Amsterdam, 18 September 2025
EMA/307148/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Zumrad

International non-proprietary name: sasanlimab

Procedure No. EMEA/H/C/006641/0000

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
ADA	Anti-drug antibody
ADR	Adverse drug rection
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AS	Active substance
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	Bacillus Calmette-Guérin
BD	Becton, Dickinson and Company
BICR	blinded independent central review
BLA	Biologics license application
Cavg	Average concentration over a dosing interval
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
Ceff	Efficacious concentration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Carcinoma in situ
CL	Clearance
Cmax	Maximum concentration
CMC	Chemistry, manufacturing, and controls
CO	Clinical overview
COVID-19	Coronavirus disease 2019
CR	Complete response
CREST	Combination of sasanlimab and alternative BCG Regimens to Evaluate outcomes with Subcutaneous anti-PD-1 Treatment / Study B8011006
CRF	Case report form
CSR	Clinical study report
CTA	Clinical trial application
CTCAE	Common terminology criteria for adverse events
Ctrough	Concentration at trough
DCE	Discrete choice experiment
DCO	Data cut-off
DDI	Drug-drug interaction
Det	Deterioration
DLT	Dose-limiting toxicity
DoCR	Duration of complete response
DSS	Disease-specific survival
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group

Abbreviation	Definition
EDMC	External data monitoring committee
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European organisation for research and treatment of cancer
ER	Exposure-response
EU	Endotoxin unit
FA	Final analysis
FAS	Full analysis set
FDA	Food and drug administration
FP	Finished product
FT3	Free tri-iodothyronine
FT4	Free thyroxine
Gr	Grade
GU	Genito-urinary
HC+LC	Heavy chain and light chain
HG	High-grade
HLT	High level term
HMMS	High molecular mass species
HR	High-risk/Hazard ratio
IA(1/2)	Interim analysis (1/2)
iAP	Integrated analysis plan
ICE(s)	Intercurrent event(s)
ICI	Immune checkpoint inhibitor
IFN	Interferon
IgG	Immunoglobulin G
IND	Induction/Investigational new drug application
INV	Investigator
IPCs	In-process controls
IPD	Important protocol deviation
IR	Immune-related
irAE	Immune-related adverse event
IRT	Interactive response technology
ISI	Integrated summary of immunogenicity
ISR	Injection site reaction
IV	Intravenous(ly)
LG	Low-grade
MAA	Marketing authorization application
MedDRA	Medical dictionary for regulatory activities
MIBC	Muscle-invasive bladder cancer
MIDD	Model-informed drug development
MNT	Maintenance
MTD	Maximum tolerated dose
NA	Not applicable
NAb	Neutralizing antibody
NBOp	Notified body opinion
NCI	National cancer institute

Abbreviation	Definition
NE	Not estimable
NMIBC	Non-muscle invasive bladder cancer
NSCLC	Non-small cell lung cancer
NTU	Nephelometric turbidity unit
OS	Overall survival
PA(5)	Protocol amendment (5)
PD	Pharmacodynamic(s)
PD-1	Programmed cell death protein-1
PD-L1/2	Programmed cell death – ligand 1/2
PDE	Permitted daily exposure
PFS	Pre-filled syringe
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PMAR	Population modelling analysis report
PopPK	Population pharmacokinetics
PP	Per protocol
PPQ	Process performance qualification
PPS	Patient preference study
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient-reported outcome
PS	Performance status
PS80	Polysorbate 80
PT	Preferred term
PTAB	Patient treatment administration burden
Q#W	Every # week(s)
Q1/3	Quartile 1/3
QLQ-C30	Quality of life questionnaire – 30 (items)
QLQ-NMIBC24	Quality of life questionnaire non-muscle invasive bladder cancer 24 (items)
QOL	Quality of life
q.s.	Quantum satis
RC	Radical cystectomy
RCI	Repeated confidence interval
RMP	Risk management plan
RO	Receptor occupancy
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SBS	Summary of biopharmaceutic studies and associated analytical methods
SC	Subcutaneous(ly)
SCE	Summary of clinical efficacy
SCP	Summary of clinical pharmacology
SCS	Summary of clinical safety

