0001
Prior Breast Cancer Surgery
Yes (n = 502) 11.9 (10.5, 13.8) 6.9 (5.8, 7.7) 0.511 (0.415, 0.628) <0.0001
No (n = 27) 9.5 (4.8, -) 7.7 (2.0, 15.6) 0.683 (0.276, 1.688) 0.4091
Prior Cancer Radiotherapy
Yes (n = 429) 11.3 (10.1, 13.8) 6.9 (5.7, 7.7) 0.506 (0.405, 0.632) <0.0001
No (n = 100) 13.5 (7.3, 17.8) 7.0 (4.7, 9.4) 0.527 (0.320, 0.869) 0.0120
BRCA 1 Status
Positive (n = 32) 15.6 (7.8, -) 4.4 (2.1, 9.7) 0.358 (0.144, 0.889) 0.0269
Negative (n = 311) 10.5 (9.3, 12.4) 7.2 (6.2, 8.2) 0.593 (0.458, 0.769) 0.0001
BRCA 1 + BRCA 2 Status
Positive (n = 43) 15.6 (7.1, -) 4.4 (2.4, 9.7) 0.411 (0.186, 0.907) 0.0278
Negative (n = 296) 10.5 (9.2, 12.2) 7.1 (5.9, 8.2) 0.595 (0.457, 0.775) 0.0001



Note: Hazard ratio and p-value are from an unstratified Cox regression analysis

Exploratory bivariate and multivariate Cox regression analyses for the BM-ve and ITT Populations confirmed the robustness of the PFS and OS results seen with SG in various subgroups.

Additional not prespecified subgroup analyses showed a consistent treatment effect for SG compared with TPC irrespective of the number of prior therapies for TNBC (1 line in metastatic setting, >1 L; 2, >2), prior treatment with a PARPi, prior anthracycline treatment, prior neoadjuvant or adjuvant treatment, and in patients with BRCA 1/2 status unknown. Results suggest a lack of cross-resistance between prior therapies and SG.

Brain metastasi- positive patients

Although not a prespecified analysis population in the SAP for Study IMMU-132-05, data were also analysed separately for the brain metastasis positive population (BM-pos. Pop.; n=61).

Demographic and baseline disease characteristics

There was no meaningful difference in demographics or baseline disease characteristics between the SG and TPC groups in subjects with brain metastases at baseline, although the numbers were more variable due to the smaller sample size. As to be anticipated, patients with brain metastases were more pre-treated and appeared to have more advanced disease compared with the ITT population (proportion of patients with >3 prior chemotherapies 42.6% vs 31%, median number of prior systemic therapies 5 vs 4, time from diagnosis of stage 4 to study entry median 22.5 months vs 16.2 months, proportion of patients with lung metastasis 67.2% vs 46.5%, proportion of patients with bone metastasis 36% vs 24% in the brain metastasis positive population compared to the ITT population, respectively).

Efficacy results

PFS

In patients with brain metastasis at baseline, median PFS was similar in the SG and TPC groups by IRC assessment (2.8 and 1.6 months, respectively) and by investigator assessment (2.9 and 2.8 months, respectively); HRs were 0.65 by IRC and 0.85 by investigator assessment.

Table 36 Primary Analysis of PFS - Independent Review BM-pos. Pop.

	IMMU-132 (N = 32)	TPC (N = 29)	Treatment Comparison
Patients With Events (%)	24 (75.0)	21 (72.4)	
Patients Without Events (Censored) (%)	8 (25.0)	8 (27.6)	
Median PFS (months) [a]	2.8	1.6	
95% CI	(1.5, 3.9)	(1.3, 2.9)	
Log-rank p-value (Stratified) [b]			0.1823
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.650
95% CI for Hazard Ratio			(0.346, 1.222)
PFS Rate (%) at 3 Months (95% CI) [c]	41.4 (23.7, 58.3)	27.7 (11.4, 46.9)	
PFS Rate (%) at 6 Months (95% CI)	9.0 (0.9, 29.2)	6.9 (0.6, 24.9)	
PFS Rate (%) at 9 Months (95% CI)	9.0 (0.9, 29.2)	0.0 (-, -)	
PFS Rate (%) at 12 Months (95% CI)	9.0 (0.9, 29.2)	0.0 (-, -)	

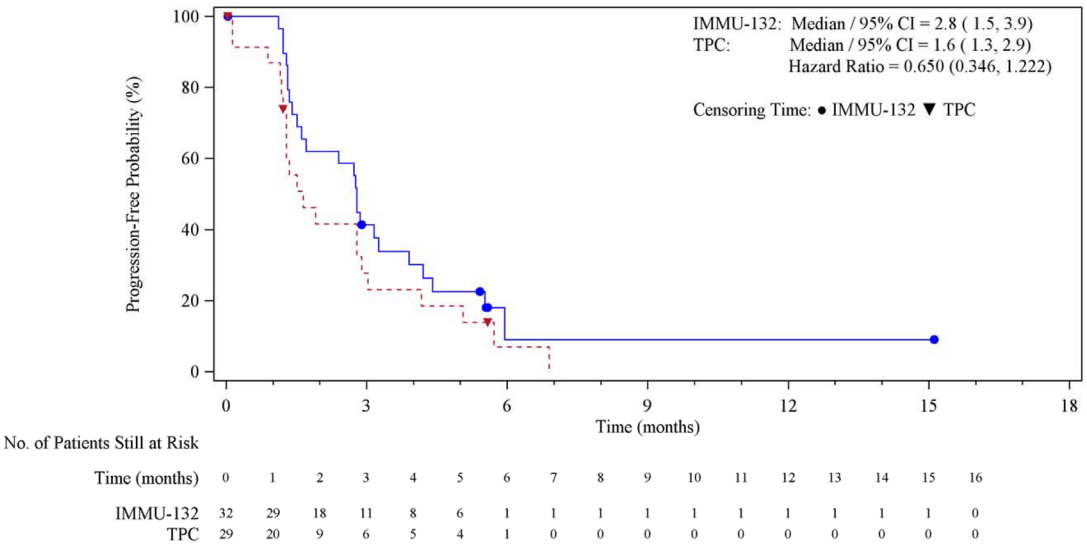
Note: PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases and sensitivity analyses of PFS.
[a] Median PFS is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method.
[b] Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
[c] Estimate and CI for PFS rate at the specified time points are from Kaplan-Meier estimate.

Table 37 Analysis of PFS - Investigator Review BM-pos. Pop.

	IMMU-132 (N = 32)	TPC (N = 29)	Treatment Comparison
Patients With Events (%)	27 (84.4)	21 (72.4)	
Patients Without Events (Censored) (%)	5 (15.6)	8 (27.6)	
Median PFS (months) [a]	2.9	2.8	
95% CI	(1.6, 4.2)	(1.3, 3.4)	
Log-rank p-value (Stratified) [b]			0.6277
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.852
95% CI for Hazard Ratio			(0.453, 1.602)
PFS Rate (%) at 3 Months (95% CI) [c]	44.8 (26.5, 61.6)	43.6 (22.5, 63.0)	
PFS Rate (%) at 6 Months (95% CI)	11.8 (3.1, 26.9)	9.7 (1.7, 26.5)	
PFS Rate (%) at 9 Months (95% CI)	3.9 (0.3, 16.7)	4.8 (0.3, 20.0)	
PFS Rate (%) at 12 Months (95% CI)	3.9 (0.3, 16.7)	0.0 (-, -)	

Note: PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases and sensitivity analyses of PFS.
[a] Median PFS is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method.
[b] Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
[c] Estimate and CI for PFS rate at the specified time points are from Kaplan-Meier estimate.

Figure 24 KM Estimates of PFS - Independent Review BM Positive Population



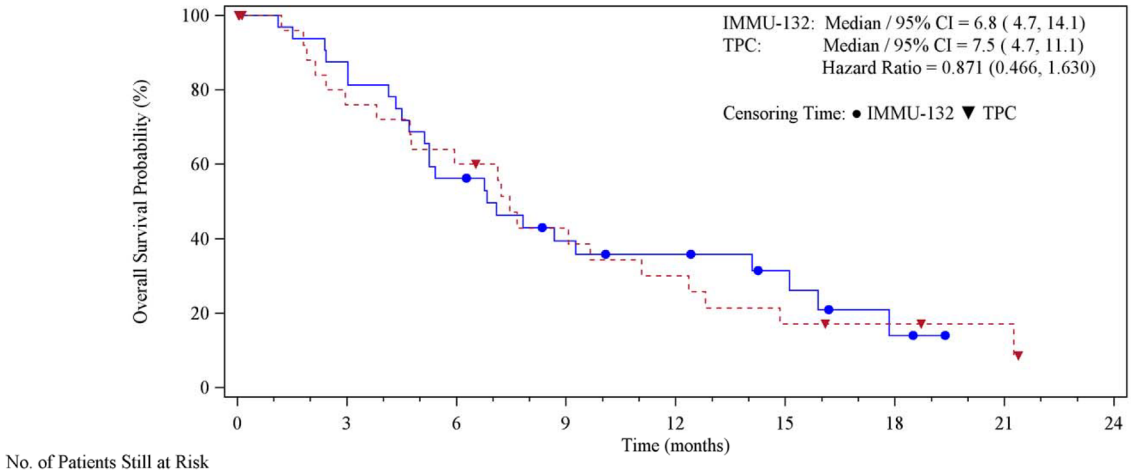
No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
IMMU-132	32	29	18	11	8	6	1	1	1	1	1	1	1	1	1	1	0
TPC	29	20	9	6	5	4	1	0	0	0	0	0	0	0	0	0	0

OS

In patients with brain metastases at baseline, median OS was similar in the SG and TPC groups.

Figure 25 KM Estimates of OS BM Positive Population



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
IMMU-132	32	32	30	28	26	22	18	15	13	11	10	9	9	8	8	6	4	3	2	1	0	0	0
TPC	29	25	22	19	18	16	15	14	10	10	8	8	7	5	5	4	4	3	3	2	2	2	0

ORR

In patients with brain metastases at baseline, 1 patient in the SG group (PR) and no patients in the TPC group had an objective response by IRC assessment. The CBR rate was 9.4% vs 3.4% for the SG compared with the TPC arm. Duration of response was reported as 2.9 months for the single responder in the SG arm.

Table 38 ***Analysis of ORR - Independent Review BM Positive Population***

	IMMU-132 (N = 32)	TPC (N = 29)
Best Overall Response, n (%)		
Complete Response (CR)	0 (0.0)	0 (0.0)
Partial Response (PR)	1 (3.1)	0 (0.0)
Stable Disease (SD)	15 (46.9)	9 (31.0)
SD > 6 months	2 (6.3)	1 (3.4)
Progressive Disease (PD)	11 (34.4)	11 (37.9)
Not Evaluable	5 (15.6)	9 (31.0)

Note: Denominator for percentages is the number of patients in the Brain Metastasis Negative Population
Note: Exact binomial CI for proportion is based on the Beta distribution. P-value is based on Cochran-Mantel-Haenszel test.
Note: Objective Response is defined as the best confirmed overall response of either CR or PR.
Note: The best overall response is derived based on independent review assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. SD requires a minimum duration of 6 weeks to be classified as SD.

Participants were included in the BM-positive population regardless of present brain metastasis at enrolment or only a history of brain metastasis. 32 participants had **brain metastases at enrolment by IRC assessment** (n=14 in the SG arm and n=18 in the TPC arm). An overview of efficacy results for this subgroup of patients with present brain metastasis at enrolment showed overall consistent results with those in the BM-positive population. For patients with present brain metastasis the stratified HRs for PFS by IRC and OS were 0.59 (n=32; 95% CI: 0.27, 1.30) and 0.81 (95% CI: 0.37, 1.78), respectively. The median PFS was 3.2 months vs 1.6 months; the median OS was 8.0 months vs 7.5 months, in patients treated with sacituzumab govitecan and TPC, respectively. Response assessments of brain metastasis for the 32 participants with brain metastases at baseline did not provide conclusive results, since brain lesions were to be considered non-target lesions and consistent follow-up was not available for all patients.

Physician´s choice of chemotherapy agent

Table 39 ***Analysis of ORR and CBR by TPC Arms – by IRC Assessment (BM-ve Population)***

	Capecitabine (N = 28)	Eribulin (N = 122)	Gemcitabine (N = 31)	Vinorelbine (N = 43)
Patients with Measurable Disease at Baseline	28	112	23	38
Objective Response Rate (CR or PR)				
n (%)	2 (7.1)	6 (5.4)	1 (4.3)	2 (5.3)
95% CI (Exact)	(0.9, 23.5)	(2.0, 11.3)	(0.1, 21.9)	(0.6, 17.7)
Clinical Benefit Rate (CR, PR and SD >= 6 months)				
n (%)	3 (10.7)	10 (8.9)	4 (17.4)	3 (7.9)
95% CI (Exact)	(2.3, 28.2)	(4.4, 15.8)	(5.0, 38.8)	(1.7, 21.4)
Best Overall Response, n (%)				
Complete Response (CR)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Partial Response (PR)	2 (7.1)	4 (3.6)	1 (4.3)	2 (5.3)
Stable Disease (SD)	7 (25.0)	30 (26.8)	8 (34.8)	8 (21.1)
SD > 6 Months	1 (3.6)	4 (3.6)	3 (13.0)	1 (2.6)
Progressive Disease (PD)	13 (46.4)	52 (46.4)	4 (17.4)	20 (52.6)
Not Evaluable (NE)	5 (17.9)	20 (17.9)	7 (30.4)	7 (18.4)

Note: Objective Response is defined as the best confirmed overall response of either CR or PR.
Note: The best overall response is derived based on independent review assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. SD requires a minimum duration of 6 weeks to be classified as SD.
Note: Clinical benefit rate (CBR) is defined as the percentage of patients with a confirmed best overall response of CR or PR, and SD with a duration of at least 6 months.
Note: Positive denotes patient is either BRCA1 positive or BRCA2 positive. Negative denotes patient is both BRCA1 negative and BRCA2 negative. Other denotes patients for whom BRCA is not done or inconclusive.

Treatment of physician's choice (TPC) was determined before randomisation. Exploratory results for ORR were provided for patients treated with each of the single-agent treatments. Since most of the patients received eribulin in the control arm (n=122), numbers of subjects treated with capecitabine, vinorelbine, or gemcitabine were rather small (between n= 28 and 43). The ORR results by TPC were in the same range with overlapping confidence intervals. The applicant provided additional efficacy analyses of PFS, OS and ORR stratified by physician's choice of chemotherapy agent prior to randomisation, which showed consistent treatment effects between the subgroups (results not shown here).

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 40 ***Summary of Efficacy for trial*** **IMMU-132-05**

Title: An international, multi-center, open-label, randomized, Phase 3 trial of sacituzumab govitecan (SG) versus treatment of physician choice (TPC) in subjects with metastatic triple-negative breast cancer (TNBC) who received at least two prior treatments		
Study identifier	IMMU-132-05 NCT No.: 02574455 EudraCT No.: 2017-003019-21	
Design	This study was a Phase 3, randomised, open-label, multicenter study of the efficacy and safety of SG in subjects with either locally-advanced or metastatic TNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy treatments.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	07 November 2017 - 11 March 2020 not applicable not applicable NB: Subjects with Metastatic Solid Tumors who have benefitted from Continuation of Therapy with SG may have been able to enrol in an Open-Label Rollover Study (IMMU 132-14) which aims to assess long term safety
Hypothesis	Superiority	
Treatments groups	Sacituzumab govitecan (SG)	SG 10 mg/kg was administered as an intravenous (IV) infusion on Days 1 and Day 8 of a 21-day treatment cycle. Treatment was continued until disease progression, unacceptable toxicity, study withdrawal or death whichever came first.

	Treatment of Physician's choice (TPC) ie, 1 of the following single-agent treatments		Eribulin 1.4 mg/m^2 at North American sites and 1.23 mg/m2 at European sites1 IV on Days 1 and 8 of a 21-day cycle. Capecitabine 1,000 to 1,250 mg/m^2 orally BID for 2 weeks followed by 1-week rest period in 21-day cycle. Gemcitabine 800-1,200 mg/m^2 IV over 30 minutes on Days 1, 8, and 15 of a 28-day Cycle Vinorelbine 25 mg/m2 weekly IV injection over 6-10 minutes Treatment was continued until disease progression or unacceptable toxicity
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	Independently-reviewed progression free survival (PFS) in subjects with locally-advanced or metastatic TNBC previously treated with at least 2 systemic chemotherapy regimens for unresectable, locally-advanced or metastatic disease and without brain metastasis at baseline (BM-ve Population).
	Secondary endpoint	PFS (ITT)	PFS for the Intent-to-Treat (ITT) Population
	Secondary endpoint	Overall survival (OS)	Overall survival (OS) in BM-ve and the ITT Population
Database lock	11 March 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PFS by IRC assessment in patients without brain metastasis at baseline (BM-ve Population); Time from randomisation until objective tumor progression or death, whichever came first		
	Treatment group	SG (N=235)	TPC (N=233)

Descriptive statistics and estimate variability	Patients with Events	166 (70.6)	150 (64.4)
	PFS (median months)	5.6	1.7
	Confidence interval	(4.3, 6.3)	(1.5, 2.6)
Effect estimate per comparison	PFS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.409
		CI	0.323, 0.519
		P-value	<0.0001
Analysis population and time point description	PFS by IRC assessment for the Intent-to-Treat (ITT) Population Time from randomisation until objective tumor progression or death, whichever came first		
Descriptive statistics and estimate variability	Treatment group	SG (N=267)	TPC (N=262)
	Patients with Events	190 (71.2)	171 (65.3)
	PFS (median months)	4.8	1.7
	Confidence interval	(4.1, 5.8)	(1.5, 2.5)
Effect estimate per comparison	PFS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.433
		CI	0.347, 0.541
		P-value	<0.0001
Analysis population and time point description	OS in BM-ve Population; Time from the start of study treatment to death from any cause		
Descriptive statistics and estimate variability	Treatment group	SG (N=235)	TPC (N=233)

	Patients with Events	155 (66.0)	185 (79.4)
	OS (median months)	12.1	6.7
	Confidence interval	(10.7, 14.0)	(5.8, 7.7)
Effect estimate per comparison	OS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.476
		CI	0.383, 0.592
		P-value	<0.0001
Analysis population and time point description	OS for the ITT Population; Time from the start of study treatment to death from any cause		
Descriptive statistics and estimate variability	Treatment group	SG (N=267)	TPC (N=262)
	Patients with Events	179 (67.0)	206 (78.6)
	OS (median months)	11.8	6.9
	Confidence interval	(10.5, 13.8)	(5.9, 7.7)
Effect estimate per comparison	OS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.508
		CI	0.414, 0.624
		P-value	<0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Table 41 ***Clinical Study Populations by Age***

		Population							
		Age < 65 Years		Age 65 – 74 Years		Age 75 – 84 Years		Age ≥ 85 Years	
		Number	%	Number	%	Number	%	Number	%
Controlled Trials IMMU-132-05	ITT Population N = 529	428	80.9	80	15.1	21	4.0	0	0.0
Non-Controlled Trials IMMU-132-01	Overall Safety Population N = 495	322	65.1	128	25.9	40	8.1	5	1.0

ITT = intent to treat

Efficacy by Age

Efficacy data per detailed age groups were provided only for the BM-ve Population.

Table 42 **PFS, OS and ORR per age group (by IRC in BM-ve Population)**

	< 65 years		65 – 74 years		≥ 75 years	
	SG (n=191)	**TPC** (n=187)	**SG** (n=37)	**TPC** (n=35)	**SG** (n=7)	**TPC** (n=11)
PFS						
Median months (95% CI)	5.6 (4.3, 6.3)	1.7 (1.5, 2.6)	8.0 (5.8, 9.0)	1.6 (1.4, 2.8)	6.8 (2.7, -)	2.9 (1.4, 5.5)
HR (95% CI)	0.411 (0.33, 0.52)		0.188 (0.09, 0.38)		0.485 (0.15, 1.57)	
OS						
Median months (95% CI)	11.2 (9.9, 13.4)	6.6 (5.3, 7.4)	14.4 (12.2, -)	6.7 (3.9, 9.3)	17.5 (4.8, -)	9.8 (4.7, 15.5)
HR (95% CI)	0.502 (0.39, 0.64)		0.344 (0.19, 0.63)		0.368 (0.09, 1.46)	
ORR						
% (95% CI)	31.4 (24.9, 38.5)	5.9 (2.97, 10.3)	54.1 (36.9, 70.5)	-	28.6 (3.7, 71.0)	-

In vitro biomarker test for patient selection for efficacy

SG binds to trophoblast cell surface antigen-2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers, including TNBC.