Abbreviation	Definition
SmPC	Summary of product characteristics
SOC	Standard of care/System organ class
T1	Stage of cancer in which the cancer cells are only growing in the most superficial layer of tissues and have not grown into deeper tissues; in bladder cancer, T1 is defined as an invasion into the lamina propria without invasion into the muscularis propria
t1/2	Terminal elimination half-life
Ta	Stage of bladder cancer defined as a non-invasive papillary carcinoma
TCC	Transitional cell carcinoma
TEAE	Treatment-emergent adverse event
Tmax	Time to first occurrence of Cmax
TNF	Tumour necrosis factor
Trt	Treatment
TSH	Thyroid-stimulating hormone
TSQ	Treatment satisfaction questionnaire
TTC	Time to cystectomy
TTR	Time to recurrence
TURBT	Transurethral resection of bladder tumour
UC	Urothelial cancer/carcinoma
US	United States
UV	Ultraviolet
Vc	Central volume of distribution
Vp	Peripheral volume of distribution
WHO	World health organization

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Zumrad
Active substance	Sasanlimab
INN or common name	Sasanlimab
Applicant	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles BELGIUM
EMA product number	EMEA/H/C/006641
ATC code and pharmacotherapeutic group	Not assigned yet. Proposed to WHO: L01FF
Pharmaceutical form(s) and strength (s)	Solution for injection 300 mg
Packaging	pre-filled syringe (glass)
Package size(s)	1 pre-filled syringe
Route of administration	Subcutaneous use
Device or diagnostic	Injection syringe
Orphan designation	No
Orphan indication status confirmed	No
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	N/A
New active substance status	Applied for

1.2. Scientific advice

The applicant received CHMP scientific advice in October 2019, October 2021, May 2022 and July 2024 on topics concerning non-clinical and clinical data for the current application.

1.3. Eligibility to the centralised procedure

The applicant Pfizer Europe MA EEIG submitted on 1 May 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Zumrad (Sasanlimab), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July

2024.

The applicant applied for the following indication:

Zumrad, in combination with Bacillus Calmette-Guérin (BCG), is indicated for the treatment of adult patients with BCG-naïve, high-risk, non-muscle invasive bladder cancer (NMIBC).

1.4. Legal basis

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, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies)/

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) [EMEA-002777-PIP01-20] on the granting of a (product-specific) waiver, P/0290/2020.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

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 from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Applicant's request(s) for consideration

1.7.1. New active substance status

The applicant requested the active substance Sasanlimab 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.

1.8. Steps taken for the assessment of the product

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

Rapporteur:	Jolien de Groot on behalf of Peter Mol
Co-rapporteur:	Ingrid Wang

The rapporteur and Co-rapporteur appointed by the PRAC were:

PRAC rapporteur:	Sonja Radowan
PRAC Co-rapporteur:	Bianca Mulder

The application was received by the EMA on	1 May 2025
The procedure started on	22 May 2025
The CHMP rapporteur's first assessment report was received on	11 Aug 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	13 Aug 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	25 Aug 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	18 Sept 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 Dec 2025

2. Introduction

2.1. Therapeutic context

Disease Background – Bladder Cancer

Urothelial cancer (UC) tumours originate from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra; more than 90% of urothelial tumours originate in the bladder. Bladder cancer is the 9th most common cancer type worldwide, with approximately 614,300 cases and 220,596 deaths reported in 2022 (Globocan), of which 224,777 and 70,383, respectively, in Europe. In 2022, the worldwide age-standardised incidence rate (per 100,000 person/years) was 9.3 in men and 2.4 in women (Globocan), and in Europe 21.1 and 5.0, respectively. Approximately 75% of newly diagnosed cases of bladder cancer are non-muscle invasive disease, papillary tumours confined largely to the mucosa (Ta) (70%-75%) or, less often, to the lamina propria (T1) (20%-25%) or flat high-grade (HG) lesions (carcinoma in situ [CIS], 5%-10%) (NCCN Bladder cancer guidelines).