Trop-2 expression was assessed in sections from formalin-fixed paraffin-embedded blocks of tissue using a qualitative immunohistochemical assay and conventional light microscopy. At the cellular level, membrane localisation was expected to predominate, with some degree of cytoplasmic localisation possible. The approximate number of viable tumor cells in a section had to be ≥100 cells for Trop-2 evaluation. Scoring included all areas of evaluable viable tumor in the section, even if the tumor was discontinuous or in separate tissue fragments in the section. Necrotic areas, poorly preserved areas, poorly fixed areas, and areas exhibiting artifactual changes were excluded from scoring. Membrane and cytoplasmic staining intensity was characterised as follows.

0:	No staining
1+:	Weak intensity For membrane staining, faint staining that does not completely encircle the cell and may require 20x to 40x magnification to detect. For cytoplasmic staining, faint light brown staining in the cytoplasm that doesn't obscure the nucleus
2+:	Moderate intensity For membrane staining, weak to moderate staining that completely encircles the cell and is readily visible at 10x magnification. For cytoplasmic staining, medium brown cytoplasmic staining that does not completely obscure nuclear detail
3+	Strong intensity For membrane staining, strong staining that completely encircles the cell and is readily visible at 4x magnification. For cytoplasmic staining, dark brown cytoplasmic staining that completely or partially obscures the nucleus.

Additionally, a histo score (H-score) was calculated for both membrane and cytoplasmic staining using the following formula:

H-score = (__% x 0) + (__% x 1+) + (__% x 2+) + (__% x 3+)

Clinical Validation:

SG is in principle a targeted therapy directed against Trop-2. Information about the predictive value of the biomarker Trop-2 was limited at initiation of the clinical development plan. Although it is acknowledged that Trop-2 is quite ubiquitous expressed in TNBC and a preselection of patients was not considered necessary for this Phase III study, the applicant was advised to further assess the correlation between Trop-2 expression and response to get as much information as possible from the pivotal study IMMU-132-05. Please refer also to the draft anticancer guideline rev.6 Biomarker section.

Exploratory data from the uncontrolled, Phase 1/2 basket study IMMU-132-01 suggested a predictive value of Trop-2 expression for patients with TNBC: ORR 16.7% vs. 40.4%, median PFS 2.7 months vs. 6.1 months and median OS 9.4 months vs. 13.7 months for patients with no/weak vs moderate/strong Trop-2 expression, respectively However, the numbers (n=6, 57 and 45) were too small to draw conclusions. In addition, Trop-2 expression was determined using an exploratory, unvalidated immunohistochemical assay based on a polyclonal antibody by an analyst not qualified in immunohistochemical evaluation.

In Study IMMU-132-05 Trop-2 status was assessed using a validated qualitative immunohistochemical assay based on a monoclonal antibody. However, collection of baseline tumor biopsies was not mandated for Study IMMU-132-05. Thus, tumor samples were available from only 364 of 529 participants (68.8%) in the ITT population. Of these, tumor samples from 46 participants failed the Trop-2 IHC test mostly due to insufficient number of tumor cells (tumor cells <100 in 38 samples) or technical issues (n=5) or "not done" (n=3), resulting in a proportion of 60.1% (n=318) with Trop-2 expression results in the ITT.

The applicant presented retrospective comparative analyses indicating similar baseline characteristics and efficacy outcomes between the subset of the study population evaluable for Trop-2 status and the overall BM-negative population to support the assumption that the subset of Trop-2–evaluable participant population would be representative. The requested Trop-2 sensitivity analyses were all conducted in the BM-negative population (with 290 participants evaluable for Trop-2 IHC staining [62% of BM-ve population]) and not in the ITT population (318 evaluable participants).

Data were analysed using different scoring methods: a) the membrane H-score that considered both, the intensity of the staining and the number of tumor cells with a membrane staining, b) the percent membrane cells I2+I3 that count the percentage of tumor cells with a membrane staining of moderate or high staining intensity and c) the total membrane score which simply adds the percentages of tumor cells with any Trop-2 expression (i.e. independent from the staining intensity). Although the total membrane score showed not to be optimal for discerning the impact of Trop-2 expression levels on efficacy, results of analyses of PFS, OS, and ORR by Trop-2 expression level were consistent across different scoring methods.

Efficacy results by Trop-2 Subgroups (excerpt) are summarised below:

Table 43 ***Analyses of PFS (IRC) by Trop-2 Subgroups (Trop-2–Evaluable Participants in BM Negative Population)***

PFS Analysis	N	HR (95% CI)
H-score Quartiles		
Q1 [0,125]	73	0.637 (0.365, 1.111)
Q2 [130,220]	72	0.397 (0.212, 0.745)
Q3 [220,275]	73	0.213 (0.111, 0.409)
Q4 [280,300]	72	0.350 (0.180, 0.682)
H-score Median		
Low	141	0.531 (0.353, 0.799)
High	149	0.263 (0.168, 0.414)
Percent Membrane Cells I2+I3		
Q1 [0,40]	73	0.640 (0.366, 1.122)
Q2 [40,80]	72	0.363 (0.194, 0.677)
Q3 [80,95]	73	0.200 (0.104, 0.385)
Q4 [100,100]	72	0.387 (0.199, 0.750)

BM = brain metastasis; HR = hazard ratio; I2 = moderate staining; I3 = intense staining; N = number of participants; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; IRC = independent review committee; PFS = progression-free survival; Trop-2 = trophoblast cell surface antigen 2
Cox model was performed by including treatment (sacituzumab govitecan, treatment of physician's choice) as the only predictor for each Trop−2 subgroup separately.

Table 44 ***Analyses of Overall Survival by Trop-2 Subgroups (Trop-2 Evaluable Participants in BM-Negative Population)***

OS Analysis	N	HR (95% CI)
H-score Quartiles		
Q1 [0,125]	73	0.708 (0.415, 1.206)
Q2 [130,220]	72	0.504 (0.277, 0.917)
Q3 [220,275]	73	0.343 (0.196, 0.599)
Q4 [280,300]	72	0.374 (0.215, 0.652)
H-score Median		
Low	141	0.637 (0.427, 0.950)
High	149	0.342 (0.232, 0.504)
Percent Membrane Cells I2+I3		
Q1 [0,40]	73	0.668 (0.392, 1.140)
Q2 [40,80]	72	0.514 (0.282, 0.935)
Q3 [80,95]	73	0.312 (0.176, 0.553)
Q4 [100,100]	72	0.403 (0.234, 0.694)

BM = brain metastasis; HR = hazard ratio; I2 = moderate staining; I3 = intense staining; N = number of participants; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; IRC = independent review committee; OS = overall survival; Trop-2 = trophoblast cell surface antigen 2
Cox model was performed by including treatment (sacituzumab govitecan, treatment of physician's choice) as the only predictor for each Trop−2 subgroup separately.

***Table 45* Objective Response Rate (IRC) by Membrane H-Score Quartile Subgroups (Trop-2 Evaluable Participants in BM-Negative Population)**

	Q1 [0, 125]		Q2 [130, 220]		Q3 [220, 275]		Q4 [280, 300]	
	SG	TPC	SG	TPC	SG	TPC	SG	TPC
	N = 32	N = 41	N = 39	N = 33	N = 37	N = 36	N = 43	N = 29
Best overall response								
CR	3	0	2	2	3	0	2	0
PR	5	2	13	3	12	0	18	0
SD	7	10	14	12	15	12	16	12
PD	14	23	7	10	6	16	6	9
NE	3	6	3	6	1	8	1	8
ORR (Relative to TPC)								
N (%)	8 (25.0%)	2 (4.9%)	15 (38.5%)	5 (15.2%)	15 (40.5%)	0	20 (46.5%)	0
95% CI (Exact)	(11.5%, 43.4%)	(0.6%, 16.5%)	(23.4%, 55.4%)	(5.1%, 31.9%)	(24.8%, 57.9%)	—	(31.2%, 62.3%)	—
Odds Ratio	6.50		3.50		NA		NA	
95% CI	(1.27, 33.20)		(1.11, 11.05)		—		—	

BM = brain metastasis; CI = confidence interval; CR = complete response; N = number of participants; NA = not applicable; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; SD = stable disease; SG = sacituzumab govitecan; TPC = treatment of physician's choice; Trop-2 = trophoblast cell surface antigen 2

The denominator for percentages is the number of participants in the BM-Negative Population under each Trop−2 subgroup.

Logistic regression model was performed by including treatment (SG, TPC) as the only predictor.

Table 46 **ORR (by IRC Assessment), PFS (by IRC Assessment), and OS in Participants with Low Trop-2 Expression (Trop-2 Evaluable Participants in BM-Negative Population)**

	Total Membrane/ H-score[a] = 0		H-score < 100		% Membrane Cells I2+I3 = 0		Total Membrane Score (%) ≤ 50		% Membrane Cells I2+I3 ≤ 50	
Outcome	**SG**	**TPC**	**SG**	**TPC**	**SG**	**TPC**	**SG**	**TPC**	**SG**	**TPC**
Number of participants	7	4	27	32	9	8	28	28	47	48
ORR, n (%)	1 (14.3%)	0 (0.0%)	6 (22.2%)	2 (6.2%)	2 (22.2%)	0 (0.0%)	5 (17.9%)	2 (7.1%)	13 (27.7%)	3 (6.2%)
Odds Ratio [95% CI]	NA[b]		4.29 [0.79, 23.34]		NA[b]		2.83 [0.50, 15.99]		5.74 [1.15, 21.73]	
HR [95% CI] for PFS	NA[b]		0.69 [0.37, 1.28]		NA[b]		0.80 (0.42, 1.53)		0.52 [0.31, 0.85]	
HR [95% CI] for OS	NA[b]		0.69 [0.38, 1.24]		NA[b]		0.78 (0.42, 1.42)		0.57 [0.35, 0.91]	

BM = brain metastasis; CI = confidence interval; HR = hazard ratio; I1 = week staining; I2 = moderate staining; I3 = intense staining; IRC = independent review committee; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice; Trop-2 = trophoblast cell surface antigen 2

The denominator for percentages is the number of participants in the BM-negative population under each Trop−2 subgroup.

Cox model was performed by including treatment (SG, TPC) as the only predictor.

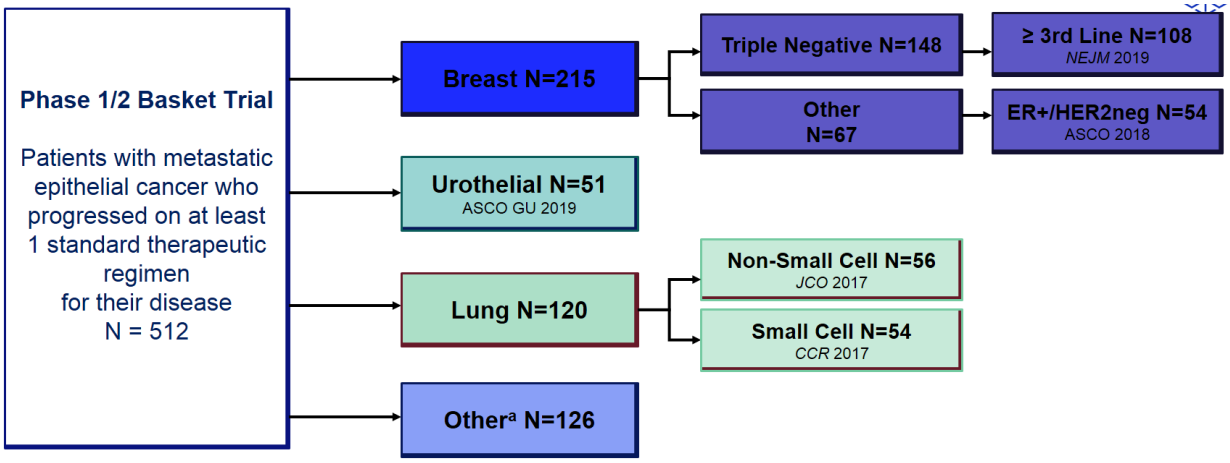
a Since H-score is defined as I1+ 2 x I2 + 3 x I3, total membrane score (I1+I2+I3) and H-score equal to 0 are the same and refer to the same participants.

b HR not evaluated for small sample size (n < 30).

Supportive study

Study IMMU-132-01 was an uncontrolled, Phase 1/2 basket study in which SG monotherapy was evaluated in metastatic epithelial cancers. The study included a cohort of 108 mTNBC patients who were either refractory to or relapsed after at least 2 prior therapies for metastatic disease and were treated with SG 10 mg/kg (ie, TNBC Target Population).

Figure 26 IMMU-132-01 Basket Trial Tumor Cohorts



[a]Tumor types also included in the Phase I/II Basket Trial: SCLC, Colorectal, Esophageal, PDC, Epithelial Ovarian, Endometrial, Gastric Adenocarcinoma, HRPC, GBM, SCCHN, Hepatocellular, Renal Cell.
ER+, estrogen receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; Trop-2, trophoblast cell surface antigen-2.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT01631552?term=NCT01631552.1. Bardia A, et al. *N Engl J Med.* 2019;380:741-751; 2. Bardia A, et al. *J Clin Oncol.* 2018;36(15 suppl): Abstract 1004; 3. Tagawa ST, et al. *J Clin Oncol.* 2019;39(suppl 7S): Abstract 354; 4. Heist RS, et al. *J Clin Oncol.* 2017;35:2790-2797; 5. Gray JE, et al. *Clin Cancer Res.* 2017;23:5711-5719

Computed tomography or magnetic resonance image scans were conducted at screening and every 8 weeks thereafter until disease progression.

Key inclusion criteria:

- ER-, PR-, and HER2- histology on most recently analysed biopsy
- Refractory to or relapsed after at least 2 prior therapies for metastatic disease, including a taxane in any setting
- ECOG status ≤1
- A life expectancy of ≥6 months
- Patients with brain metastases were excluded until protocol amendment 9 when 405 of 495 patients had been enrolled (then patients required adequate treatment for CNS metastases and had to be symptom-free with no evidence of progression for at least 3 months).
- Adequate haematology, renal and hepatic function

Key exclusion criteria:

- Bulky disease defined as any single mass >7 cm in its greatest dimension
- Gilbert´s disease
- Infection requiring IV antibiotic use within 1 week of treatment initiation
- Active ≥grade 2 anorexia, nausea, or vomiting or a prior history of clinically significant bleeding, intestinal obstruction, or gastrointestinal perforation within 6 months of initiation of study treatment
- Human immunodeficiency virus, hepatitis B, or hepatitis C positive
- History of any of the following:
    - Anaphylactic reaction to irinotecan
    - Unstable angina, myocardial infarction, or congestive heart failure present within 6 months of randomisation or a clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy
    - Clinically significant active chronic obstructive pulmonary disease or other moderate-to-severe chronic respiratory illness present within 6 months of randomisation
    - Clinically significant bleeding, intestinal obstruction, or gastrointestinal perforation within 6 months of treatment initiation

Treatment:

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

Endpoints:

ORR by investigator assessment using RECIST v1.1 criteria was the primary endpoint. Secondary endpoints included DOR, TTR, CBR, and PFS by investigator assessment as well as OS.

Patient Disposition and Characteristics

Study IMMU-132-01 was conducted at 13 centers in the US. Results from the final analysis are based on the database cut-off date of 01 March 2019.

Most patients in the TNBC Target Population have permanently discontinued SG (97.2%), with PD (78.7%) as the most frequent reason for treatment discontinuation. The majority have discontinued the study (90.7%), with death (80.6%) as the most frequent reason for study discontinuation.

Patients were predominantly ≤65 years old (87.0%), female (99.1%), White (75.9%), and had an ECOG PS of 1 (71.3%). Patients in the TNBC Target Population were heavily pretreated (median number of 3 previous anticancer regimens). Prior therapies included platinum (76.9% of patients) gemcitabine (54.6%), capecitabine (50.9%), and eribulin (45.4%). The mean duration of the immediate previous anticancer regimen was 3.7 months.

Efficacy results

Table 47 ***Efficacy Results in Study IMMU-132-01 (assessment by investigator)***

	TNBC Target Population (N=108) n (%)
Objective Response Rate (CR or PR)	36 (**33.3**)
[95% 2-Sided Exact Binomial CI]	[24.6, 43.1]
Best Overall Response	
CR[1]	3 (2.8)
PR[1]	33 (30.6)
SD	40 (37.0)
SD ≥ 6 months	13 (12.0)
PD	28 (25.9)
Not Assessed	4 (3.7)
Median **DOR**	**7.7** months
Median **time to response**	**2.0** months
CBR	45.4%
Median **PFS**	**5.6** months
Median **OS**	**13.0** months

Data Cutoff Date: 01Mar2019
[1]CR or PR required a confirmation scan.
CBR=clinical benefit rate; CI=confidence interval; CR=complete response; DOR=duration of response; OS=overall survival PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease; TNBC=triple-negative breast cancer

No meaningful differences in response rates, PFS, or OS were seen in subgroups defined by age, ECOG performance status 0 vs 1, and the number of prior therapies for TNBC.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for sacituzumab govitecan (SG) for the treatment of triple-negative breast cancer (TNBC) is based on the pivotal Study IMMU-132-05. This is an open-label, randomised, phase 3 trial of SG versus treatment of physician's choice (TPC) in patients with unresectable locally advanced or metastatic TNBC who received at least two prior treatments. Supportive data were provided from Study IMMU-132-01, an uncontrolled phase 1/2 basket trial that included a cohort of 108 mTNBC patients after at least 2 prior therapies for metastatic disease. Single-agent chemotherapy according to physician's choice were to be determined prior to randomisation and included several options, as there is no definitive standard of care in the proposed treatment setting for the targeted patient population. The choice of comparator treatments, either eribulin, capecitabine, gemcitabine, or vinorelbine and the selected dosing regimens are in line with international guideline recommendations (e.g. ESMO and NCCN); Given the different treatment options in the control arm, the open-label design is acceptable. Stratification factors were number of prior lines of therapies [2-3 vs >3], known brain metastasis and region [North America vs Europe]. The study design of IMMU-132-05 is endorsed.

The eligibility criteria were overall adequate to select an advanced TNBC population. Diagnosis of TNBC were to be confirmed per ASCO/CAP criteria (using a cutoff of <1% for ER and PR negativity) based on local assessment of the most recent biopsy.

The choice of PFS as primary endpoint and OS as secondary endpoint as well as the proposed hierarchical testing of PFS/OS in the ITT had been accepted by CHMP in previous Scientific Advice received by the applicant. With protocol amendment 4 (May 2018; first patient enrolled Nov 2017), the analysis plan was changed to analyse the primary endpoint of PFS by IRC assessment first in patients without known brain metastases, the brain metastasis negative (BM-ve) Population. If the primary analysis was significant, subsequent key secondary endpoints (OS in the BM-ve population, PFS by IRC assessment in the ITT population, OS in the ITT population) were tested in a sequential manner. As clarified at the presubmission meeting, the statistical analysis was modified based on input by FDA to address the uncertain efficacy in patients with brain metastases (considering the MoA of SG as an antibody drug conjugate with uncertain crossing of the blood-brain barrier).

Other secondary efficacy objectives (ORR, DOR, CBR, and QoL) are standard in oncology trials and endorsed. No PFS2 data were provided; however, this can be accepted in view of the favourable OS results (see below).

The analysis of efficacy by Trop-2 tumor expression, the target of SG, was introduced as exploratory analysis with amendment 4 (May 2018). However, obviously eligibility criteria were not adapted to ensure that all patients had to provide tumor biopsies for central testing of Trop-2 expression.

Recruitment, study conduct and baseline characteristics

The study randomised 529 patients 1:1 in both treatment arms. At the data cut-off date of 11 March 2020, the median survival follow-up in the ITT population was 8.4 months (10.6 months for SG and 6.3 for TPC). A higher percentage of patients in the TPC group compared with the SG group were randomised but not treated

(14.5% and 3.4%, respectively) or discontinued treatment due to withdrawal of consent (6.9% vs. 1.9%, respectively). In view of the open-label study, this is likely due to patients´ expectations of receiving experimental treatment, yet this imbalance might have impacted efficacy outcomes. At request the applicant provided a conservative sensitivity analysis (tipping point analysis) that confirmed the robustness of the results for PFS, OS and ORR with regard to worse-case imputation of non-treated randomised patients. This is reassuring considering the lower than anticipated PFS and OS results in the control arm.

Patients with brain metastasis were allowed if adequately pre-treated, stable for at least 4 weeks and without high-dose steroids or anti-seizure medication. According to information at randomisation, 61 patients (11.5% of study population) were considered to be brain metastases-positive. Of note, 26 patients failed screening due to lack of stable CNS disease, suggesting that the extensive and detailed inclusion criteria limited the number of patients included with this disease manifestation. It would have been preferred to perform an MRI of the brain for all patients at baseline, considering that the incidence of brain metastases is high in the targeted patient population. This would have allowed a better estimation of activity of SG in the brain. With the response to the D90 LoQ the selected criteria for stable brain metastases have been adequately reflected in the SmPC.