The most important risk factor for developing bladder cancer is tobacco smoking, followed by occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons (ESMO Bladder cancer guideline; EAU NMIBC guidelines). To facilitate treatment recommendations, the guidelines recommend the stratification of patients into risk groups based on their probability of progression to muscle-invasive disease. Based on the WHO 2004/2016 risk group definition, non-muscle-invasive bladder cancer (NMIBC) is classified as low, intermediate, high, and very high risk and the probability of progression within 1 to 10 years of diagnosis ranges respectively from 0.06-3.7%, 1.0-8.5%, 3.5-14%, and 16-53%, respectively (EAU NMIBC guidelines).

Patients with high-risk (HR) NMIBC represent a challenging patient population to treat, with a 2-year rate of recurrence or progression of 30% and 10%, respectively (Frau et al. Arch Esp Urol. 2016; Cambier et al. Eur Urol. 2016; Shore et al. Urol Oncol. 2021). The 5-year survival rate is around 90% (Knowles et al. Nat Rev Cancer. 2015). Indeed, patients who have high- or very HR NMIBC recurrence before radical cystectomy (RC) have shorter recurrence-free survival, cancer-specific survival, and overall survival compared to those with primary high- or very high-risk NMIBC (Grossmann et al. Eur Urol Open Sci. 2022). When the cancer reaches the MIBC stage, there is significant negative impact on metastasis-free and cancer-specific survival: approximately 50% of MIBC patients will progress to metastatic UC within two to three years post-cystectomy (Tian et al. Transl Androl Urol. 2021). Considering the unpredictable, heterogeneous, and partly aggressive natural behaviour of very HR and HR NMIBC, these patients deserve special consideration, close follow-up, and enhanced treatment options.

Current Standard of Care and Unmet Medical Need

Optimal treatment of NMIBC is the complete removal of all visible lesions in the bladder, followed by intravesical instillations (with chemotherapy or Bacillus Calmette-Guérin [BCG]) or early RC, according to risk stratification (ESMO guideline). For patients with HR NMIBC, **the current standard of care** (SOC) **is transurethral resection of bladder tumour (TURBT) followed by** intravesical instillations of **BCG**, typically induction followed by maintenance therapy (EAU guidelines). Treatment with BCG has been shown to reduce the risk of tumour recurrence; however, BCG therapy will eventually fail in up to 60% of patients with NMIBC resulting in recurrence or progression to more advanced disease (Shore et al. Urol Oncol. 2021; Knowles et al. Nat Rev Cancer. 2015; Babjuk et al. Eur Urol. 2017). At the time of BCG treatment failure, limited bladder-sparing therapeutic options exist. An **unmet medical need**, therefore, remains for new, effective and safe treatment options to improve the treatment outcome in patients with HR NMIBC, i.e., to delay HG tumour recurrence and progression into MIBC or advanced disease, thereby preventing RC (and/or systemic therapy).

2.2. Aspects of development

The current submission to support a marketing application for sasanlimab includes clinical data from a single, pivotal Phase 3 study and three supportive studies, as summarized below. See also Table 1.

Pivotal Phase 3 Study B8011006 (CREST) (Shore et al. Nat Med. 2025): This is a Phase 3, randomized, open-label study of sasanlimab (300 mg SC Q4W) in combination with BCG (induction ± maintenance) vs BCG alone (induction + maintenance) in patients with BCG-naive, HR NMIBC (Cohort A) or sasanlimab as a single agent in patients with BCG-unresponsive NMIBC (Cohort B1 and B2).

Phase 1 Study B8011001 (Johnson et al. JAMA Oncol. 2019; Cho et al. ESMO Open. 2023): This was a Phase 1, open-label, dose-escalation and expansion study of sasanlimab in previously-treated patients with locally advanced or metastatic solid tumours.

Phase 1b/2 Study B8011007 (Penkov et al. Ther Adv Med Oncol. 2024): This is a Phase 1b/2, open-label study to evaluate PK, safety, efficacy and PD of sasanlimab in Asian patients with advanced malignancies (Phase 1b) and global patients with NSCLC in the 1L or 2L treatment setting (Phase 2).

Patient-Preference Study B8011013: To gain an understanding on the perspectives and preferences held by patients with HR NMIBC regarding current and potential treatment options for their disease, a Discrete Choice Experiment (DCE) was conducted to elicit their treatment preferences.

Scientific advice/Protocol assistance

Sasanlimab has not received marketing approval in any country or region worldwide. Specific guidance on the development program supporting the proposed indication has been received from several meetings with health authorities globally. Key interactions of pre-submission/submission regulatory activities involving the US FDA and EMA are summarized in **Error! Reference source not found.**.

2.3. Description of the product

Mode of action – Sasanlimab is a humanized hinge region-stabilized IgG4, monoclonal antibody specific for human programmed cell death protein-1 (PD-1) that blocks the interaction between PD-1 and PD-L1/PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands

occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.

Increased PD-L1 expression was observed in bladder cancer cells in response to BCG treatment both *in vitro* and *in vivo* preclinical models and the combination of BCG and anti-PD-L1 agent induced an antitumour immune response (Wang et al. Onco Targets Ther. 2018). Moreover anti-PD-1/PD-L1 agents have demonstrated clinical activity in the treatment of advanced UC or BCG-unresponsive CIS (Balar et al. Lancet Oncol. 2021; Bellmunt et al. Cancer Treat Rev. 2017).

Initially proposed indication – Zumrad, in combination with Bacillus Calmette-Guérin (BCG), is indicated for the treatment of adult patients with BCG-naïve, high-risk, non-muscle invasive bladder cancer (NMIBC).

Initially proposed posology – The recommended dose of sasanlimab is 300 mg every 4 weeks (Q4W) administered as a single 2 mL subcutaneous injection. Treatment with sasanlimab should be given in combination with BCG induction and maintenance, and should be continued until recurrence of HG disease, disease progression, persistence of carcinoma in situ (CIS), unacceptable toxicity or up to 24 months. No dose reductions of sasanlimab are recommended. Sasanlimab should be withheld or discontinued to manage adverse reactions.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required. Sufficient information on EU-GMP compliance has been provided for all sites.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

A request for routine GCP inspection has been adopted for the pivotal Phase 3 Study B8011006. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181. Based on the review of clinical data, there are no specific points the Rapporteurs would like the inspectors to specifically investigate.

3. Quality aspects

3.1. Introduction

The finished product is presented as a solution for injection containing 300 mg of sasanlimab active substance in 2 mL, i.e. 150 mg/mL.

3.2. Active substance

3.2.1. General information

Sasanlimab is an IgG4 kappa, humanized monoclonal antibody (mAb) with two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds. Sasanlimab is designed to bind the PD-1 receptor and block the interaction between PD-1 and PD-L1/PD-L2, thus restoring T-cell function in the immune response. The complete, confirmed amino acid sequence of sasanlimab is presented by the Applicant.

3.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

The DS manufacturing process is straightforward and common for a recombinant DNA technology based monoclonal antibody production system, comprising cell culture, expression of antibody, harvesting, antibody capture, virus inactivation, purification, concentration by UF/DF, final formulation and DS filling in storage containers.

The Applicant provided clear flow diagrams and sufficiently detailed descriptions of the manufacturing process, including process parameters, material attributes and applied in-process controls and their criticality for each manufacturing step. It is however noted that high level information would be expected in Module 2, while these are currently only presented in Module 3. It is therefore requested to update module 2 in line with the Notice to Applicants Medicinal products for human use (volume 2B).