Inconsistencies were noted in the dossier regarding the reported number of patients with brain metastases. While the BM-positive population included n=32 in SG arm and n=29 in the TPC arm, 31 patients in the TPC arm were reported to have received prior radiotherapy to the brain (Table 29) and only 33 patients and not all 61 patients in the brain metastasis positive population were reported to have tumor locations in the brain based on IRC assessment (Table 30). In response to the D90 LoQ the applicant clarified that due to erroneous entries in the Eligibility Review Forms during randomisation, two patients with brain metastasis in the TPC group were not included in the BM-positive population. Moreover, participants were considered positive for brain metastasis (included in the BM-positive population) regardless of present brain metastasis or only a history of brain metastasis (e.g. prior brain radiotherapy or cancer-related surgery). Consequently, only 32 of 61 participants in the BM-positive population had baseline tumor locations in the brain based on IRC assessment.

An imbalance on withdrawals was noted. A conservative sensitivity analysis addressing the potential impact of the imbalance on the efficacy outcome was provided. The results of a tipping point analyses confirmed the robustness of the results for PFS, OS and ORR with regard to worse-case imputation of non-treated randomised patients. Only in a very unrealistic scenario the statistical inference flipped from being significant to being insignificant for the SG group.

Failure of at least two prior standard-of-care chemotherapy regimens was required for recruitment, including at least one prior therapy for locally advanced or metastatic disease and including a taxane in any setting. Earlier (neo)adjuvant therapy qualified as 1 of the required prior regimens in case of disease recurrence within 12-months after completion of chemotherapy. Next to taxanes, also anthracyclines and platinum compound are considered important and efficacious options in earlier lines. For enrolment in IMMU-132-05 only prior treatment with a taxane was required, but it is acknowledged that the majority of patients had received prior anthracyclines (82%) and platinum compounds (77%). Anthracyclines appeared to be applied only in the (neo)adjuvant setting in clinical practice. Subgroup analyses showed a similar treatment effect of SG independent from prior therapies.

Demographics and baseline disease characteristics were generally balanced between both treatment arms and reflected a heavily pre-treated patient population with a median number of 4 prior systemic therapy regimens. The low number of male patients (n=2) is considered acceptable, since breast cancer is rare in

men and the results from the pivotal trial is considered extrapolatable to men with mTNBC in line with previous EMA decisions.

Based on more detailed information in response to the D90 LoQ, numbers and distribution of important protocol deviations and provided rationale and background for implemented changes of the protocol and SAP were not considered to have a relevant impact on the study results.

Efficacy data and additional analyses

The primary analysis of PFS by IRC assessment in the BM-ve population as well as secondary endpoints of PFS by IRC assessment in the ITT population and OS in both the BM-ve and the ITT populations were statistically significant and demonstrated clinically meaningful superiority of SG over TPC (**ITT** population: **PFS HR 0.43** [95% CI 0.35, 0.54]; **OS HR 0.51** [95% CI 0.41, 0.62], median OS 12.1 vs 6.7 months for SG compared to TPC). Sensitivity analyses of PFS supported the robustness of the treatment effect of SG. The data were sufficiently mature (OS event rates 66% in the SG arm and 79% in the TPC arm).

ORR by IRC and investigator assessment in the BM-ve and ITT Populations favoured SG over TPC (p-values nominal); nonetheless, the applicant was asked to clarify the high proportion of 30.5% of patients not evaluable for response evaluation in the TPC arm (s. Table 3.3.5.10). More participants in the TPC arm (n=71) were not evaluable for response than in the SG arm (n=18). A total of 62.0% (44 of 71) of participants in the TPC treatment group were not evaluable for response because they were either randomised but never treated or withdrew consent before the first postbaseline efficacy assessment. This is likely related to the preference of patients receiving SG instead of SOC treatment in the open-label study.

DOR by IRC and investigator assessment in the BM-ve and ITT Populations favoured SG over TPC; however, results for duration of response are not considered meaningful in the TPC group in view of the low number of responders and the even lower number of patients with an event.

Results of ORR and CBR supported the benefit of SG with superior treatment effects in both analyses populations (ITT and BM-ve) by IRC and investigator-based assessments. Quality of life, assessed using the EORTC-QoL-C30, showed overall similar results between both treatment arms with the exception of a clinically meaningful worsening of diarrhoea; however, interpretation of PRO data are hampered by the open-label study design and therefore not included in the SmPC.

The applicant provided updated data from the final database lock (25 February 2021), which included further efficacy data collected from the remaining 17 participants after the final data cut for the CSR (11 March 2020). Clinically relevant endpoints of PFS, OS and ORR were consistent with the original submission and updated PFS and OS data are adequately reflected in the SmPC.

Results of subgroup analyses showed consistent effects across different age groups, regions, prior treatments (including prior checkpoint inhibitors or PARP-inhibitors), original diagnosis of TNBC, and presence of liver metastases.

However, due to the small number of patients with **BRCA** positive status (n=43; 8.1%) no firm conclusions can be drawn from these results. Since testing was not required, information on BRCA mutational status was lacking for 35% of study population. This is reflected in the SmPC.

Efficacy results were similar in both treatment arms for patients with known brain metastasis. In the BM-positive population (n=61) stratified HRs for PFS were 0.65 [0.35, 1.22] by IRC and 0.86 [0.45, 1.60] by INV assessment; the stratified OS HR was 0.87 [0.47, 1.63], the median OS was 6.8 months in the SG arm and

7.5 months in the TPC arm. In response to the D90 LoQ the applicant clarified that participants were considered positive for brain metastasis regardless of present brain metastasis at enrolment or only a history of brain metastasis. 32 of 61 participants in the BM-positive population had baseline tumor locations in the brain based on IRC assessment. The efficacy results for this subgroup of patients with present brain metastasis at enrolment showed overall consistent results with those in the BM-positive population. Despite the recognised methodological limitations of these retrospective analyses in subgroups with small sample size, it is reassuring that results do not indicate a detrimental effect of SG relative to TPC for patients with brain metastasis.

The reported median OS for patients with brain metastasis in the control arm is in the upper range of what was reported for TNBC patients with brain metastasis in historical controls (between 3 and 6 months, e.g. Pestalozzi, 2009) and it was somewhat unexpected that the median OS in the TPC arm for patients with brain metastasis was not lower compared to the ITT population or the BM-ve population (7.5 months vs. 6.9 months vs. 6.7 months, respectively). In this context it is again highlighted that only patients with stable and pre-treated brain metastases were enrolled. For these patients the treatment effect of SG on simultaneous peripheral metastases might be relevant for determining the individual prognosis even if there are uncertainties about the effect of SG in the brain. Given the overall non-detrimental efficacy of SG in patients with brain metastasis compared to TPC, SG can be considered as an alternative treatment option.

Available data do not raise concerns regarding a lower treatment effect in elderly; however, data for patients ≥75 are too limited to draw conclusions. The limited data for this age group has been described in section 4.2 of the SmPC.

Paediatric patients or patients with moderate or severe hepatic or renal impairment were not included in the clinical studies. The lack of these data is adequately reflected in the SmPC. An open-label, non-randomised, dose-escalation study, IMMU-132-15, to determine an appropriate starting dose of SG in patients with moderate hepatic impairment is ongoing and anticipated to be completed by December 2021 with the final report available by Q3 2022.

Initially provided exploratory analyses of efficacy by Trop-2 tumor expression showed a treatment benefit of SG in tumors above and below the chosen cut-off for Trop-2 expression but these results suggested a predictive value of Trop-2 expression. The selected method and the single cut-off to determine Trop-2 tumor expression status was not considered sufficient to determine the benefit in patients with tumors that show only a weak or no TROP-2 expression. This is of relevance in view of the MoA of SG as targeted therapy and the proportion of about 20% of patients with TNBC without overexpression of Trop-2 according to literature data.

Trop-2 expression data were provided for only 60% of study populations (although the importance of the evaluation was highlighted during EMA and national SA meetings). The main reason for the limited number of participants with evaluable tumor samples for Trop-2 expression was that collection of baseline tumor biopsies was not mandated for Study IMMU-132-05.

Overall results (HRs for PFS and OS as well as odds ratios for ORR) showed a benefit of SG over the treatment of physician's choice (TPC) for all participants; however, the treatment effect of SG was consistently smaller in the lowest quartile Q1 and subgroups with low Trop-2 expression (H-scores <100, percent membrane cells I2+I3 scores ≤50 and total membrane scores ≤50) than in the higher quartiles. Efficacy results in subjects with low Trop-2 expression showed an increased variability with the 95% CIs crossing 1, but numerically, the point estimates of HRs were beneficial for SG over TPC for both PFS and OS.

This was also supported by ORR results that showed lower values for SG in lower Trop-2 expression groups, but these were still superior compared to those for TPC.

An association between Trop-2 tumor expression and efficacy outcome could be shown with a smaller treatment effect in subgroups with low relative to participants with high Trop-2 expression. However, conclusions on the clinical relevance of different levels of tumor Trop-2 expression for the treatment with SG are hampered by the retrospective character of the analyses and the limited sample size of the Trop-2–evaluable population (with even smaller numbers per quartile). Therefore, available data do not support a restricted indication. Efficacy of SG appeared superior compared to the control arm also for patients with low Trop-2 expression.

The initially proposed indication wording does not refer to any specific agent when defining required prior treatment; however, subgroup analyses indicated a treatment effect of SG independent of prior treatment (see above) and the open wording allows more flexibility regarding changes in clinical practise. The requirement of prior taxane therapy is reflected in section 5.1 of the SmPC. As requested, the applicant revised the indication to reflect the target population more clearly (in bold the new text and strikethrough the deletions):

Trodelvy **as monotherapy** is indicated for the treatment of adult patients with unresectable ~~*locally advanced*~~ or metastatic triple-negative breast cancer (mTNBC) who have received ~~*at least*~~ two **or more** prior **systemic** therapies, including at least one **of them** ~~*prior therapy*~~ for ~~*locally*~~ advanced ~~*or metastatic*~~ disease (see section 5.1).

The indication wording encompasses the treatment of patients with unresectable or metastatic TNBC; yet only a single participant was enrolled with unresectable locally advanced cancer in Study IMMU-132-05. The applicant argued that the low number was not unexpected, as the natural history of locally advanced breast cancer is progression to distant metastatic disease with each line of therapy. ESMO clinical practice guidelines do not distinguish between unresectable locally advanced and metastatic breast cancer treatment paradigms due to the similar biological and demographic characteristics, but provide treatment recommendations for "advanced breast cancer". In view of the high unmet medical need and expected similar treatment benefits for patients with unresectable disease, who are eligible for systemic treatment, the extrapolation of data is considered acceptable in line with other approved breast cancer indications in the EU.

2.5.4. Conclusions on the clinical efficacy

A clinically meaningful benefit in progression free and overall survival was demonstrated in the intended target population of patients with advanced TNBC and at least 2 prior systemic therapies.

Provided subgroup results for patients considered as brain metastasis positive (n=61) indicated a similar benefit of SG compared to control. Despite remaining uncertainties about the treatment effect on brain metastasis, the benefit of SG in distant metastases can be clinically relevant for patients with pretreated and stable brain metastasis and SG is considered as a treatment option also in this population.

2.6. Clinical safety

The clinical safety data supporting this Marketing Authorisation Application (MAA) are derived from 2 clinical studies:

1) a Phase 1/2 basket study, IMMU-132-01, that included a cohort of patients with mTNBC that received a starting dose of 10 mg/kg SG and

2) a confirmatory Phase 3 study in patients with mTNBC, IMMU-132-05, that evaluated SG at a starting dose of 10 mg/kg compared with single-agent chemotherapy (ie, treatment of physician's choice [TPC]; either eribulin, capecitabine, gemcitabine, or vinorelbine).

Safety data are also provided for 2 pools:

1) pooled data from triple-negative breast cancer (TNBC) patients who received 10 mg/kg SG in either the IMMU-132-01 or IMMU-132-05 study; this pool is referred to as **the Overall Targeted TNBC pool and includes 366 patients** and

2) all patients treated with an SG starting dose of 10 mg/kg in either of the clinical studies; IMMU-132-01 or IMMU-132-05 this pool is referred to as the **All Treated pool** and includes **660 patients.**

The safety database cut-off date of the initial submission was 11 March 2020. With the responses to the first round of question the applicant provided treatment and follow-up durations and safety data were provided using the final database lock for both IMMU-132-01 (final database lock 02 April 2021) and IMMU-132-05 (final database lock 25 February 2021). As of the prior data DCO date of 11 March 2020, there were no participants continuing SG treatment in Study IMMU-132-01, and 17 participants continuing treatment in the SG group in Study IMMU-132-05, and no participants in the TPC group Overall, the updated safety and treatment and follow-up duration data are similar to the 11 March 2020 DCO data, therefore, the tables included refer to the DCO Date of 11 March 2020 unless otherwise indicated (updated safety data 02/04/2021(IMMU-132-01) 25/02/2021(IMMU-132-05)).

Table 48 Safety Database for 10 mg/kg SG in mTNBC

Clinical Trial Groups	**SG 10 mg/kg**	**Active Control**
Controlled trials conducted for proposed indication		
IMMU-132-05	258	224[1]
Uncontrolled trials for proposed indication		
IMMU-132-01[2]	108	-
TNBC Total	**366**	**224**
Uncontrolled trials in other indications		
IMMU-132-01[3]	294	-
Overall total	**660**	**224**

[1]Single-agent chemotherapy with either eribulin, capecitabine, gemcitabine, or vinorelbine; referred to as treatment of physician's choice.
[2]A total of 144 patients with TNBC were enrolled in the study and received at least 1 dose of SG. Of these 144 patients, 108 had received at least 2 prior therapies for metastatic disease and were treated with SG at a starting dose of 10 mg/kg; these patients were included in the safety analyses.
[3]Other tumor types included ovarian, endometrial, cervical, HR+/HER2- mBC, castration-resistant prostate cancer, colorectal cancer, NSCLC, SCLC, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and mUC. Patients with mTNBC who were not included in the Overall TNBC pool are also included in this total.
GBM=glioblastoma multiforme; HER2 =human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; mBC=metastatic breast cancer; mUC=metastatic urothelial cancer; NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; SG=sacituzumab govitecan; mTNBC=metastatic triple-negative breast cancer; TPC=treatment of physician's choice

2.6.1. Patient exposure

Table 49 Treatment Exposure (Safety Population IMMU-132-05)

	SG (N = 258)	Eribulin (N = 122)	Capecitabine (N = 22)	Gemcitabine (N = 31)	Vinorelbine (N = 43)
Treatment Duration (months) [a]					
n	258	122	22	31	43
Mean	5.767	2.270	2.156	2.250	1.732
SD	4.9046	2.1827	2.5623	2.0067	2.3122
Median	4.386	1.643	1.183	1.413	0.953
Minimum	0.03	0.03	0.33	0.23	0.03
Maximum	22.87	15.34	10.58	8.08	11.53
Treatment Duration (Cycles) [b]					
n	258	122	22	31	43
Mean	8.5	3.8	3.3	3.0	2.9
SD	6.70	2.97	3.62	2.06	2.97
Median	7.0	3.0	2.0	2.0	2.0
Minimum	1	1	1	1	1
Maximum	33	21	15	9	15

Note: An additional 6 patients were treated with capecitabine that was supplied by another source (ie, not the pharmacy at the investigational site) and thus, exposure data for these patients are not available.
[a] Treatment duration (months) is calculated as (date of last treatment administration – date of first treatment administration + 1)/30.4375.
[b] Treatment duration (cycles) is calculated as number of cycles that a patient had at least one dose.
SD=standard deviation; SG=sacituzumab govitecan
Source: Table 14.3

Table 50. Summary of Treatment Exposure (Pooled Population for TNBC) (updated safety data 02/04/2021(IMMU-132-01) 25/02/2021(IMMU-132-05)).

	IMMU-132-01 Target TNBC (N = 108)	IMMU-132-05 SG (N = 258)	IMMU-132-05 TPC (N = 224)	Overall Target TNBC (N = 366)	All Treated SG (10 mg/kg) (N = 660)
Duration of Treatment (months)					
N	108	258	224	366	660
Mean (SD)	7.6 (9.63)	6.2 (5.92)	2.1 (2.20)	6.6 (7.23)	6.2 (7.52)
Median	5.1	4.4	1.3	4.9	4.1
Q1, Q3	1.7, 8.1	2.3, 8.1	0.9, 2.7	2.1, 8.1	1.6, 7.7
Min, Max	0.0, 62.6	0.0, 29.6	0.0, 15.3	0.0, 62.6	0.0, 62.6
≥ 6 months	44 (40.7%)	95 (36.8%)	13 (5.8%)	139 (38.0%)	226 (34.2%)
≥ 12 months	19 (17.6%)	29 (11.2%)	1 (0.4%)	48 (13.1%)	75 (11.4%)
≥ 24 months	6 (5.6%)	7 (2.7%)	0	13 (3.6%)	26 (3.9%)
≥ 36 months	3 (2.8%)	0	0	3 (0.8%)	8 (1.2%)

Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice
Duration of treatment (months) = (date of last dose of study drug - date of first dose of study drug + 1)/30.4375.
Source: Ad Hoc Table 10866.10

Table 51. Summary of Duration of Follow-up (Pooled Population for TNBC) (updated safety data 02/04/2021(IMMU-132-01) 25/02/2021(IMMU-132-05)).

	IMMU-132-01 Target TNBC (N = 108)	IMMU-132-05 SG (N = 258)	IMMU-132-05 TPC (N = 224)	Overall Target TNBC (N = 366)	All Treated SG (10 mg/kg) (N = 660)
Duration of Follow Up (months)					
N	108	258	224	366	660
Mean (SD)	15.6 (13.11)	12.8 (7.54)	8.6 (6.67)	13.7 (9.60)	13.8 (11.07)
Median	12.6	11.7	6.7	11.7	10.9
Q1, Q3	7.2, 19.4	6.9, 18.3	3.6, 11.3	6.9, 18.3	5.8, 18.8
Min, Max	0.3, 64.0	0.6, 30.7	0.1, 30.4	0.3, 64.0	0.3, 66.6

Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SG = sacituzumab govitecan; TNBC = triple negative breast cancer; TPC = treatment of physician's choice
Duration of follow-up is defined as the time from the first dose date to the death date or the last date known alive.
Source: Ad Hoc Table 10866.11

2.6.2. Adverse events

Table 52 Overall Summary of AEs in Study IMMU-132-01, IMMU-132-05 and the Overall Targeted TNBC and All Treated Pools ((updated safety data 02/04/2021(IMMU-132-01) 25/02/2021(IMMU-132-05)).

	IMMU-132-01 Target TNBC (N = 108)	IMMU-132-05 SG (N = 258)	IMMU-132-05 TPC (N = 224)	Overall Target TNBC (N = 366)	All Treated SG (10 mg/kg) (N = 660)
Number of participants with any TEAEs	108 (100.0%)	257 (99.6%)	219 (97.8%)	365 (99.7%)	659 (99.8%)
Number of participants with any treatment-related TEAEs	105 (97.2%)	252 (97.7%)	192 (85.7%)	357 (97.5%)	645 (97.7%)
Number of participants with any TEAEs with CTCAE Grade 3, 4, or 5	78 (72.2%)	188 (72.9%)	145 (64.7%)	266 (72.7%)	495 (75.0%)
Number of participants with any serious TEAEs	33 (30.6%)	69 (26.7%)	64 (28.6%)	102 (27.9%)	229 (34.7%)
Deaths within 30 days of last dose date	1 (0.9%)	1 (0.4%)	2 (0.9%)	2 (0.5%)	12 (1.8%)
Treatment-related deaths	0	0	1 (0.4%)	0	1 (0.2%)
TEAEs leading to study drug withdrawal/discontinuation	4 (3.7%)	12 (4.7%)	12 (5.4%)	16 (4.4%)	46 (7.0%)
TEAEs leading to study drug dose reduction	0	57 (22.1%)	59 (26.3%)	57 (15.6%)	57 (8.6%)
TEAEs leading to study drug interruption	51 (47.2%)	162 (62.8%)	87 (38.8%)	213 (58.2%)	364 (55.2%)

CTCAE = Common Terminology Criteria for Adverse events; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice
Percentages are based on big N. For each row category, a participant with 2 or more adverse events in that category is counted only once. Participants may be counted in multiple categories.
Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related or probably related to study drug or TEAEs with a missing causality.
Adverse events were graded using CTCAE version 5.0.