The manufacturing process for sasanlimab DS uses a recombinant Chinese hamster ovary (CHO) cell line that contains the DNA encoding the sequence for sasanlimab. Cells from the working cell bank (WCB) are thawed, and the culture is progressively expanded. *Raw materials and starting materials*

Materials used in the manufacture of DS have been listed, including their grade (i.e. pharmacopoeial or in-house). Non-compendial/in-house materials are tested according to specifications provided in the CTD. The provided information is sufficient. However, several comments are made on the Cell culture and feeding media, specifically information about composition and quality oversight of the media and reagents are requested. The analytical columns used in all chromatographic methods should be provided.

Acceptable documentation has been provided for raw materials of biological origin used in the establishment of cell substrate.

Control of critical steps

Information is provided on tests and control limits performed at the identified critical steps. Actions taken if limits are exceeded are specified. It is confirmed that deviation from acceptance criteria would lead to batch termination for safety related critical in-process controls. In general, the presented process controls for DS manufacturing are considered appropriate. However, it is requested to lay down in the dossier the exact/quantitative acceptance criterion for filter integrity testing for the virus retaining filtration.

Process validation

The AS manufacturing process has been validated adequately. This included validation of the upstream and downstream process using consecutive batches at the commercial scale and validation of

reprocessing, clearance of process related impurities, reuse of resins and membrane, viral clearance, in-process pool hold-times and transport.

The validation of the DS manufacturing process was performed at the commercial scale. Pre-defined acceptance criteria for performance parameters and product quality (IPC and DS specification) determined on the basis of risk assessment and process characterization studies performed on sasanlimab DS were met in all cases. Deviations were investigated and did not impact the product quality attributes or PPQ acceptance criteria. This is endorsed.

Taken together, the presented process validation studies are considered to be appropriately addressed and in line with current guidance.

Manufacturing process development

Comprehensive development data are provided entailing aspects such as process evaluation studies, comparability of product quality and process performance, analytical method changes and bridging throughout the development lifecycle, process risk assessment and definition of control strategy, in-process extractables and leachable.

The manufacture development has been described in detail.

The modifications introduced to the manufacturing processes during the development have been adequately described and sufficient details and rationale for each step has been provided.

The batch release data show that the batches met the release criterion in place at the time of release and no new impurities were detected. The comparability acceptance criteria were met in most cases. The observed differences are adequately justified and are not considered to impact the quality of the AS.

A risk assessment has been performed taking into account the principles of ICH Q9 to assess all all process contact surface materials used during the sasanlimab drug substance manufacturing process. Additional E&L data is described and evaluated in Section 3.2.S.6.

A comprehensive description of the systematic approach taken to develop the control strategy for DS has been provided. Information regarding the identification of CQAs has been provided in P.2.3.1. Risk assessment to identify PPs that may have an impact on these CQAs has been performed. The final selection and categorization of PPs into CPPs or non-CPPs and their proposed acceptable ranges is supported by a risk assessment, by available prior knowledge and the outcome of the characterization and validation studies as well. Overall, the rationale for control strategy is clearly presented.

Small-scale models were developed and qualified where appropriate and were used to execute the process characterization studies. Small-scale models are considered equivalent to the commercial scale. Small-scale studies have been used for virus clearance studies related to steps, which are discussed in CTD section 3.2.A.2. The cumulative process knowledge gained from process development and process characterization studies, were leveraged to determine acceptance criteria prior to executing the PPQ. Multivariate interactions studies to support process parameter ranges were performed, however no design space is claimed. Taken together, the process design and process characterisation studies are considered sufficiently addressed. Also the PPs identified by the Applicant in general are in line with the expectations. Further justification is requested about PP's steps (**Rapp OCs**).

Characterisation

Characterization of sasanlimab includes primary structure, posttranslational modifications, charge and size heterogeneity, higher order structure, biological activity, and degradation profile. For the

degradation pathways and products, sasanlimab material representative of the commercial process, stored under various stressed conditions was used. The AS has been sufficiently characterised by biochemical, biophysical and biological state-of-the-art assays. All in all, the characterization results confirm the expected structure and target binding properties.