The percentage of patients with at least one AE was similar in the SG and TPC groups (99.6% vs 97.8%) in Study IMMU-132-05. The most frequent AEs in the SG group compared with the TPC group in Study IMMU-132-05 included the following:

- Diarrhoea (65.1% vs 17.0%)
- Neutropenia (64.0% vs 43.8%)
- Nausea (62.4% vs 30.4%)
- Fatigue (51.6% vs 39.7%)
- Alopecia (46.9% vs 16.1%)
- Anaemia (39.5% vs 27.7%)
- Constipation (37.2 % vs 23.2%)
- Vomiting (33.3 % vs 16.1%)

Table 53 Treatment-Emergent Adverse Events in Study IMMU-132-05 by System Organ Class (≥ 1 Participant in Either Group) and by Preferred Term (≥ 2 Participants With Worst CTCAE of Grade 3 or Higher in Either Group)

MedDRA System Organ Class Preferred Term	SG N = 258		TPC N = 224	
	All	Grade 3 or Higher	All	Grade 3 or Higher
Any TEAEs	257 (99.6)	186 (72.1)	219 (97.8)	145 (64.7)
Blood and lymphatic system disorders	198 (76.7)	144 (55.8)	132 (58.9)	90 (40.2)
Neutropenia	165 (64.0)	134 (51.9)	98 (43.8)	76 (33.9)
Anemia	102 (39.5)	24 (9.3)	62 (27.7)	13 (5.8)
Leukopenia	43 (16.7)	27 (10.5)	27 (12.1)	13 (5.8)
Lymphopenia	25 (9.7)	5 (1.9)	13 (5.8)	5 (2.2)
Thrombocytopenia	16 (6.2)	4 (1.6)	28 (12.5)	5 (2.2)
Febrile neutropenia	15 (5.8)	15 (5.8)	6 (2.7)	6 (2.7)
Leukocytosis	3 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)
Cardiac disorders	22 (8.5)	1 (0.4)	14 (6.3)	4 (1.8)
Pericardial effusion	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)
Ear and labyrinth disorders	14 (5.4)	0 (0.0)	6 (2.7)	0 (0.0)
Endocrine disorders	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)

MedDRA System Organ Class Preferred Term	SG N = 258		TPC N = 224	
	All	Grade 3 or Higher	All	Grade 3 or Higher
Eye disorders	24 (9.3)	0 (0.0)	15 (6.7)	1 (0.4)
Gastrointestinal disorders	238 (92.2)	40 (15.5)	141 (62.9)	11 (4.9)
Diarrhoea	168 (65.1)	29 (11.2)	38 (17.0)	2 (0.9)
Nausea	161 (62.4)	8 (3.1)	68 (30.4)	1 (0.4)
Constipation	96 (37.2)	1 (0.4)	52 (23.2)	0 (0.0)
Vomiting	86 (33.3)	4 (1.6)	36 (16.1)	3 (1.3)
Abdominal pain	55 (21.3)	7 (2.7)	18 (8.0)	3 (1.3)
Stomatitis	26 (10.1)	2 (0.8)	14 (6.3)	0 (0.0)
Enteritis	2 (0.8)	2 (0.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	200 (77.5)	23 (8.9)	149 (66.5)	34 (15.2)
Fatigue	133 (51.6)	11 (4.3)	89 (39.7)	19 (8.5)
Asthenia	40 (15.5)	4 (1.6)	29 (12.9)	3 (1.3)
Pyrexia	38 (14.7)	1 (0.4)	32 (14.3)	5 (2.2)
Oedema peripheral	24 (9.3)	0 (0.0)	24 (10.7)	2 (0.9)
Mucosal inflammation	20 (7.8)	2 (0.8)	14 (6.3)	3 (1.3)
Pain	19 (7.4)	2 (0.8)	11 (4.9)	2 (0.9)
Gait disturbance	4 (1.6)	1 (0.4)	2 (0.9)	2 (0.9)
Hepatobiliary disorders	11 (4.3)	3 (1.2)	8 (3.6)	4 (1.8)
Hyperbilirubinaemia	2 (0.8)	1 (0.4)	2 (0.9)	2 (0.9)
Immune system disorders	8 (3.1)	0 (0.0)	2 (0.9)	0 (0.0)
Infections and infestations	137 (53.1)	25 (9.7)	80 (35.7)	18 (8.0)
Urinary tract infection	33 (12.8)	1 (0.4)	18 (8.0)	1 (0.4)
Upper respiratory tract infection	31 (12.0)	0 (0.0)	7 (3.1)	0 (0.0)
Pneumonia	13 (5.0)	9 (3.5)	11 (4.9)	6 (2.7)
Device related infection	6 (2.3)	3 (1.2)	0 (0.0)	0 (0.0)
Influenza	6 (2.3)	2 (0.8)	0 (0.0)	0 (0.0)
Cellulitis	5 (1.9)	2 (0.8)	7 (3.1)	2 (0.9)
Sepsis	2 (0.8)	2 (0.8)	5 (2.2)	5 (2.2)
Injury, poisoning and procedural complications	28 (10.9)	4 (1.6)	20 (8.9)	2 (0.9)
Investigations	87 (33.7)	14 (5.4)	60 (26.8)	12 (5.4)
Aspartate aminotransferase increased	29 (11.2)	7 (2.7)	27 (12.1)	6 (2.7)
Alanine aminotransferase increased	27 (10.5)	3 (1.2)	22 (9.8)	3 (1.3)
Blood alkaline phosphatase increased	19 (7.4)	3 (1.2)	12 (5.4)	2 (0.9)
Blood bilirubin increased	6 (2.3)	3 (1.2)	1 (0.4)	1 (0.4)
Gamma-glutamyltransferase increased	7 (2.7)	1 (0.4)	6 (2.7)	4 (1.8)

MedDRA System Organ Class Preferred Term	SG N = 258		TPC N = 224	
	All	Grade 3 or Higher	All	Grade 3 or Higher
Metabolism and nutrition disorders	133 (51.6)	26 (10.1)	94 (42.0)	9 (4.0)
Decreased appetite	71 (27.5)	4 (1.6)	46 (20.5)	2 (0.9)
Hypokalaemia	41 (15.9)	7 (2.7)	29 (12.9)	1 (0.4)
Hypomagnesaemia	32 (12.4)	0 (0.0)	13 (5.8)	0 (0.0)
Hypocalcaemia	17 (6.6)	3 (1.2)	5 (2.2)	1 (0.4)
Hyperglycaemia	17 (6.6)	2 (0.8)	12 (5.4)	3 (1.3)
Hypophosphataemia	15 (5.8)	9 (3.5)	9 (4.0)	3 (1.3)
Hyponatraemia	8 (3.1)	3 (1.2)	6 (2.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	117 (45.3)	15 (5.8)	91 (40.6)	11 (4.9)
Back pain	42 (16.3)	3 (1.2)	31 (13.8)	4 (1.8)
Arthralgia	32 (12.4)	1 (0.4)	16 (7.1)	0 (0.0)
Pain in extremity	20 (7.8)	6 (2.3)	17 (7.6)	2 (0.9)
Myalgia	11 (4.3)	1 (0.4)	19 (8.5)	2 (0.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	11 (4.3)	4 (1.6)	4 (1.8)	0 (0.0)
Tumour pain	5 (1.9)	2 (0.8)	3 (1.3)	0 (0.0)
Nervous system disorders	120 (46.5)	3 (1.2)	92 (41.1)	10 (4.5)
Headache	46 (17.8)	2 (0.8)	28 (12.5)	1 (0.4)
Dizziness	26 (10.1)	0 (0.0)	16 (7.1)	0 (0.0)
Neuropathy peripheral	9 (3.5)	0 (0.0)	24 (10.7)	3 (1.3)
Peripheral sensory neuropathy	4 (1.6)	0 (0.0)	11 (4.9)	2 (0.9)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Product issues	3 (1.2)	0 (0.0)	2 (0.9)	0 (0.0)
Psychiatric disorders	50 (19.4)	1 (0.4)	32 (14.3)	3 (1.3)
Insomnia	29 (11.2)	0 (0.0)	11 (4.9)	0 (0.0)
Mental status changes	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)
Renal and urinary disorders	20 (7.8)	3 (1.2)	9 (4.0)	0 (0.0)
Reproductive system and breast disorders	28 (10.9)	3 (1.2)	15 (6.7)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	133 (51.6)	21 (8.1)	103 (46.0)	30 (13.4)
Cough	61 (23.6)	0 (0.0)	40 (17.9)	1 (0.4)
Dyspnoea	43 (16.7)	10 (3.9)	47 (21.0)	12 (5.4)
Pulmonary embolism	7 (2.7)	5 (1.9)	8 (3.6)	7 (3.1)
Pleural effusion	7 (2.7)	2 (0.8)	14 (6.3)	9 (4.0)
Hypoxia	4 (1.6)	4 (1.6)	3 (1.3)	3 (1.3)
Respiratory failure	2 (0.8)	2 (0.8)	2 (0.9)	2 (0.9)

MedDRA System Organ Class Preferred Term	SG N = 258		TPC N = 224	
	All	Grade 3 or Higher	All	Grade 3 or Higher
Skin and subcutaneous tissue disorders	166 (64.3)	1 (0.4)	77 (34.4)	6 (2.7)
Alopecia	121 (46.9)	0 (0.0)	36 (16.1)	0 (0.0)
Rash	32 (12.4)	1 (0.4)	12 (5.4)	1 (0.4)
Pruritis	26 (10.1)	0 (0.0)	7 (3.1)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	5 (1.9)	0 (0.0)	6 (2.7)	2 (0.9)
Vascular disorders	50 (19.4)	5 (1.9)	45 (20.1)	8 (3.6)
Hypertension	17 (6.6)	2 (0.8)	13 (5.8)	1 (0.4)
Hypotension	11 (4.3)	0 (0.0)	9 (4.0)	2 (0.9)
Deep vein thrombosis	4 (1.6)	2 (0.8)	4 (1.8)	3 (1.3)
Embolism	1 (0.4)	0 (0.0)	3 (1.3)	2 (0.9)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
The denominator for percentages is the number of participants in the Safety Population for each treatment group.
A TEAE is defined as an AE with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.
If a participant had 2 or more AEs in the same system organ class (or with the same preferred term) with different CTCAE grades, then the event with the highest grade was used for that participant. Participants with missing CTCAE grade for a nonfatal AE are counted under 'missing' category unless the participant already has another AE with CTCAE grade of 4, in which case the participant is counted under CTCAE grade of 4.
AE terms were coded using MedDRA version 23.0.
For summary purposes, the following PTs have been re-coded. Neutrophil count decreased to neutropenia, white blood cell count decreased to leukopenia, lymphocyte count decreased to lymphopenia, hemoglobin decreased and red blood cell count decreased to anemia, and platelet count decreased to thrombocytopenia.

2.6.2.1. Treatment related AEs

The table below provides background and justification for inclusion of adverse events as ADRs in the proposed product information, presented by System Organ Class (SOC) and preferred term (PT) (or pooled PTs).

Table 54 ADRs for Inclusion in Product Information by SOC and PT

System Organ Class	Preferred Term or Pooled PTs	Reason for Exclusion/ Inclusion in SmPC	Frequency in TNBC Pool (Irrespective of Causality)
Infections and Infestations			
	Urinary tract infection	15.3 % (TNBC) vs 8.0% (TPC)	Very common

System Organ Class	Preferred Term or Pooled PTs	Reason for Exclusion/ Inclusion in SmPC	Frequency in TNBC Pool (Irrespective of Causality)
	Upper respiratory tract infection	13.1 % (TNBC) vs 3.1% (TPC)	Very common
	Nasopharyngitis	5.2 % (TNBC) vs 2.2% (TPC)	Common
	Sinusitis	4.4 % (TNBC) vs 0.4% (TPC)	Common
	Bronchitis	3.8 % (TNBC) vs 0.4% (TPC)	Common
	Influenza	2.5 % (TNBC) vs 0% (TPC)	Common
	Oral herpes	2.5% (TNBC) vs 0.4% (TPC)	Common
Blood and Lymphatic System Disorders			
	Neutropenia[1]	64.2% (TNBC) vs 43.8% (TPC)	Very common
	Anaemia[2]	43.2% (TNBC) vs 27.7% (TPC)	Very common
	Leukopenia[3]	19.4% (TNBC) vs 12.1% (TPC)	Very common
	Lymphopenia[4]	10.9% (TNBC) vs 5.8% (TPC)	Very common
	Febrile neutropenia	6.6% (TNBC) vs 2.7% (TPC)	Common
Immune System Disorders			
	Hypersensitivity[5]	36.6% (TNBC) vs 20.5% (TPC)	Very common
Metabolism and Nutrition Disorders			
	Decreased appetite	28.1% (TNBC) vs 20.5% (TPC)	Very common
	Hypokalaemia	16.7% (TNBC) vs 12.9% (TPC)	Very common
	Hypomagnesaemia	15.0% (TNBC) vs 5.8% (TPC)	Very common
	Hyperglycaemia	11.7% (TNBC) vs 5.4% (TPC)	Very common
	Hypophosphataemia	8.7% (TNBC) vs 4.0% (TPC)	Common
	Hypocalcaemia	7.1% (TNBC) vs 2.2% (TPC)	Common
Psychiatric Disorders			
	Insomnia	11.7% (TNBC) vs 4.9% (TPC)	Very common
	Anxiety	6.3% (TNBC) vs 3.6% (TPC)	Common
Nervous System Disorders			
	Headache	19.4% (TNBC) vs 12.5% (TPC)	Very common
	Dizziness	13.7% (TNBC) vs 7.1% (TPC)	Very common

System Organ Class	Preferred Term or Pooled PTs	Reason for Exclusion/ Inclusion in SmPC	Frequency in TNBC Pool (Irrespective of Causality)
	Dysgeusia	9.0% (TNBC) vs 2.7% (TPC)	Common
Eye Disorders			
	Dry eye	Excluded: 4.6% (TNBC) vs 0.4% (TPC) Low incidence of related events. Close safety monitoring did not identify a relevant safety signal.	Not applicable
	Vision blurred	Excluded:3.6% (TNBC) vs 0.4% (TPC) Low incidence of related events. Close safety monitoring did not identify a relevant safety signal.	Not applicable
Cardiac Disorders			
	Sinus tachycardia	Excluded:3.0% (TNBC) vs 0.9% (TPC) Low incidence of related events. Close safety monitoring did not identify a relevant safety signal.	Not applicable
Respiratory, Thoracic and Mediastinal Disorders			
	Cough	22.7% (TNBC) vs 17.9% (TPC)	Very common
	Rhinorrhoea	6.6% (TNBC) vs 0.4% (TPC)	Common
	Nasal congestion	6.0% (TNBC) vs 1.3% (TPC)	Common
	Epistaxis	5.2% (TNBC) vs 0.4% (TPC)	Common
	Dyspnoea exertional	4.1% (TNBC) vs 1.3% (TPC)	Common
	Productive cough	3.8% (TNBC) vs 0.4% (TPC)	Common
	Upper airway cough syndrome	2.7% (TNBC) vs 0.4% (TPC)	Common
Gastrointestinal Disorders			
	Diarrhoea	64.5% (TNBC) vs 17.0% (TPC)	Very common
	Nausea	64.2% (TNBC) vs 30.4% (TPC)	Very common
	Vomiting	38.0% (TNBC) vs 16.1% (TPC)	Very common
	Constipation	36.3% (TNBC) vs 23.2% (TPC)	Very common
	Abdominal pain	20.8% (TNBC) vs 8.0% (TPC)	Very common
	Stomatitis	9.6% (TNBC) vs 6.3% (TPC)	Common
	Abdominal pain upper	6.8% (TNBC) vs 3.6% (TPC)	Common
	Gastrooesophageal reflux disease	5.7% (TNBC) vs 3.1% (TPC)	Common
	Abdominal distension	5.5% (TNBC) vs 3.1% (TPC)	Common
	Haemorrhoids	Excluded: 3.8% (TNBC) vs 1.3% (TPC) Low incidence of related events. Close safety monitoring did not identify a relevant safety signal.	Not applicable
Skin and Subcutaneous Tissue Disorders			
	Alopecia	44.3% (TNBC) vs 16.1% (TPC)	Very common
	Rash	15.8% (TNBC) vs 5.4% (TPC)	Very common

System Organ Class	Preferred Term or Pooled PTs	Reason for Exclusion/ Inclusion in SmPC	Frequency in TNBC Pool (Irrespective of Causality)
	Pruritus	12.0% (TNBC) vs 3.1% (TPC)	Very common
	Dry Skin	9.0% (TNBC) vs 1.3% (TPC)	Common
	Rash maculopapular	6.8% (TNBC) vs 1.3% (TPC)	Common
Musculoskeletal and Connective Tissue Disorders			
	Back pain	18.3% (TNBC) vs 13.8% (TPC)	Very common
	Arthralgia	13.7% (TNBC) vs 7.1% (TPC)	Very common
	Musculoskeletal chest pain	6.3% (TNBC) vs 3.1% (TPC)	Common
	Muscle spasms	5.2% (TNBC) vs 2.2% (TPC)	Common
Renal and Urinary Disorders			
	Haematuria	2.7% (TNBC) vs 0.4% (TPC)	Common
	Dysuria	4.4% (TNBC) vs 1.8% (TPC)	Common
General Disorders and Administration Site Conditions			
	Fatigue	52.5% (TNBC) vs 39.7% (TPC)	Very common
	Pain	7.1% (TNBC) vs 4.9% (TPC)	Common
	Chills	5.5% (TNBC) vs 2.7% (TPC)	Common
Investigations			
	Weight decreased	10.1% (TNBC) vs 6.7% (TPC)	Very common
	Blood alkaline phosphatase increased	8.5% (TNBC) vs 5.4% (TPC)	Common
	Activated partial thromboplastin time prolonged	4.1% (TNBC) vs 0% (TPC)	Common
	Electrocardiogram QT prolonged	Excluded: 3.8% (TNBC) vs 1.3% (TPC) No evidence for QTc prolongation was seen with SG in the PK-ECG substudy of Study IMMU-132-05 (Module 5.3.3.5 CSR IMMX-PMX-SN38-2457).	Not applicable
	Blood creatinine increased	Excluded:3.0% (TNBC) vs 0% (TPC) Low incidence of related events. Close safety monitoring did not identify a relevant safety signal.	Not applicable

[1] Includes events coded to the following preferred terms: neutropenia; neutrophil count decreased.
[2] Includes events coded to the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.
[3] Includes events coded to the following preferred terms: leukopenia; white blood cell count decreased.
[4] Includes events coded to the following preferred terms: lymphopenia; lymphocyte count decreased.
[5] Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: Cough; dyspnoea; rash; pruritus; stomatitis; hypotension; rash maculopapular; flushing; erythema; chest discomfort; hypersensitivity; rhinitis allergic; wheezing; localised oedema; dermatitis acneiform; conjunctivitis; rash pruritic; oedema; rash macular; rash pustular; swelling; swelling face; urticaria; anaphylactic reaction; asthma; bronchospasm; conjunctivitis allergic; dermatitis; dermatitis contact; eye pruritus; mouth ulceration; periorbital oedema; rash erythematous; scrotal oedema; seasonal allergy; skin exfoliation; swollen tongue; tachypnoea; throat tightness; Type IV hypersensitivity reaction; choking.

Table 55 Treatment-Related AEs in Study IMMU-132-05 by System Organ Class (≥ 1 Participant in Either Group) and Preferred Term (≥ 10% Participants in Either Group), the Overall Target TNBC, and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated N = 258	IMMU-132-05 TPC N = 224	Overall Target TNBC N = 366	All Treated SG (10 mg/kg) N = 660
Any Treatment-related TEAEs	252 (97.7)	192 (85.7)	357 (97.5)	645 (97.7)
Blood and lymphatic system disorders	190 (73.6)	122 (54.5)	277 (75.7)	479 (72.6)
Neutropenia	163 (63.2)	96 (42.9)	233 (63.7)	397 (60.2)
Anemia	89 (34.5)	54 (24.1)	140 (38.3)	236 (35.8)
Leukopenia	41 (15.9)	25 (11.2)	69 (18.9)	117 (17.7)
Thrombocytopenia	14 (5.4)	25 (11.2)	26 (7.1)	46 (7.0)
Cardiac disorders	8 (3.1)	3 (1.3)	11 (3.0)	16 (2.4)
Ear and labyrinth disorders	4 (1.6)	0 (0.0)	6 (1.6)	8 (1.2)
Endocrine disorders	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Eye disorders	12 (4.7)	6 (2.7)	18 (4.9)	23 (3.5)
Gastrointestinal disorders	216 (83.7)	110 (49.1)	311 (85.0)	558 (84.5)
Diarrhoea	153 (59.3)	27 (12.1)	214 (58.5)	381 (57.7)
Nausea	147 (7.0)	59 (26.3)	213 (58.2)	403 (61.1)
Vomiting	75 (29.1)	23 (10.3)	122 (33.3)	230 (34.8)
Constipation	44 (17.1)	32 (14.3)	65 (7.8)	126 (19.1)
Abdominal pain	29 (11.2)	9 (4.0)	41 (11.2)	72 (10.9)
General disorders and administration site conditions	164 (63.6)	97 (43.3)	226 (61.7)	394 (59.7)
Fatigue	115 (44.6)	68 (30.4)	169 (46.2)	304 (46.1)
Asthenia	31 (12.0)	23 (10.3)	35 (9.6)	46 (7.0)
Hepatobiliary disorders	2 (0.8)	3 (1.3)	4 (1.1)	5 (0.8)
Immune system disorders	1 (0.4)	1 (0.4)	5 (1.4)	8 (1.2)
Infections and Infestations	30 (11.6)	22 (9.8)	50 (13.7)	83 (12.6)
Injury, poisoning and procedural complications	3 (1.2)	3 (1.3)	5 (1.4)	10 (1.5)
Investigations	46 (17.8)	32 (14.3)	83 (22.7)	155 (23.5)
Metabolism and nutrition disorders	85 (32.9)	53 (23.7)	138 (37.7)	282 (42.7)
Decreased appetite	51 (19.8)	32 (14.3)	81 (22.1)	167 (25.3)
Musculoskeletal and connective tissue disorders	32 (12.4)	28 (12.5)	42 (11.5)	61 (9.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	1 (0.4)	4 (1.1)	5 (0.8)
Nervous system disorders	64 (24.8)	53 (23.7)	106 (29.0)	168 (25.5)
Pregnancy, Puerperium and perinatal conditions	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Psychiatric disorders	7 (2.7)	7 (3.1)	18 (4.9)	33 (5.0)

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated N = 258	IMMU-132-05 TPC N = 224	Overall Target TNBC N = 366	All Treated SG (10 mg/kg) N = 660
Renal and urinary disorders	2 (0.8)	3 (1.3)	8 (2.2)	20 (3.0)
Reproductive system and breast disorders	4 (1.6)	2 (0.9)	7 (1.9)	7 (1.1)
Respiratory, thoracic and mediastinal disorders	41 (15.9)	17 (7.6)	61 (16.7)	109 (16.5)
Skin and subcutaneous tissue disorders	147 (57.0)	53 (23.7)	200 (54.6)	361 (54.7)
Alopecia	119 (46.1)	35 (15.6)	157 (42.9)	274 (41.5)
Vascular disorders	17 (6.6)	7 (3.1)	25 (6.8)	41 (6.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice
Percentages are based on big N.
AE terms were coded using MedDRA version 23.0.
Treatment-related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
For summary purposes, the following PTs have been re-coded. Neutrophil count decreased to neutropenia, white blood cell count decreased to leukopenia, lymphocyte count decreased to lymphopenia, hemoglobin decreased and red blood cell count decreased to anemia, and platelet count decreased to thrombocytopenia.

Grade 3-5 events

Table 56 Summary of NCI-CTCAE Grade 3 or Higher Treatment-Emergent Adverse Events Reported by >=5% Patients in Any Treatment Arm by Preferred Term Safety Population

Preferred Term	IMMU-132 (N = 258) n (%)	TPC (N = 224) n (%)	Total (N = 482) n (%)
Patients with Any NCI-CTCAE Grade 3 or Higher Treatment-Emergent Adverse Events	186 (72.1)	145 (64.7)	331 (68.7)
Neutropenia	89 (34.5)	45 (20.1)	134 (27.8)
Neutrophil count decreased	54 (20.9)	34 (15.2)	88 (18.3)
Diarrhoea	29 (11.2)	2 (0.9)	31 (6.4)
Anaemia	24 (9.3)	13 (5.8)	37 (7.7)
White blood cell count decreased	20 (7.8)	11 (4.9)	31 (6.4)
Febrile neutropenia	15 (5.8)	6 (2.7)	21 (4.4)
Fatigue	11 (4.3)	19 (8.5)	30 (6.2)
Dyspnoea	10 (3.9)	12 (5.4)	22 (4.6)

Note: The denominator for percentages is the number of patients in the Safety Population for each treatment group.
Note: Treatment-emergent adverse event is defined as an adverse event with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.
Note: Patients may report more than one event per preferred term and are counted once for the preferred term. Table is sorted by descending frequency of preferred term in IMMU-132 arm.
Note: MedDRA Version 22.1 was used for coding.
Source: Listing 16.2.7.1 Program Name: t_ae2.sas Date Generated: 14JUL2020 Page 1 of 1

Table 14.3.1.3
Summary of NCI-CTCAE Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	IMMU-132 (N = 258) n (%)	TPC (N = 224) n (%)	Total (N = 482) n (%)
Patients with Any NCI-CTCAE Grade 3 or Higher Treatment-Emergent Adverse Events	186 (72.1)	145 (64.7)	331 (68.7)
Renal and urinary disorders	3 (1.2)	0	3 (0.6)
Dysuria	1 (0.4)	0	1 (0.2)
Haematuria	1 (0.4)	0	1 (0.2)
Urinary incontinence	1 (0.4)	0	1 (0.2)

Hepatobiliary disorders	3 (1.2)	4 (1.8)	7 (1.5)
Hyperbilirubinaemia	1 (0.4)	2 (0.9)	3 (0.6)
Jaundice	1 (0.4)	1 (0.4)	2 (0.4)
Liver disorder	1 (0.4)	0	1 (0.2)
Bile duct obstruction	0	1 (0.4)	1 (0.2)

Table 57 AEs Leading to a Study Drug Dose Reduction in Study IMMU-132-05 and the Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Any TEAE leading to Dose Reduction	56 (21.7)	59 (26.3)	56 (15.3)	56 (8.5)
Blood and lymphatic system disorders	30 (11.6)	46 (20.5)	30 (8.2)	30 (4.5)
Neutropenia	23 (8.9)	43 (19.2)	23 (6.3)	23 (3.5)
Febrile neutropenia	7 (2.7)	0 (0.0)	7 (1.9)	7 (1.1)
Anemia	3 (1.2)	1 (0.4)	3 (0.8)	3 (0.5)
Leukopenia	2 (0.8)	3 (1.3)	2 (0.5)	2 (0.3)
Thrombocytopenia	1 (0.4)	2 (0.9)	1 (0.3)	1 (0.2)
Lymphopenia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	16 (6.2)	3 (1.3)	16 (4.4)	16 (2.4)
Diarrhoea	12 (4.7)	1 (0.4)	12 (3.3)	12 (1.8)
Nausea	5 (1.9)	0 (0.0)	5 (1.4)	5 (0.8)
Enteritis	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Gastrooesophageal reflux disease	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Stomatitis	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Vomiting	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Abdominal pain upper	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	11 (4.3)	9 (4.0)	11 (3.0)	11 (1.7)
Asthenia	5 (1.9)	3 (1.3)	5 (1.4)	5 (0.8)
Fatigue	5 (1.9)	6 (2.7)	5 (1.4)	5 (0.8)
Pyrexia	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Infections and infestations	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Pneumonia	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Investigations	2 (0.8)	5 (2.2)	2 (0.5)	2 (0.3)
Alanine aminotransferase increased	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.2)
Aspartate aminotransferase increased	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.2)
Weight decreased	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.2)
Blood alkaline phosphatase increased	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	3 (1.2)	1 (0.4)	3 (0.8)	3 (0.5)
Decreased appetite	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Hypokalaemia	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Hypomagnesaemia	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Hypophosphataemia	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Hyperglycaemia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.4)	3 (1.3)	1 (0.3)	1 (0.2)
Headache	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Dysaesthesia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Neurotoxicity	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.4)	3 (1.3)	1 (0.3)	1 (0.2)
Rash	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)

If a patient had two or more adverse events in the same system organ class (or with the same preferred term) with different CTCAE grades, then the event with the highest grade was used for that patient. Patients with a missing CTCAE grade for a non-fatal AE were

counted under the ‘missing’ category unless the patient already had another AE with CTCAE grade of 4, in which case patient was counted under CTCAE grade of 4.
Adverse events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.
'Neutrophil count decreased', 'white blood cell count decreased', 'lymphocyte count decreased', 'hemoglobin decreased', 'red blood cell count decreased' and 'platelet count decreased' have been re-coded to Neutropenia, Leukopenia, Lymphopenia, Anemia, and Thrombocytopenia, correspondingly, for summary purposes.

Table 58 Frequent (≥2 Patients in either Group in Study IMMU-132-05) AEs Leading to a Treatment Interruption in Study IMMU-132-05 and the Overall Targeted TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Any TEAE leading to Study Drug Interruption	162 (62.8)	87 (38.8)	211 (57.7)	361 (54.7)
Neutropenia	119 (46.1)	47 (21.0)	153 (41.8)	237 (35.9)
Diarrhoea	14 (5.4)	1 (0.4)	16 (4.4)	24 (3.6)
Leukopenia	13 (5.0)	4 (1.8)	22 (6.0)	31 (4.7)
Anemia	11 (4.3)	6 (2.7)	14 (3.8)	32 (4.8)
Pyrexia	8 (3.1)	3 (1.3)	9 (2.5)	12 (1.8)
Nausea	5 (1.9)	0 (0.0)	7 (1.9)	16 (2.4)
Upper respiratory tract infection	5 (1.9)	2 (0.9)	5 (1.4)	11 (1.7)
Dyspnoea	4 (1.6)	1 (0.4)	5 (1.4)	9 (1.4)
Febrile neutropenia	4 (1.6)	1 (0.4)	8 (2.2)	14 (2.1)
Pneumonia	4 (1.6)	4 (1.8)	5 (1.4)	9 (1.4)
Fatigue	3 (1.2)	4 (1.8)	4 (1.1)	15 (2.3)
Asthenia	3 (1.2)	2 (0.9)	3 (0.8)	3 (0.5)
Thrombocytopenia	3 (1.2)	6 (2.7)	5 (1.4)	6 (0.9)
Vomiting	3 (1.2)	0 (0.0)	5 (1.4)	11 (1.7)
Tachycardia	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Abdominal pain	2 (0.8)	0 (0.0)	2 (0.5)	4 (0.6)
Dehydration	2 (0.8)	1 (0.4)	2 (0.5)	8 (1.2)
Device related infection	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Headache	2 (0.8)	0 (0.0)	3 (0.8)	3 (0.5)
Herpes zoster	2 (0.8)	1 (0.4)	2 (0.5)	5 (0.8)
Hypophosphataemia	2 (0.8)	1 (0.4)	4 (1.1)	4 (0.6)
Hypotension	2 (0.8)	1 (0.4)	2 (0.5)	4 (0.6)
Hypoxia	2 (0.8)	0 (0.0)	2 (0.5)	3 (0.5)
Pleural effusion	2 (0.8)	0 (0.0)	3 (0.8)	5 (0.8)
Respiratory tract infection	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Rash	2 (0.8)	0 (0.0)	2 (0.5)	3 (0.5)
Urinary tract infection	1 (0.4)	3 (1.3)	2 (0.5)	3 (0.5)
Sepsis	1 (0.4)	2 (0.9)	1 (0.3)	2 (0.3)
Cough	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.2)
Neuropathy peripheral	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)

Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.
Neutrophil count decreased', 'White blood cell count decreased', 'Lymphocyte count decreased', 'Hemoglobin decreased', 'Red blood cell count decreased' and 'Platelet count decreased' have been re-coded to Neutropenia, Leukopenia, Lymphopenia, Anemia, and Thrombocytopenia, correspondingly, for summary purposes.

Selected Adverse Events/ AEs of Special Interest

The adverse events of special interest (AESI) with SG were neutropenia, anaemia, infections, GI AESIs (diarrhoea, nausea, and vomiting), hypersensitivity, ILD, neuropathy and fatigue (table below). The most clinically relevant are shown here, i.e. neutropenia, anaemia, infections and diarrhoea.

Table 59 Summary of Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term Safety Population

Category Preferred Term	IMMU-132 (N = 258) n (%)	TPC (N = 224) n (%)	Total (N = 482) n (%)
Patients with Any Treatment-Emergent Adverse Events of Special Interest	255 (98.8)	201 (89.7)	456 (94.6)
Fatigue	168 (65.1)	112 (50.0)	280 (58.1)
Fatigue	133 (51.6)	89 (39.7)	222 (46.1)
Asthenia	40 (15.5)	29 (12.9)	69 (14.3)
Neutropenia	168 (65.1)	99 (44.2)	267 (55.4)
Neutropenia	110 (42.6)	57 (25.4)	167 (34.6)
Neutrophil count decreased	71 (27.5)	46 (20.5)	117 (24.3)
Febrile neutropenia	15 (5.8)	6 (2.7)	21 (4.4)
Diarrhea	168 (65.1)	38 (17.0)	206 (42.7)
Diarrhoea	168 (65.1)	38 (17.0)	206 (42.7)
Nausea	161 (62.4)	68 (30.4)	229 (47.5)
Nausea	161 (62.4)	68 (30.4)	229 (47.5)
Infections	137 (53.1)	80 (35.7)	217 (45.0)

Note: The denominator for percentages is the number of patients in the Safety Population for each treatment group.
Note: Treatment-emergent adverse event is defined as an adverse event with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.
Note: Patients may report more than one event per system organ class or preferred term. At each level of summarization, a patient is counted once if he/she reported one or more adverse events.
Note: Adverse Events of Special Interest are defined in Section 5.12.2 of the SAP.
Note: MedDRA Version 22.1 was used for coding.
Source: Listing 16.2.7.3 Program Name: t_ae1_spl.sas Date Generated: 14JUL2020 Page 1 of 12

AEs of Neutropenia and Febrile Neutropenia

Table 60 Neutropenia and Febrile Neutropenia in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Neutropenia[1]	168 (65.1)	99 (44.2)	240 (65.6)	409 (62.0)
Grade 3 neutropenia	125 (48.4)	65 (29.0)	172 (47.0)	275 (4.7)
Grade 4 neutropenia	46 (17.8)	30 (13.4)	63 (17.2)	103 (15.6)
Serious neutropenia	19 (7.4)	6 (2.7)	28 (7.7)	45 (6.8)
Neutropenia leading to permanent discontinuation of study drug	0 (0.0)	3 (1.3)	0 (0.0)	3 (0.5)
Neutropenia leading to dose interruption	120 (46.5)	48 (21.4)	156 (42.6)	244 (37.0)
Neutropenia leading to dose reduction	28 (10.9)	43 (19.2)	33 (9.0)	33 (5.0)
Febrile neutropenia	15 (5.8)	5 (2.2)	24 (6.6)	38 (5.8)
Grade 3 febrile neutropenia	12 (4.7)	5 (2.2)	19 (5.2)	30 (4.5)
Grade 4 febrile neutropenia	3 (1.2)	1 (0.4)	5 (1.4)	7 (1.1)
Serious febrile neutropenia	13 (5.0)	4 (1.8)	20 (5.5)	30 (4.5)
Febrile neutropenia leading to permanent discontinuation of study drug	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Febrile neutropenia leading to dose interruption	4 (1.6)	1 (0.4)	8 (2.2)	14 (2.1)
Febrile neutropenia leading to dose reduction	7 (2.7)	0 (0.0)	7 (1.9)	7 (1.1)

[1]Neutropenia, neutrophil count decreased, and febrile neutropenia

Anaemia

The AESI of anaemia included the preferred terms anaemia, hemoglobin decreased, and red blood cell count decreased.

Anaemia occurred in a higher percentage of patients in the SG group compared with the TPC group (39.5% vs 27.7%) in Study IMMU-132-05.

Table 61 Anaemia in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Anemia[1]	102 (39.5)	62 (27.7)	158 (43.2)	272 (41.2)
Grade 3 anemia	24 (9.3)	13 (5.8)	37 (10.1)	77 (11.7)
Grade 4 anemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Serious anemia	3 (1.2)	2 (0.9)	5 (1.4)	7 (1.1)
Anemia leading to permanent discontinuation of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia leading to dose interruption	11 (4.3)	6 (2.7)	14 (3.8)	32 (4.8)
Anemia leading to dose reduction	3 (1.2)	1 (0.4)	5 (1.4)	5 (0.8)

[1]Included the preferred terms anemia, hemoglobin decreased, and red blood cell count decreased.

Infections

Table 62 Infections in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Infection[1]	137 (53.1)	80 (35.7)	196 (53.6)	323 (48.9)
Grade 3 infection	24 (9.3)	13 (5.8)	36 (9.8)	62 (9.8)
Grade 4 infection	2 (0.8)	7 (3.1)	3 (0.8)	4 (0.6)
Serious infection	21 (8.1)	15 (6.7)	30 (8.2)	54 (8.2)
Infection leading to permanent discontinuation of study drug	3 (1.2)	2 (0.9)	3 (0.8)	7 (1.1)
Infection leading to dose interruption	27 (10.5)	14 (6.3)	36 (9.8)	58 (8.8)
Infection leading to dose reduction	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)

[1]Infection is the System Organ Class of infections and infestations.

Gastrointestinal AESI

Diarrhoea

Table 63 Diarrhoea in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Diarrhea	168 (65.1)	38 (17.0)	236 (64.5)	419 (63.5)
Grade 3 diarrhea	29 (11.2)	2 (0.9)	39 (10.7)	68 (10.3)
Grade 4 diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious diarrhea	9 (3.5)	0 (0.0)	13 (3.6)	25 (3.8)
Diarrhea leading to permanent discontinuation of study drug	1 (0.4)	0 (0.0)	1 (0.3)	5 (0.8)
Diarrhea leading to dose interruption	14 (5.4)	1 (0.4)	16 (4.4)	24 (3.6)
Diarrhea leading to dose reduction	12 (4.7)	1 (0.4)	12 (3.3)	12 (1.8)

Neutropenic colitis occurred in 2 patients (0.5%) in the Overall Target TNBC pool and 3 patients (0.5%) in the All Treated Pool.

Nausea and Vomiting

Table 64 Nausea and Vomiting in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Nausea	161 (62.4)	68 (30.4)	235 (64.2)	440 (66.7)
Grade 3 nausea	29 (11.2)	2 (0.9)	14 (3.8)	28 (4.2)
Grade 4 nausea	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Serious nausea	2 (0.8)	0 (0.0)	5 (1.4)	12 (1.8)
Nausea leading to permanent discontinuation of study drug	1 (0.4)	0 (0.0)	1 (0.3)	5 (0.8)
Nausea leading to dose interruption	5 (1.9)	0 (0.0)	7 (1.9)	16 (2.4)
Nausea leading to dose reduction	5 (1.9)	0 (0.0)	5 (1.4)	5 (0.8)
Vomiting	86 (33.3)	36 (16.1)	139 (38.0)	263 (39.8)
Grade 3 vomiting	3 (1.2)	3 (1.3)	10 (2.7)	18 (2.7)
Grade 4 vomiting	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Serious vomiting	2 (0.8)	0 (0.0)	7 (1.9)	12 (1.8)
Vomiting leading to permanent discontinuation of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting leading to dose interruption	3 (1.2)	0 (0.0)	5 (1.4)	11 (1.7)
Vomiting leading to dose reduction	1(0.4)	0 (0.0)	1 (0.3)	1 (0.2)

Hypersensitivity

Hypersensitivity occurred in a higher percentage of patients in the SG group compared with the TPC group (34.1% vs 20.5%) in Study IMMU-132-05.

The most frequent hypersensitivity events in both the SG and TPC groups were cough (7.4% vs 6.7%, respectively) and dyspnea (7.0% vs 6.7%, respectively). Most of the cases of hypersensitivity were nonsevere, nonserious, and did not lead to either treatment discontinuation interruption, or a dose reduction.

The percentage of SG-treated patients with hypersensitivity was higher in Study IMMU-132-01 compared with Study IMMU-132-05 (42.6% vs 34.1%) and similar in the Overall Target TNBC and All Treated Pools (36.6% vs 36.8%).

Table 65 Hypersensitivity in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Hypersensitivity[1]	88 (34.1)	46 (20.5)	134 (36.6)	243 (36.8)
Grade 3 hypersensitivity	3 (1.7)	3 (1.3)	24 (6.6)	9 (1.4)
Grade 4 hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Serious hypersensitivity	1 (0.4)	3 (1.3)	2 (0.5)	3 (0.5)
Hypersensitivity leading to permanent discontinuation of study drug	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.5)
Hypersensitivity leading to dose interruption	3 (1.2)	1 (0.4)	3 (0.8)	7 (1.1)
Hypersensitivity leading to dose reduction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[1]Hypersensitivity SMQ (broad) and anaphylactic reactions SMQ (broad)

Interstitial Lung Disease

Table 66 Interstitial Lung Disease AEs in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
ILD[1]	2 (0.8)	1 (0.4)	3 (0.8)	4 (0.6)
Grade 3 ILD AE	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Grade 4 ILD AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious ILD AE	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
ILD AE leading to permanent discontinuation of study drug	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
ILD AE leading to dose interruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ILD AE leading to dose reduction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[1]Interstitial lung disease SMQ (narrow)

Neuropathy

Table 67 Neuropathy in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Neuropathy[1]	38 (14.7)	49 (21.9)	64 (17.5)	119 (18.0)
Grade 3 neuropathy	1 (0.4)	6 (2.7)	1 (0.3)	4 (0.6)
Grade 4 neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Neuropathy leading to permanent discontinuation of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy leading to dose interruption	2 (0.8)	5 (2.2)	3 (0.8)	6 (0.9)
Neuropathy leading to dose reduction	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

[1]Neuropathy is the combination of the preferred terms of gait disturbance, hypoesthesia, muscular weakness, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy.

Fatigue

Table 68 Fatigue in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Fatigue[1]	168 (65.1)	112 (50.0)	230 (62.8)	404 (61.2)
Serious fatigue	1 (0.4)	1 (0.4)	2 (0.5)	9 (1.4)
Fatigue leading to permanent discontinuation of study drug	2 (0.8)	1 (0.4)	3 (0.8)	6 (0.9)
Fatigue leading to dose interruption	6 (2.3)	6 (2.7)	7 (1.9)	18 (2.7)
Fatigue leading to dose reduction	10 (3.9)	9 (4.0)	12 (3.3)	12 (1.8)

[1]Fatigue is the combination of the preferred terms of fatigue and asthenia.

Serious adverse event/deaths/other significant events

Table 69 Summary of Death (Pooled Population for TNBC) (updated safety data 02/04/2021(IMMU-132-01) 25/02/2021(IMMU-132-05)).

	IMMU-132-01 Target TNBC (N = 108)	IMMU-132-05 SG (N = 258)	IMMU-132-05 TPC (N = 224)	Overall Target TNBC (N = 366)	All Treated SG (10 mg/kg) (N = 660)
Number of Deaths within 30 days of Last Study Drug dose	**8 (7.4%)**	**14 (5.4%)**	**16 (7.1%)**	**22 (6.0%)**	**47 (7.1%)**
Cause of death					
Disease progression	7 (6.5%)	12 (4.7%)	14 (6.3%)	19 (5.2%)	31 (4.7%)
Adverse event	1 (0.9%)	1 (0.4%)	2 (0.9%)	2 (0.5%)	12 (1.8%)
Other	0	1 (0.4%)	0	1 (0.3%)	3 (0.5%)
Missing	0	0	0	0	1 (0.2%)
Overall Number of Deaths	**98 (90.7%)**	**193 (74.8%)**	**198 (88.4%)**	**291 (79.5%)**	**541 (82.0%)**
Cause of death					
Disease progression	93 (86.1%)	182 (70.5%)	187 (83.5%)	275 (75.1%)	494 (74.8%)
Adverse event	1 (0.9%)	3 (1.2%)	2 (0.9%)	4 (1.1%)	16 (2.4%)
Other	4 (3.7%)	7 (2.7%)	9 (4.0%)	11 (3.0%)	27 (4.1%)
Missing	0	1 (0.4%)	0	1 (0.3%)	4 (0.6%)

SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice
The denominator for percentages is the number of participants in the Safety Population for each treatment group.

Table 70 Fatal AEs in Studies IMMU-132-01 and IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-01 Target TNBC (N = 108) n (%)	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	A SG
Number of Patients with Any Serious TEAE leading to Death	1 (0.9)	1 (0.4)	3 (1.3)	2 (0.5)	
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	
General physical health deterioration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	
Infections and infestations	0 (0.0)	0 (0.0)	2(0.9)	0 (0.0)	
Enterocolitis infectious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Neutropenic sepsis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	
Sepsis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)	0 (0.0)	0 (0.0)	1(0.3)	
Metastases to central nervous system	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Metastases to spine	1 (0.9)	0 (0.0)	0 (0.0)	1(0.3)	
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.4)	0 (0.0)	1 0.3)	
Respiratory failure	0 (0.0)	1 (0.4)	0 (0.0))	1 0.3)	
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

MedDRA System Organ Class Preferred Term	IMMU-132-01 Target TNBC (N = 108) n (%)	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	A SG
Pneumonia aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Respiratory, thoracic and mediastinal disorders					
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Respiratory distress	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

If a patient had two or more adverse events in the same system organ class (or with the same preferred term) with different CTCAE grades, then the event with the highest grade was used for that patient. Patients with a missing CTCAE grade for a non-fatal AE were counted under the 'missing' category, unless the patient already had another AE with CTCAE grade of 4, in which case patient was counted under CTCAE grade of 4.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.
Neutrophil count decreased', 'White blood cell count decreased', 'Lymphocyte count decreased', 'Hemoglobin decreased', 'Red blood cell count decreased' and 'Platelet count decreased' have been re-coded to Neutropenia, Leukopenia, Lymphopenia, Anemia, and Thrombocytopenia, correspondingly, for summary purposes.

Serious Adverse events

The most common SAEs (≥2 patients) in the SG-treated group were febrile neutropenia (5%), diarrhoea (3,5%), neutropenia (2.7%) and pneumonia (2.7%).

Table 71 Serious TEAEs in Study IMMU-132-05 by System Organ Class (≥ 1 Participant in Either Group) and Preferred Term (≥ 2 Participants in Either Group), the Overall Target TNBC, and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated N = 258	IMMU-132-05 TPC N = 224	Overall Target TNBC N = 366	All Treated SG (10 mg/kg) N = 660
Any Serious TEAEs	69 (26.7)	63 (28.1)	102 (27.9)	229 (34.7)
Blood and lymphatic system disorders	23 (8.9)	8 (3.6)	33 (9.0)	52 (7.9)
Febrile neutropenia	13 (5.0)	4 (1.8)	20 (5.5)	30 (4.5)
Neutropenia	7 (2.7)	2 (0.9)	9 (2.5)	16 (2.4)
Anemia	3 (1.2)	2 (0.9)	5 (1.4)	7 (1.1)
Thrombocytopenia	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Cardiac disorders	1 (0.4)	4 (1.8)	1 (0.3)	6 (0.9)
Pericardial effusion	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	17 (6.6)	5 (2.2)	27 (7.4)	69 (10.5)
Diarrhoea	9 (3.5)	0 (0.0)	13 (3.6)	25 (3.8)
Nausea	2 (0.8)	0 (0.0)	5 (1.4)	12 (1.8)
Vomiting	2 (0.8)	0 (0.0)	7 (1.9)	12 (1.8)
Abdominal pain	3 (1.2)	3 (1.3)	3 (0.8)	7 (1.1)
General disorders and administration site conditions	7 (2.7)	10 (4.5)	11 (3.0)	30 (4.5)
Pyrexia	3 (1.2)	5 (2.2)	4 (1.1)	7 (1.1)
Hepatobiliary disorders	2 (0.8)	1 (0.4)	4 (1.1)	6 (0.9)
Infections and infestations	21 (8.1)	15 (6.7)	30 (8.2)	54 (8.2)
Pneumonia	7 (2.7)	4 (1.8)	10 (2.7)	20 (3.0)

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated N = 258	IMMU-132-05 TPC N = 224	Overall Target TNBC N = 366	All Treated SG (10 mg/kg) N = 660
Sepsis	2 (0.8)	4 (1.8)	2 (0.5)	5 (0.8)
Urinary tract infection	2 (0.8)	1 (0.4)	3 (0.8)	4 (0.6)
Device related infection	3 (1.2)	0 (0.0)	3 (0.8)	3 (0.5)
Cellulitis	2 (0.8)	2 (0.9)	2 (0.5)	2 (0.3)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.4)	1 (0.3)	5 (0.8)
Investigations	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	1 (0.4)	1 (0.4)	4 (1.1)	8 (1.2)
Musculoskeletal and connective tissue disorders	4 (1.6)	5 (2.2)	5 (1.4)	10 (1.5)
Back pain	2 (0.8)	4 (1.8)	2 (0.5)	4 (0.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	0 (0.0)	2 (0.5)	4 (0.6)
Nervous system disorders	2 (0.8)	2 (0.9)	2 (0.5)	8 (1.2)
Headache	2 (0.8)	0 (0.0)	2 (0.5)	2 (0.3)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Psychiatric disorders	0 (0.0)	1 (0.4)	1 (0.3)	7 (1.1)
Reproductive system and breast disorders	1 (0.4)	1 (0.4)	1 (0.3)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	13 (5.0)	20 (8.9)	20 (5.5)	46 (7.0)
Dyspnoea	2 (0.8)	7 (3.1)	5 (1.4)	14 (2.1)
Pleural effusion	2 (0.8)	6 (2.7)	4 (1.1)	8 (1.2)
Pulmonary embolism	3 (1.2)	2 (0.9)	3 (0.8)	7 (1.1)
Hypoxia	2 (0.8)	1 (0.4)	2 (0.5)	5 (0.8)
Respiratory failure	2 (0.8)	2 (0.9)	2 (0.5)	5 (0.8)
Skin and subcutaneous tissue disorders	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.3)
Vascular disorders	2 (0.8)	3 (1.3)	3 (0.8)	7 (1.1)
Deep vein thrombosis	2 (0.8)	1 (0.4)	3 (0.8)	4 (0.6)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

Percentages are based on big N.

If a participant had 2 or more adverse events in the same system organ class (or with the same preferred term) with different CTCAE grades, then the event with the highest grade was used for that participant. Participants with a missing CTCAE grade for a non-fatal AE were counted under the 'missing' category unless the participant already had another AE with CTCAE grade of 4, in which case the participant was counted under CTCAE grade of 4.

AE terms were coded using MedDRA version 23.0.

For summary purposes, the following PTs have been re-coded. Neutrophil count decreased to neutropenia, white blood cell count decreased to leukopenia, lymphocyte count decreased to lymphopenia, hemoglobin decreased and red blood cell count decreased to anemia, and platelet count decreased to thrombocytopenia.

2.6.3. Laboratory findings

Table 72 Summary of Haematology Parameters per NCI-CTCAE v5.0 in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Hemoglobin (g/L)				
Decrease ≥1 grade from baseline to grade 3 or grade 4 higher	23 (8.9)	13 (5.8)	28 (7.7)	51 (7.7)
Grade 3	23 (8.9)	13 (5.8)	28 (7.7)	51 (7.7)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worst grade during study				
Grade 0	15 (5.8)	29 (12.9)	23 (6.3)	34 (5.2)
Grade 1	106 (41.1)	83 (37.1)	138 (37.7)	264 (40.0)
Grade 2	113 (43.8)	94 (42.0)	173 (47.3)	305 (46.2)
Grade 3	23 (8.9)	13 (5.8)	28 (7.7)	51(7.7)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (0.4)	5 (2.2)	4 (1.1)	6 (0.9)
Leukocytes				
Decrease ≥1 grade from baseline to grade 3 or grade 4 higher	106 (41.1)	57 (25.4)	129 (35.2)	170 (25.8)
Grade 3	91 (35.3)	45 (20.1)	112 (30.6)	149 (22.6)
Grade 4	15 (5.8)	12 (5.4)	17 (4.6)	21 (3.2)
Worst grade during study				
Grade 0	31 (12.0)	61 (27.2)	40 (10.9)	99 (15.0)
Grade 1	35 (13.6)	42 (18.8)	59 (16.1)	129 (19.5)
Grade 2	85 (32.9)	58 (25.9)	134 (36.6)	256 (38.8)
Grade 3	91 (35.3)	45 (20.1)	112 (30.6)	149 (22.6)
Grade 4	15 (5.8)	12 (5.4)	17 (4.6)	21 (3.2)
Missing	1 (0.4)	5 (2.2)	4 (1.1)	6 (0.9)
Lymphocytes				
Decrease ≥1 grade from baseline to grade 3 or grade 4 higher	63 (24.4)	40 (17.9)	83 (22.7)	150 (22.7)
Grade 3	54 (20.9)	35 (15.6)	72 (19.7)	130 (19.7)
Grade 4	9 (3.5)	4 (1.8)	12 (3.3)	20 (3.0)
Worst grade during study				
Grade 0	52 (20.2)	64 (28.6)	84 (23.0)	165 (25.0)
Grade 1	38 (14.7)	47 (21.0)	49 (13.4)	93 (14.1)
Grade 2	83 (32.2)	51 (22.8)	117 (32.0)	202 (30.6)
Grade 3	71 (27.5)	50 (22.3)	96 (26.2)	170 (25.8)
Grade 4	10 (3.9)	4 (1.8)	13 (3.6)	21 (3.2)
Missing	4 (1.6)	7 (3.1)	7 (1.9)	9 (1.4)
Neutrophils				
Decrease ≥1 grade from baseline to grade 3 or grade 4 higher	125 (48.4)	79 (35.2)	151 (41.2)	206 (31.2)
Grade 3	81 (31.4)	46 (20.5)	100 (27.3)	140 (21.2)
Grade 4	44 (17.0)	33 (14.7)	51 (13.9)	66 (10.0)
Worst grade during study				
Grade 0	55 (21.3)	84 (37.5)	77 (21.0)	182 (27.6)
Grade 1	18 (7.0)	19 (8.5)	30 (8.2)	6 (8.5)
Grade 2	57 (22.1)	35 (15.6)	102 (27.9)	208 (31.5)
Grade 3	82 (31.8)	47 (21.0)	101 (27.6)	141 (21.4)
Grade 4	44 (17.1)	33 (4.7)	51 (13.9)	66 (10.0)
Missing	2 (0.8)	6 (2.7)	5 (1.4)	7 (1.1)
Platelets				
Decrease ≥1 grade from baseline to grade 3 or grade 4 higher	3 (1.2)	6 (2.6)	6 (1.6)	29 (4.4)
Grade 3	2 (0.8)	5 (2.2)	3 (0.8)	8 (1.2)

	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Grade 4	1 (0.4)	1 (0.4)	3 (0.8)	21 (3.2)
Worst grade during study				
Grade 0	199 (77.1)	146 (65.2)	275 (75.1)	472 (71.5)
Grade 1	48 (18.6)	58 (25.9)	70 (19.1)	131 (19.8)
Grade 2	7 (2.7)	8 (3.6)	11 (3.0)	22 (3.3)
Grade 3	2 (0.8)	5 (2.2)	3 (0.8)	8 (1.2)
Grade 4	1 (0.4)	1 (0.4)	3 (0.8)	21 (3.2)
Missing	1 (0.4)	6 (2.7)	4 (1.1)	6 (0.9)

Liver Function

Mean and median changes from baseline in liver function tests were similar over time for the SG and TPC groups in Study IMMU-132-05. Additionally, grade 3 and grade 4 increases in ALT, AST, alkaline phosphatase, and total bilirubin were seen in a similar percentage of patients in the SG and TPC groups in Study IMMU-132-05.

An evaluation of drug-induced serious hepatotoxicity plot of peak total bilirubin versus peak serum ALT for the Overall Target TNBC pool is provided in Figure below.

Overall, 5 patients with mTNBC and 3 patients with a different metastatic epithelial cancer who received 10 mg/kg SG in Study IMMU-132-01 had AST or ALT >3x ULN with concurrent total bilirubin >2x ULN within 30 days of study drug discontinuation, and thus, met the laboratory criteria for a potential Hy's law case. All of these patients were evaluated for evidence of drug-induced liver injury, including whether or not the liver injury was primarily hepatocellular without a prominent cholestatic component and for the presence of alternative etiologies. None of the patients were found to meet the criteria for drug-induced liver injury because alternative etiologies, including progression of liver metastases, bile duct obstruction due to metastatic disease, concomitant medications, and cholecystitis, were present.

Kidney Function

Grade 3 or grade 4 changes in creatinine were seen in a low and similar percentage of patients in the SG and TPC groups in Study IMMU-132-05. Additionally, the percentage of SG-treated patients with a grade 3 or grade 4 change in creatinine and the worst grade on study was similar in Studies IMMU-132-01 and IMMU-132-05 and the Overall Target TNBC and All Treated Pools.

Integrated Summary of Safety

Table 14.3.3.3.1.1
Shifts from Baseline to Worst Post-baseline Evaluation per NCI-CTCAE v5.0 for Chemistry Parameters
Pooled Population for TNBC

Creatinine (umol/L)
IMMU-132-05 SG Treated

	Worst Post-baseline NCI-CTCAE Grade						
Baseline Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Total n (%)
Grade 0	240(93.0)	16(6.2)	0(0.0)	1(0.4)	0(0.0)	1(0.4)	258(100.0)
Grade 1	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Grade 2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Grade 3	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Grade 4	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total	240(93.0)	16(6.2)	0(0.0)	1(0.4)	0(0.0)	1(0.4)	258(100.0)

Table 73 Grade 1-2 and Grade ≥ 3 Treatment-Emergent Adverse Events in the System Organ Class of Renal and Urinary Disorders and Select Treatment-Emergent Adverse Events in the System Organ Classes of Metabolism and Nutrition Disorders and Investigations in ≥ 1% of Participants in the Overall Target TNBC Population by Preferred Term (Pooled Population for TNBC)

MedDRA System Organ Class Preferred Term CTCAE Grade	**IMMU-132-01 Target TNBC (N = 108) n (%)**	**IMMU-132-05 SG Treated (N = 258) n (%)**	**IMMU-132-05 TPC (N = 224) n (%)**	**Overall Target TNBC (N = 366) n (%)**	**All Treated SG (10 mg/kg) (N = 660) n (%)**
Renal and urinary disorders	23 (21.3)	20 (7.8)	9 (4.0)	43 (11.7)	102 (15.5)
Dysuria					
1-2	6 (5.6)	9 (3.5)	4 (1.8)	15 (4.1)	26 (3.9)
Haematuria					
1-2	5 (4.6)	4 (1.6)	1 (0.4)	9 (2.5)	27 (4.1)
Pollakiuria					
1-2	4 (3.7)	0 (0.0)	2 (0.9)	4 (1.1)	11 (1.7)
Proteinuria					
1-2	7 (6.5)	1 (0.4)	2 (0.9)	8 (2.2)	17 (2.6)
Metabolism and nutrition disorders	73 (67.6)	133 (51.6)	94 (42.0)	206 (56.3)	400 (60.6)
Hyperglycaemia					
1-2	22 (20.4)	15 (5.8)	9 (4.0)	37 (10.1)	56 (8.5)
≥ 3	4 (3.7)	2 (0.8)	3 (1.3)	6 (1.6)	10 (1.5)
Hypernatraemia					
1-2	3 (2.8)	1 (0.4)	0 (0.0)	4 (1.1)	5 (0.8)
Hypocalcaemia					
1-2	9 (8.3)	14 (5.4)	4 (1.8)	23 (6.3)	35 (5.3)

MedDRA System Organ Class Preferred Term CTCAE Grade	IMMU-132-01 Target TNBC (N = 108) n (%)	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Hypoglycaemia					
1-2	4 (3.7)	1 (0.4)	0 (0.0)	5 (1.4)	7 (1.1)
Hypokalaemia					
1-2	18 (16.7)	34 (13.2)	28 (12.5)	52 (14.2)	88 (13.3)
≥ 3	2 (1.9)	7 (2.7)	1 (0.4)	9 (2.5)	22 (3.3)
Hypomagnesaemia					
1-2	22 (20.4)	32 (12.4)	13 (5.8)	54 (14.8)	100 (15.2)
Hyponatraemia					
1-2	3 (2.8)	5 (1.9)	6 (2.7)	8 (2.2)	23 (3.5)
≥ 3	2 (1.9)	3 (1.2)	0 (0.0)	5 (1.4)	18 (2.7)
Hypophosphataemia					
1-2	7 (6.5)	6 (2.3)	6 (2.7)	13 (3.6)	40 (6.1)
≥ 3	10 (9.3)	9 (3.5)	3 (1.3)	19 (5.2)	37 (5.6)
Investigations	51 (47.2)	87 (33.7)	60 (26.8)	138 (37.7)	264 (40.0)
Blood creatinine increased					
1-2	3 (2.8)	6 (2.3)	0 (0.0)	9 (2.5)	25 (3.8)
Blood phosphorous increased					
1-2	4 (3.7)	0 (0.0)	0 (0.0)	4 (1.1)	7 (1.1)

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer
Source: Trodelvy TNBC ISS, Table 14.3.2.3.1

Other Chemistry Tests

Mean and median changes from baseline in electrolytes and glucose were similar over time in the SG and TPC groups in Study IMMU-132-05. Additionally, grade 3 or grade 4 increases or decreases in electrolytes and glucose were seen in a low and similar percentage of patients in the SG and TPC groups in Study IMMU-132-05. Changes from baseline in electrolytes and glucose in SG-treated patients were also similar in Studies IMMU-132-01 and IMMU-132-05 and in the overall target TNBC and all treated Pools. The percentage of SG-treated patients with a grade 3 or grade 4 increase or decrease in electrolytes and glucose and the worst grade on study was similar in Studies IMMU-132-01 and IMMU-132-05 and the Overall Target TNBC and All Treated Pools.

Vital Signs

Mean and median changes from baseline over time in systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature were similar in the SG and TPC groups in Study IMMU-132-05. Changes from baseline over time for vital signs were also similar in SG-treated patients in studies IMMU-132-01 and IMMU-132-05 and in the overall target TNBC and all treated Pools

ECG

Mean and median changes from baseline over time in ventricular rate and the QT, QTcB, QTcF, PR, QRS, and RR intervals were similar in the SG and TPC groups in Study IMMU-132-05. Changes from baseline over time for ECG parameters were also similar in SG-treated patients in studies IMMU-132-01 and IMMU-132-05 and in the overall target TNBC and all treated pools. A slightly higher percentage of patients in the SG group compared with the TPC group in Study IMMU-132-05 had treatment-emergent maximum QTcB and QTcF changes >60 msec and QTcB values of >500 msec (Table 38).

All patients with a QTcF >500 msec and/or QTcF change >60 msec or a cardiac AE in Study IMMU-132-05 were reviewed by an independent cardiologist; the review for each patient is provided in the CSR of IMMU-132-05. For each of these patients, the QTc prolongation was a small increase from baseline and the patient was receiving a concomitant medication that is known to prolong QTc. Additionally, no evidence for QTc prolongation was seen for SG in the PK-QTc substudy of Study IMMU-132-05.

The percentage of patients with a QTcF >500 msec and/or QTcF change >60 msec was similar in SG-treated patients in studies IMMU-132-01 and IMMU-132-05 and in the overall target TNBC and all treated pools.

Table 74 QTc Intervals by Prespecified Criteria

Maximal Over ALL Post-baseline Evaluations	**IMMU-132-05 SG Treated (N = 258) n (%)**	**IMMU-132-05 TPC (N = 224) n (%)**	**Overall Target TNBC (N = 366) n (%)**	**All Treated SG (10 mg/kg) (N = 660) n (%)**
Subjects with both baseline and at least one post-baseline QTcF evaluation	244 (94.6)	190 (84.8)	336 (91.8)	570 (86.4)
QTcF				
≤450 msec	194 (75.2)	171 (76.3)	258 (70.5)	428 (64.8)
>450 msec	50 (19.4)	19 (8.5)	78 (21.3)	142 (21.5)
>450 to ≤480 msec	45 (17.4)	16 (7.1)	62 (16.9)	108 (16.4)
>480 msec	5 (1.9)	3 (1.3)	16 (4.4)	34 (5.2)
>480 to ≤500 msec	3 (1.2)	2 (0.9)	10 (2.7)	21 (3.2)
>500 msec	2 (0.8)	1 (0.4)	6 (1.6)	13 (2.0)
Change from Baseline				
≤30 msec	197 (76.4)	165 (73.7)	267 (73.0)	441 (66.8)
>30 msec	47 (18.2)	25 (11.2)	69 (18.9)	129 (19.5)
>30 to ≤60 msec	36 (14.0)	21 (9.4)	51 (13.9)	97 (14.7)

Maximal Over ALL Post-baseline Evaluations	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
>60 msec	11 (4.3)	4 (1.8)	18 (4.9)	32 (4.8)
Subjects with both baseline and at least one post-baseline QTcB evaluation	244 (94.6)	190 (84.8)	336 (91.8)	570 (86.4)
QTcB				
≤450 msec	118 (45.7)	115 (51.3)	155 (42.3)	257 (38.9)
>450 msec	126 (48.8)	75 (33.5)	181 (49.5)	313 (47.4)
>450 to ≤480 msec	90 (34.9)	65 (29.0)	129 (35.2)	222 (33.6)
>480 msec	36 (14.0)	10 (4.5)	52 (14.2)	91 (13.8)
>480 to ≤500 msec	25 (9.7)	6 (2.7)	32 (8.7)	55 (8.3)
>500 msec	11 (4.3)	4 (1.8)	20 (5.5)	36 (5.5)
Change from Baseline				
≤30 msec	182 (70.5)	161 (71.9)	247 (67.5)	425 (64.4)
>30 msec	62 (24.0)	29 (12.9)	89 (24.3)	145 (22.0)
>30 to ≤60 msec	50 (19.4)	25 (11.2)	72 (19.7)	108 (16.4)
>60 msec	12 (4.7)	4 (1.8)	17 (4.6)	37 (5.6)

A higher percentage of patients in the SG group compared with the TPC group in Study IMMU-132-05 had treatment-emergent maximum QTcB and QTcF changes >60 msec and QTcB values of >500 msec. All patients with a QTcF >500 msec and/or QTcF change >60 msec or a cardiac AE in Study IMMU-132-05 were reviewed by an independent cardiologist; the review for each patient is provided in CSR IMMU-132-05. For each of these patients, the QTc prolongation was a small increase from baseline and the patient was receiving a concomitant medication that is known to prolong QTc.

2.6.4. Safety in special populations

UGT1A1 Genotype

Table 75 Overall Summary of AEs in SG Group by UGT1A1 Genotype in Study IMMU-132-05

	*1/*1 (N = 113) n (%)	*1/*28 (N = 96) n (%)	*28/*28 (N = 34) n (%)	Other (N = 7) n (%)
Treatment-emergent Adverse Events (TEAEs)	113 (100.0)	95 (99.0)	34 (100.0)	7 (100.0)
Treatment-related TEAEs	112 (99.1)	91 (94.8)	34 (100.0)	7 (100.0)
Treatment-emergent Serious Adverse Events (SAEs)	25 (22.1)	27 (28.1)	13 (38.2)	2 (28.6)
Treatment-emergent Treatment-related SAEs	15 (13.3)	12 (12.5)	10 (29.4)	2 (28.6)
TEAEs Leading to Dose Reduction	20 (17.7)	18 (18.8)	12 (35.3)	3 (42.9)
TEAEs Leading to Study Drug Interruption	73 (64.6)	57 (59.4)	22 (64.7)	6 (85.7)
TEAEs Leading to Study Drug Discontinuation	5 (4.4)	4 (4.2)	2 (5.9)	0
Treatment-related TEAEs Leading to Study Drug Discontinuation	2 (1.8)	1 (1.0)	2 (5.9)	0
TEAEs Leading to Death	0	1 (1.0)	0	0

Note: The denominator for percentages is the number of patients in the Safety Population with the UGT1A1 genotype for the SG treatment group.
Note: Treatment-emergent adverse event is defined as an adverse event with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.
SG=sacituzumab govitecan; UGT1A1=uridine diphosphate-glucuronosyl transferase 1A1

Age

The majority of patients in the SG and TPC groups in Study IMMU-132-05 were either <50 years (35.7% vs 31.7%) or 50 to 64 years (45.3% vs 46.9%); approximately 20% of patients in the SG and TPC groups were ≥65 years (19.0% vs 21.4%). Median duration of SG treatment in Study IMMU-132-05 was similar across the age subgroups and was longer for the SG group compared with the TPC group within each age subgroup.

The overall incidence of each AE was similar across the age subgroups in Study IMMU-132-05 and in the pooled TNBC population. However, data are too limited to draw conclusions.

Table 76 Treatment-Emergent Adverse Events by Age Group (< 65, 65-74, 75-84, ≥ 85 Years Old) (Overall Target TNBC Population)

MedDRA Terms	Age < 65 Years (N = 298)	Age 65-74 Years (N = 58)	Age 75-84 Years (N = 10)	Age ≥ 85 Years (N = 0)
Total TEAEs	297 (99.7%)	58 (100.0%)	10 (100.0%)	0
Serious TEAEs - total	87 (29.2%)	12 (20.7%)	3 (30.0%)	0
Fatal	1 (0.3%)	1 (1.7%)	0	0
Hospitalization/prolong existing hospitalization	84 (28.2%)	12 (20.7%)	3 (30.0%)	0
Life-threatening	10 (3.4%)	1 (1.7%)	0	0
Disability/incapacity	1 (0.3%)	1 (1.7%)	0	0
Other (medically significant)	8 (2.7%)	1 (1.7%)	0	0
TEAEs leading to drop-out	14 (4.7%)	1 (1.7%)	1 (10.0%)	0
Psychiatric disorders (SOC)	85 (28.5%)	18 (31.0%)	3 (30.0%)	0
Nervous system disorders (SOC)	174 (58.4%)	40 (69.0%)	6 (60.0%)	0
Accidents and injuries (SMQ narrow)	16 (5.4%)	9 (15.5%)	0	0
Cardiac disorders (SOC)	120 (40.3%)	30 (51.7%)	5 (50.0%)	0
Vascular disorders (SOC)	120 (40.3%)	33 (56.9%)	4 (40.0%)	0
Cerebrovascular disorders (SMQ narrow)	1 (0.3%)	1 (1.7%)	0	0
Infections and infestations (SOC)	154 (51.7%)	36 (62.1%)	6 (60.0%)	0
Anticholinergic syndrome (PT anticholinergic syndrome)	0	0	0	0
Quality of life decreased (PT Quality of life decreased)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures (MST)	50 (16.8%)	15 (25.9%)	3 (30.0%)	0

MedDRA = Medical Dictionary for Regulatory Activities; MST = medical search term; PT = preferred term; SAE = serious adverse event; SMQ = Standardized MedDRA Query; SOC = system organ class; TEAE = treatment-emergent adverse event; TNBC = triple-negative breast cancer
Percentages are based on big N. For each row category, a participant with 2 or more adverse events in that category is counted only once. Participants may be counted in multiple categories.
Adverse event terms were coded using MedDRA Version 23.0.
Treatment-emergent adverse event is defined as an adverse event with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment. One Subject had nonserious viral upper respiratory tract infection recorded as disability/incapacity. This participant was excluded from SAE total but included in the subcategory disability/incapacity.

Race

The majority of patients in the SG and TPC groups in the pivotal study were White (81.8% vs 76.8%); the remainder of patients were Black or African American (9.7% vs 13.8%), Asian (4.3% vs 4.0%), or Other (4.3% vs 5.4%). Similar race distributions were seen in study IMMU-132-01 and the overall target TNBC and all treated pools (Table 11). Median duration of SG treatment was similar across the race subgroups and within each race subgroup, median duration of treatment was longer for the SG group compared with the TPC group.

The overall incidence of AEs, ≥grade 3 AEs, SAEs, and AEs leading to discontinuation of study drug across the race subgroups was similar in the SG and TPC groups and in either Study IMMU-132-01 or the overall target TNBC or all treated pool. Moreover, the incidence of each AE was similar across the race subgroups in study IMMU-132-05. GI AEs (nausea and diarrhoea) and myelosuppressive AEs (neutropenia, febrile neutropenia, and anaemia) were seen in a higher percentage of the SG group compared with the TPC group in each race subgroup in Study IMMU-132-05. Additionally, no difference was seen in the incidence of any AE across the race subgroups in study IMMU-132-01 and the overall target TNBC and all treated pools.

Ethnicity

The majority of patients in the SG and TPC groups in Study IMMU-132-05 were not Hispanic or Latino (88.0% vs 86.2%; Table 11). Similar ethnic distributions were seen in study IMMU-132-01 and the overall target TNBC and all treated pools. Median duration of SG treatment in the pivotal study was lower in Hispanics or Latinos compared with Whites; however, this difference might be a result of the small number of Hispanics or Latinos who were enrolled (n=36 in the all treated SG pool). Median duration of treatment was longer for the SG group compared with the TPC group in each ethnic subgroup.

The overall incidence of AEs, ≥grade 3 AEs, SAEs, and AEs leading to discontinuation of study drug was similar for the 2 ethnic subgroups in the SG and TPC groups in Study IMMU-132-05 and no difference was observed across the 2 ethnic subgroups in either study IMMU-132-01 or the overall target TNBC or all treated pool.

The overall incidence of each AE was generally similar between the 2 ethnic subgroups in the pivotal study. GI AEs (nausea and diarrhoea) and myelosuppressive AEs (neutropenia, febrile neutropenia, and anaemia) were seen in a higher percentage of the SG group compared with the TPC group in each ethnic subgroup. Additionally, no difference was observed in the incidence of any AE in the 2 ethnic subgroups in study IMMU-132-01 and the overall target TNBC and all treated pools.

Region

In the pivotal study, 167 and 91 patients in the SG group and 140 and 84 patients in the TPC group were from North America and the ROW, respectively. All patients in Study IMMU-132-01 were from the US.

Median duration of SG treatment in Study IMMU-132-05 was shorter in North America compared with the ROW (4.0 months vs 5.1 months. Median duration of treatment was longer for the SG group compared with the TPC group in both regions. The overall incidence of AEs, ≥grade 3 AEs, SAEs, and AEs leading to discontinuation of study drug was similar for the 2 regions in the SG and TPC arm of the pivotal study. The overall incidence of each AE was generally similar between the 2 regions in Study IMMU-132-05. GI AEs (nausea and diarrhoea) and myelosuppressive AEs (neutropenia, febrile neutropenia, and anaemia) were seen in a higher percentage of the SG arm compared with the TPC arm in each region.

Baseline Hepatic and Renal Function

Almost all patients in the SG and TPC arms of the pivotal study had normal renal function (100% vs 97.3%) and normal hepatic function (98.1% vs 97.3%; Table 11). Similar results were seen in Study IMMU-132-01 and the overall target TNBC and all treated pools (Table 11). Thus, no conclusions can be drawn about either exposure or AEs by baseline hepatic and renal function.

Potential off-target effect of SG:

Trop 2- Expression was detected in several tissues. To assess specificity, a tumor micro array (TMA) containing 95 normal tissues, in triplicate when possible, was tested. The distribution of positive staining was predominantly membrane and in epithelial structures. The applicant was asked to review the toxicities that could be likely related to a potential off-target toxicity given the observed Trop-2 expression in tissues (see below). However, no specific safety concerns have been identified.

Indication	Numbers of different samples	
Bladder	3	3+ staining
Bone Marrow	1	No staining
Breast	3	3+staining ductal epithelium
Fallopian tube	3	2+
Esophagus	3	3+ squamous epithelium
Kidney	6	1-2+ staining
Liver	3	1-3+ staining bile duct epithelium
Lung	3	1+ alveolar lining
Pancreas	3	3+ membrane ductal epithelium
Placenta	3	2+
Prostate	3	1-3+ glandular epithelium
Skin	2	2-3+ epidermis
Thymus	3	2-3+
Tonsil	3	3+ staining

Ureter	3	3+
Cervix	3	2-3+
Endometrium	3	1-3+ endometrial glands
Stomach/small intestine/colon/ rectum Cerebellum/Cerebral Cortex Heart Ovary Paratyroid/Pituitary Spleen Skeletal muscle Testis Thyreoid		No staining

2.6.5. Immunological events

The analysis of immunogenicity of SG in serum samples from 106 patients with mTNBC in Study IMMU-132-01 showed that 2% (2/106) of patients developed treatment-emergent anti-drug antibodies (ADA; ie, persistent positive at the end of therapy).

Table 77. Anti-Drug Antibodies in mTNBC Population of Study IMMU-132-01

ADA Category	Target mTNBC Population 01 Mar 2019 N = 108 n (%)
Negative [1]	98 (90.7)
Positive [2]	10 (9.3)
Baseline Positive [3]	2 (1.9)
Transient Positive [4]	3 (2.8)
Persistent Positive [5]	1 (0.9)
Persistent Positive End of Therapy [6]	2 (1.9)
Not available [7]	2 (1.9)

ADA=anti-drug antibodies.
[1]Negative = all available samples negative for presence of ADA.
[2]Positive = at least one confirmed positive result at any timepoint, including baseline and/or post-baseline timepoints.
[3]Baseline Positive = Baseline only = one confirmed positive result, at baseline only.
[4]Transient Positive = Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period or Treatment-induced ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

[5]Persistent Positive = Treatment-induced ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples are separated by a period of 16 weeks or longer.
[6]Persistent Positive End of Therapy = Treatment-induced ADA incidence in the last sampling time point of the treatment study period.
[7]Not available = no samples available.

No data on the immunogenicity of SG for Study IMMU-132-05 are provided in this application because the Sponsor is in the process of developing and validating ADA assays for SG. See also section 2.4.5.

2.6.6. Safety related to drug-drug interactions and other interactions

No *in vitro* or *in vivo* drug-drug interaction studies for SG have been conducted.

2.6.7. Discontinuation due to adverse events

Table 78 Reason for Discontinuation from Treatment in Study IMMU-132-05 and the Overall Targeted TNBC and All Treated Pools

Disposition Category	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC [1] (N = 224) n (%)	Overall Target TNBC [2] (N = 366) n (%)	All Treated SG (10 mg/kg) [3] (N = 660) n (%)
Permanently Discontinued Treatment	241 (93.4)	224 (100.0)	346 (94.5)	632 (95.8)
Reason of End of Treatment				
Progressive disease	222 (86.0)	184 (82.1)	307 (83.9)	496 (75.2)
Death	1 (0.4)	4 (1.8)	1 (0.3)	9 (1.4)
Treatment delay > 3 weeks	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)
Withdrawal of consent	5 (1.9)	18 (8.0)	7 (1.9)	22 (3.3)
Adverse event	10 (3.9)	8 (3.6)	14 (3.8)	45 (6.8)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Unacceptable toxicity	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Physician Decision	3 (1.2)	5 (2.2)	10 (2.7)	25 (3.8)
Other	0 (0.0)	0 (0.0)	7 (1.9)	34 (5.2)
Missing [4]	17 (6.6)	0 (0.0)	20 (5.5)	28 (4.2)

Percentages are based on big N.
The data cut-off date Study IMMU-132-05 is 11 MAR 2020.
[1] TPC is patients who received eribulin, capecitabine, gemcitabine, or vinorelbine as a single agent in IMMU-132-05.
[2] Overall TNBC is TNBC patients from IMMU-132-01 treated with 10 mg/kg SG and all patients from IMMU-132-05 treated with SG.
[3] All Treated is all patients who received SG with 10 mg/kg SG regardless of tumor type in IMMU-132-01 and all patients treated with SG from IMMU-132-05.
[4] Missing patient category includes ongoing patients at data cutoff date.

Table 79 AEs Leading to Permanent Discontinuation of Study Drug (≥1 Patient in either Group in Study IMMU-132-05) in Study IMMU-132-05 and the Overall Target TNBC and All Treated Pools

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Any TEAE leading to Study Drug Discontinuation	12 (4.7)	12 (5.4)	16 (4.4)	46 (7.0)
Neutropenia	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.3)
Febrile neutropenia	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Thrombocytopenia	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Lymph node pain	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Diarrhoea	1 (0.4)	0 (0.0)	1 (0.3)	5 (0.8)
Fatigue	2 (0.8)	1 (0.4)	3 (0.8)	6 (0.9)
Implant site extravasation	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Pain	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Performance status decreased	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonia	2 (0.8)	1 (0.4)	2 (0.5)	5 (0.8)
Sepsis	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.3)
Neutropenic sepsis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Metastases to meninges	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Mental status changes	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Breast pain	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.3)
Vaginal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Dyspnoea	1 (0.4)	2 (0.9)	1 (0.3)	1 (0.2)
Pneumonitis	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)
Respiratory failure	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Skin mass	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.2)

Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Neutrophil count decreased', 'White blood cell count decreased', 'Lymphocyte count decreased', 'Hemoglobin decreased', 'Red blood cell count decreased' and 'Platelet count decreased' have been re-coded to Neutropenia, Leukopenia, Lymphopenia, Anemia, and Thrombocytopenia, correspondingly, for summary purposes

2.6.8. Post marketing experience

FDA granted accelerated approval for the treatment of adult patients with mTNBC who have received at least two prior therapies for metastatic disease and treatment of locally advanced and metastatic urothelial cancer following a platinum-containing chemotherapy and a PD-1/PD-L1 Inhibitor in April 2020. SG has not been approved in any country or region outside of the US.

2.6.9. Discussion on clinical safety

Sacituzumab govitecan consists basically of 2 components: the anti-Trop 2 AB sacituzumab and SN-38 (the active metabolite of irinotecan). Common AEs known to be associated with sacituzumab are unknown; however, Trop-2 is not exclusively overexpressed in cancer cells, but also in some epithelial structures. Irinotecan is a cytotoxic agent that inhibits the topoisomerase I. Known common adverse events are neutropenia, anaemia and gastrointestinal disorders.

The clinical safety database consists of results from 660 patients receiving single-agent SG at the proposed dose of 10 mg/kg IV, derived primarily from the pivotal, randomised, open-label, Phase III study IMMU 132-05, which evaluated Sacituzumab govitecan (SG) versus treatment of physician´s choice (TPC), eribulin, capecitabine, gemcitabine or vinorelbine. In total, 4 analysis groups of safety data have been presented,

including 2 pooled population analyses, the "overall target TNBC population" (including patients from 2 studies IMMU 132-01 and IMMU 132-05) and the "all treated SG" including patients who received at least one dose of SG 10 mg/kg, and 1 analysis presented by treatment group of the randomised study IMMU 132-05.

The safety data cut-off date for the pivotal trial (IMMU 132-05) was 11 March 2020. Updated safety data were presented for IMMU 132-01 (02 April 2021) and IMMU 132-05 (25 February 2021). The safety database at initial submission consisted of 366 TNBC patients exposed to at least one dose of SG of 10 mg/kg, with total median treatment duration of 4.9 months. With the updated data, the median duration of treatment in Study IMMU-132-05 for the SG group compared with the TPC group was 4.4 months versus 1.3 months A higher percentage of the SG group compared with the TPC group received study treatment ≥ 6 months (36.8% vs 5.8%) and ≥ 12 months (11.2% vs 0.4%). The median duration of treatment for SG was similar in Studies IMMU 132 01 and IMMU 132 05 (5.1 and 4.4 months, respectively) and the median for Overall Target TNBC and All Treated pools were 4.9 months and 4.1 months, respectively. Given that the studies were conducted in the metastatic setting, the number of patients as well as the duration of exposure is considered sufficient to assess the overall safety profile of the drug; however, long term safety data (i.e. exposure of at least 12 months) are only available for a limited number (11%) of patients exposed to SG. This observation, together with the relatively small dataset of non-randomised patients, must be considered in the interpretation of safety data.

In the pivotal study IMMU 132-05 patients continued treatment until progression of disease requiring treatment discontinuation or occurrence of unacceptable AEs. The median treatment duration was higher in the SG arm (4.4 months) compared to 1.3 months in the TPC arm.

Overall, the proportions of patients with any AE and Grade ≥ 3 AEs as well as SAEs, deaths, AEs leading to SG discontinuation, reduction or dose delay, were generally consistent among the pivotal study IMMU 132-05, the total SG-exposed population and the overall target TNBC group.

The proportions of patients with any treatment related AE and Grade ≥ 3 AEs were higher in the SG treated group compared to the TPC group (TEAEs: 97.7% vs. 85.7% and Grade ≥ 3 TEAEs 72.1% vs. 64.7%).

In the pivotal Study IMMU 132-05, the more frequently **reported treatment-related AEs** in the SG arm in comparison to the TPC group were diarrhoea (65.1% vs 17.0%), neutropenia (64.0% vs 43.8%), nausea (62.4% vs 30.4%), fatigue (51.6% vs 39.7%), alopecia (46.9% vs 16.1%), anaemia (39.5% vs 27.7%), constipation (37.2 % vs 23.2%) and vomiting (33.3 % vs 16.1%). Neutropenia was the most common **Grade ≥ 3 AE**; other Grade ≥ 3 AEs occurring in at least 5% of patients were: neutrophil count decreased, diarrhoea, anaemia, white blood cell count decreased, febrile neutropenia, fatigue, and dyspnoea.

A similar frequency of **SAEs** was observed in the SG arm (26.7%) compared to the TPC arm (28.1%) in the pivotal trial. The most common (>2%) SAEs in the SG arm were febrile neutropenia (5%), diarrhoea (3.5%), neutropenia (2.7%) and pneumonia (2.7%). In the total SG-exposed safety population 34.7 % of patients had reported SAEs which is in line with the frequency observed in the pivotal trial.

Overall, 261 **deaths** (71.3%) have been reported in the Overall Target TNBC patient population, mostly occurring more than 30 days after last study drug administration. 4.1% of deaths (15 patients) were due to causes other than PD. Two AEs leading to death were reported (respiratory failure and metastases to the central nervous system).

Regarding dose reduction, a slightly lower number of AEs leading to dose reduction has been observed in the SG arm compared with the TPC arm. The AEs that most frequently led to a reduction of SG included neutropenia and diarrhoea. In contrast, AEs leading to a treatment interruption occurred in a higher

percentage of patients in the SG group compared with the TPC group (62.8% vs 38.8%) in Study IMMU-132-05. Neutropenia was the most frequent AE leading to a treatment interruption in the SG and TPC groups (46.1% vs 21.0%).

Identified and potential risks of treatment with SG were based on the available nonclinical and clinical data relating to SG and known toxicities associated with irinotecan. Events of special interest included neutropenia, anaemia, infections, diarrhoea, nausea and vomiting, hypersensitivity, interstitial lung disease, neuropathy and fatigue.

Neutropenia is an identified risk of SG, and haematologic parameters, including platelets count, must be monitored before starting and at regular intervals during SG treatment. Neutropenia is the AE that most frequently led to a dose reduction or dose delay of SG. Grade ≥3 neutropenia occurred in 48.4% of all the neutropenia cases.

Anaemia occurred in a higher percentage of patients in the SG group compared with the TPC group (39.5% vs 27.7%) in Study IMMU-132-05. Infections were more frequent in the SG group than the TPC group (53.1% vs 35.7%) in Study IMMU-132-05. Infections that were more frequent (approximately ≥5%) with SG than TPC included the following: Urinary tract infection (12.8% vs 8.0%), Upper respiratory tract infection (12.0% vs 3.1%), and Nasopharyngitis (7.0% vs 2.2%). The location of the infections seems to be related to the mechanism of action of SG, as the monoclonal antibody part binds to trophoblast cell surface antigen-2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers; however, this should be further clarified (OC). The most common gastrointestinal AESI was diarrhoea with 65.1% of the patients with an event of any grade, 11.3% with grade 3 events and 3.5% with SAE.

In pivotal study IMMU 132-05, hypersensitivity occurred in a higher percentage of patients in the SG group compared with the TPC group (34.1% vs 20.5%). The most frequent hypersensitivity events in both the SG and TPC groups were cough (7.4% vs 6.7%, respectively) and dyspnoea (7.0% vs 6.7%, respectively). Premedication was highly recommended in this study, which is reflected in the SmPC.

In general, concomitant medications were taken by a significantly higher percentage (more than 20%) of the SG group compared with the TPC group.

The incidence rate of peripheral neuropathy in the SG arm of the pivotal trial (14.7%) was lower compared to the rate in the total SG population (18%), while a higher rate (21%) was reported in the TPC group.

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 neutropenia, febrile neutropenia, and anaemia from Trodelvy. 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. The percentage of patients with ≥grade 3 AEs and treatment-emergent SAEs was higher in patients who were homozygous for the UGT1A1*28 allele compared with patients who were either heterozygous or did not have this allele (82.4% vs 70.8% and 69.9%, respectively for grade ≥3 AEs and 38.2% vs. 28.1% and 22.1%, respectively for SAEs) in Study IMMU-132-05. AEs that occurred in a higher percentage (>10%) of patients who were homozygous for the UGT1A1*28 allele compared with patients who did not have this allele were diarrhoea, anaemia, decreased appetite, cough, constipation, peripheral oedema, and febrile neutropenia in study IMMU-132-05. No mandatory testing for the UGT1A1*28 allele before treatment is suggested by the applicant. Instead, monitoring of important AEs is recommended for all patients given the

rate of severe toxicities also in patients without an UGT1A1*28 allele deficiency. Information about the increased risk of toxicities for patients with known deficiencies is reflected in the SmPC, and it is stated in the SmPC, section 4.4, that testing of UGT1A1 variation status is not recommended, as the AEs of SG will be handled the same way for all patients regardless of presence of this gene variation.

Data on the elderly population are limited.

No immunogenicity data have been provided yet since the validation of neutralising ADA assays is currently still ongoing. The applicant will provide the missing immunogenicity data as a post-authorisation measure. From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of SG can be regarded as manageable and overall acceptable in the proposed indication of advanced mTNBC. Most severe toxicities are haematological events (severe neutropenia) and gastrointestinal disorders with severe diarrhoea, nausea and vomiting. From currently available safety data, it seems that SG is tolerable in the target population of pre-treated metastatic TNBC as the rate of discontinuations due to AEs is low.

2.7. Risk Management Plan

Table: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Serious infections secondary to neutropenia Severe diarrhoea Hypersensitivity
Important potential risks	Embryo-Foetal Toxicity
Missing information	Use in patients with moderate or severe hepatic impairment Immunogenicity

2.7.1. Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

Other forms of routine pharmacovigilance activities:

Table: Ongoing and Planned Additional Pharmacovigilance Activities

Study (study short name, and title) **Status** (Planned/Ongoing)	**Summary of Objectives**	**Safety concerns Addressed**	**Milestones**	**Due dates**
Study IMMU-132-15 A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment CAT 3 Ongoing	To identify the safe starting dose of SG in subjects with solid tumour and moderate hepatic impairment. To evaluate the PK of SG, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. 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 First Subject enrolled Last subject enrolled CSR filing	30 Oct 2020 April 2021 Dec 2021 Q3 2022

Overall conclusions on the PhV Plan

The proposed pharmacovigilance activities is accepted.

Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies.

2.7.2. Risk minimisation measures

Table: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	**Risk minimisation measures (routine and additional)**	**Pharmacovigilance activities**
Serious infections secondary to neutropenia	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, 4.8, 4.9 PL section 2 and 4 Restricted medical prescription **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*

Severe diarrhoea	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, 4.8 PL section 2 and 4 Restricted medical prescription **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Hypersensitivity	**Routine risk minimisation measures:** SmPC Section 4.2, 4.3, 4.4, 4.8 PL section 2 and 4 Restricted medical prescription **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** None
Embryo-foetal toxicity	**Routine risk minimisation measures:** SmPC Section 4.4, 4.6, 5.3 PL section 2 Restricted medical prescription **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Use in patients with moderate or severe hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2, 5.2 PL section 2 Restricted medical prescription **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Study *IMMU-132-15*
Immunogenicity	**Routine risk minimisation measures:** **SmPC Section 4.8 (**Information that no conclusions can be drawn based on the limited immunogenicity data available on the efficacy and safety of Trodelvy) **Restricted medical prescription** **Additional risk minimisation measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** **None.** **Additional pharmacovigilance activities:** None

Overall conclusions on risk minimisation measures

The proposed risk minimisation activities are accepted.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22.04.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that sacituzumab govitecan has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers sacituzumab govitecan to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group considered the applicant's proposal acceptable, provided the concentration after reconstitution is also included on the vial label. The applicant should also explore the possibility of including the warning about

visual inspection of the content after reconstitution, and the storage conditions, if feasible.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Trodelvy (sacituzumab govitecan) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The revised indication is:

> "Trodelvy as monotherapy is indicated 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 (see section 5.1).".

TNBC, defined by a lack of tumor-cell expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), accounts for approximately 15% of invasive breast cancers. TNBC is more common in younger women and is often associated with visceral metastases, aggressive tumour biology, and a poor prognosis. The treatment aim of mTNBC is palliative.

3.1.2. Available therapies and unmet medical need

The standard of care for patients with mTNBC remain sequential single-agent chemotherapy, whereas combination regimens are recommended for patients who present with visceral crisis. Depending on prior use in the (neo)adjuvant setting, recommended first line treatments are taxanes, anthracyclines and also platinum compounds. Further therapeutic options include capecitabine, gemcitabine, vinorelbine or eribulin. Standard chemotherapy is associated with low response rates (10 to 15%) and short progression-free survival (2 to 3 months) among patients with pretreated mTNBC.

Recently, atezolizumab in combination with nab-paclitaxel has been approved for mTNBC in 1L for patients with PD-L1 positive tumours while the PARP inhibitors, olaparib and talazoparib, have been approved for patients with TNBC who harbour a germline BRCA 1 or 2 mutation and have been previously treated with chemotherapy.

3.1.3. Main clinical studies

The open-label study IMMU-132-05 randomly assigned 529 patients with unresectable locally advanced or mTNBC in a 1:1 ratio to receive sacituzumab govitecan (SG) or treatment of physician´s choice (eribulin, vinorelbine, gemcitabine, or capecitabine). Patients had received at least 2 prior standard-of care chemotherapy regimens.

3.2. Favourable effects

The efficacy results in the BMNeg population showed a statistical significant improvement of sacituzumab govitecan over TPC in PFS and OS with hazard ratios (HR) of 0.41 (n=468; 95% CI: 0.32, 0.52; p-value: <0.0001) and 0.48 (n=468; 95% CI: 0.38, 0.59; p-value: <0.0001), respectively. The median PFS was 5.6 months *vs* 1.7 months; the median OS was 12.1 months *vs* 6.7 months, in patients treated with sacituzumab govitecan and TPC, respectively. The efficacy results in the overall population (ITT principle) were consistent with the BMNeg population in the pre-specified final analysis (11 March 2020 cut-off date) PFS and OS with hazard ratios (HR) of 0.43 (n=529; 95% CI: 0.35, 0.54; p-value: <0.0001) and 0.51 (n=468; 95% CI: 0.41, 0.62; p-value: <0.0001), respectively.

PFS results by investigator assessment and sensitivity analyses of PFS showed consistency with the primary analysis. Overall response rates and CBRs support the benefit of SG compared to TPC. In an updated efficacy analysis (final database lock 25 February 2021), results were consistent with the pre-specified final analysis.

3.3. Uncertainties and limitations about favourable effects

Results of exploratory analyses by Trop-2 tumour expression were available for only 60% of study population. Data indicate a smaller treatment effect of SG in subgroups with low relative to participants with high Trop-2 expression; however, efficacy of SG appeared superior compared to the control arm also for patients with low Trop-2 expression. Only one patient was enrolled with unresectable locally advanced disease; however, extrapolation of efficacy is considered justified.

Efficacy results appear to be consistent regardless of BRCA positive status; however due to the small number of patients with BRCA positive status (n=43; 8.1%) no firm conclusions can be drawn from these results. Information on BRCA mutational status was lacking for 35% of study population.

3.4. Unfavourable effects

Almost all of the patients experienced adverse events in the pivotal study and both safety pools and most adverse events were treatment-related. Common AEs were diarrhoea (65.1%), neutropenia (64.0%), nausea (62.4%), fatigue (51.6%), alopecia (46.9%) anaemia (39.5%), constipation (37.2 %) and vomiting (33.3 %). Neutropenia was the most common Grade ≥ 3 AE; other Grade ≥ 3 AEs occurring in at least 5% of patients were: neutrophil count decreased, diarrhoea, anaemia, white blood cell count decreased, febrile neutropenia, fatigue, and dyspnoea.

Serious adverse events (SAEs) were observed with a frequency of 26.7% in the SG arm (26.7%) of the pivotal trial. The most common (>2%) SAEs in the SG arm were febrile neutropenia (5%), diarrhoea (3.5%), neutropenia (2.7%) and pneumonia (2.7%).

Overall, 261 deaths (71.3%) have been reported in the Overall Target TNBC patient population, mostly occurring more than 30 days after last study drug administration. 4.1% of deaths (15 patients) were due to causes other than PD. Among the AE leading to death, 2 AEs (respiratory failure, metastases to the central nervous system).

The percentage of patients with an AE leading to permanent discontinuation of study drug was 4.7%. Fatigue and pneumonia (0.8% each) were the only AEs leading to permanent discontinuation of study drug that occurred in more than 1 patient in the SG group in Study IMMU-132-05.

3.5. Uncertainties and limitations about unfavourable effects

- No data in patients with moderate hepatic impairment have been provided; open-label, non-randomised, dose-escalation study, IMMU-132-15, to determine an appropriate starting dose in this population is being conducted, with data to inform a labelling update anticipated in 2022
- The median duration of treatment for the all treated pool and the target TNBC pool was 4.1 months and 4.9 months, respectively (DCO 11 MAR 2020), and approximately a third of the patients in both pools were treated for more than 6 months. Only 10.9% and 12.3% were exposed for more than 12 months in the two pools, respectively. With updated safety data for IMMU-132-01 (02 April 2021) and IMMU 132-05 (25 February 2021), the median duration of treatment in Study IMMU-132-05 for the SG group compared with the TPC group was 4.4 months versus 1.3 months and the median for Overall Target TNBC and All Treated pools were 4.9 months and 4.1 months, respectively. Hence, the median exposure is considered short.
- Safety according to the UGT1A1 genotype was provided and the applicant claims that inhibitors or inducers of UGT1A1 are expected to increase or decrease SN-38 exposure, respectively. This is adequately reflected in the SmPC.
- Data on the immunogenicity of SG for the pivotal study IMMU-132-05 were not provided because the applicant is still in the process of developing and validating ADA assays for SG. Bioanalytical study reports for antidrug-antibody (ADA) and neutralizing antibody (NAb) determination for both Studies IMMU-132-01 and IMMU-132-05, the NAb assay method validation report as well as an integrated summary of immunogenicity will be provided as a post-authorisation measure by Q3 2022.

3.6. Effects Table

Table 80. Effects table for Trodelvy (SG) for the treatment of unresectable locally advanced or metastatic TNBC who have received at least two prior therapies (data cut-off: 11-Mar-2020)

Effect	Short description	Unit	SG	TPC	Uncertainties / Strength of evidence
Favourable Effects in ITT population					Clinically meaningful benefit of SG based on mature data; updated results (final database lock Feb 2021) confirm the treatment effect of SG in the ITT population; Benefit in patients with Trop-2 weak expressing tumors appears lower compared to higher expression groups; however, efficacy results still superior compared to control arm;
PFS, median	Based on IRC per RECIST 1.1	months	4.8	1.7	
		HR, 95% CI	0.43 (0.35, 0.54)		
OS, median	Time from randomisation until death	months	11.8	6.9	
		HR,	0.51		

Effect	Short description	Unit	SG	TPC	Uncertainties / Strength of evidence
		95% CI	(0.41, 0.62)		Benefit for brain metastasis positive population (n=61) is similar to TPC - PFS by IRC HR 0.65 [0.35, 1.22] - OS HR 0.95 [0.52, 1.72] - ORR 3% vs. 0% for comparison of SG vs TPC;
ORR	Confirmed CR + PR, by IRC per RECIST 1.1	%	31.1	4.2	
		Odds ratio 95%CI	10.99 (5.7, 21.4)		
DOR median		Months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, NE)	
Unfavourable Effects					
Tolerability	Grade 3-5 AEs	%	72.1	64.7	Safety database is limited No data in patients with moderate hepatic impairment have been provided
	SAEs	%	26.7	28.1	
	Discontinuation due to drug-related AEs	%	4.7	5.4	

Abbreviation: SG: Sacituzumab Govitecan; TPC=treatment of physician' choice; IRC: Independent Review Committee

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study IMMU-132-05 demonstrated a statistically significant and clinically meaningful improvement in progression free and overall survival for sacituzumab govitecan (SG) compared to treatment of physician´s choice in a heavily pretreated metastatic TNBC population.

The treatment effect of SG for patients with previously treated, stable brain metastasis appears similar to that of TPC; taking the benefit of SG in distant metastases into account, SG is considered a treatment option also for patients with stable brain metastases.

The safety profile of SG is considered rather unfavourable compared to the chemotherapeutic agents of the control arm, mainly due to high rates of haematological events (severe neutropenia) and gastrointestinal disorders (severe diarrhoea); nonetheless, toxicities can be regarded as manageable by support with GCS-factor and dose modifications.

3.7.2. Balance of benefits and risks

Given the significant improvement in overall survival, the benefit of a treatment with SG outweighs the increased toxicities compared to standard chemotherapy options.

3.7.3. Additional considerations on the benefit-risk balance

Conclusions on the clinical relevance of different levels of tumor Trop-2 expression for the treatment with SG are hampered by the retrospective character of the analyses and the limited size of the Trop-2–evaluable population (data available for only 60% of study population with even smaller numbers for patients with low

tumor Trop-2 expression status). However, available data suggest that even though the treatment effect of SG was smaller in subgroups with low Trop-2 expression relative to participants with high Trop-2 expression, efficacy of SG appeared superior compared to the control arm also for patients with low Trop-2 expression.

3.8. Conclusions

The overall B/R of Trodelvy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Trodelvy is favourable in the following indication:

Trodelvy as monotherapy is indicated 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 (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP

presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sacituzumab govitecan is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.