The impurity profile includes process-related impurities and product-related impurities as defined in ICH Q6B.

All in all, the characterisation methods used to provide additional detail on the nature of the product-related impurities are considered appropriate and product-related impurities are considered in general appropriately addressed.

All product-related impurities are routinely controlled by release and shelf-life testing to assure consistency of DS manufacturing.

3.2.3. Specification

Specifications

The specification for sasanlimab drug substance at release and during stability studies is provided. The acceptance criteria are applicable from batch release to end of shelf-life.

The parameters proposed for DS routine testing are considered appropriate to ensure the quality of each batch and test items are in line with ICH Q6B.

For the proposed acceptance criteria, adequate justification is provided. The approach to set release and shelf-life acceptance criteria is based on manufacturing experience, clinical experience and characterization/development data. In general, the approach is considered appropriate. Overall, the acceptance criteria are supported, except those for revision of the acceptance criteria where requested.

Analytical procedures and reference standards

Sasanlimab is tested using a combination of compendial and non-compendial methods.

For compendial methods, reference is made to the Ph. Eur.

The compendial methods for bioburden and endotoxin were appropriately verified for their intended use. In general, validation of the non-compendial analytical procedures is performed in line with ICHQ2 (R2).

Reference standard

During clinical development, clinical reference material (CRM) was used for release and stability testing of sasanlimab, as well as release and stability testing of the sasanlimab PPQ materials. For the commercial process, a two-tiered reference material system (i.e. primary working material (PRM) and working reference material (WRM)) has been established.

Relevant information on the clinical, PRM and WRM has been provided, including release and characterization results for PRM. Clinical Reference Material (CRM) was used as the reference material in testing of PRM and WRM. The PRM and WRM are considered acceptable for use.

The PRM and WRM are subjected to stability studies.

Batch analysis

Release data have been provided for DS batches. The provided batch genealogy information is considered sufficiently clear.

Comparability between the batches manufactured with the different manufacturing processes has been presented and discussed in S.2.6. In general, comparability has been demonstrated.

The batch release results are presented against the acceptance criteria at the time of release. The data provided are generally consistent from batch to batch and support the suitability of the manufacturing process and do not give raise to concerns.

3.2.4. Stability

The stability data provided include data of clinical batches and process performance qualification (PPQ) batches. Stability studies include storage at the recommended, accelerated, and stressed storage conditions.

The stability sampling strategy and stability testing panel are in line with ICH Q1A (R2) and ICH Q5C and are considered appropriate.

The shelf life at the recommended storage condition is supported by long-term/real-time data at the recommended storage condition, which are available for the primary batches.

Additional studies included stability studies under accelerated and stressed conditions, a freeze-thaw study and a photostability study.

A commitment is provided for routine annual stability testing at the recommended storage condition.

Overall, the DS stability has been appropriately addressed in line with current guidance. The provided stability data for DS samples stored under real-time conditions support the proposed shelf life.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

Sasanlimab finished product (FP) is presented as a sterile liquid solution for injection. The liquid bulk FP is formulated at 150 mg/mL sasanlimab and is intended for subcutaneous administration.

Pharmaceutical development

Detailed history of active substance (AS) and FP formulation development has been provided. Choice of excipients is based on the Applicant's prior experience and formulation studies. The proposed commercial formulation is appropriate for the stability of FP. The formulation development studies are sufficiently described and support the proposed commercial formulation of FP.

The quality target product profile of the FP is presented. Key physicochemical characteristics of the FP are the same as the for the AS. Sufficient information on the manufacturing process development of FP is provided. The modifications introduced during development have been adequately described and sufficient details and rationale for each step has been provided. The Applicant has performed extensive assessments to evaluate the comparability of FP manufactured through the developmental phases. DP is considered well-characterised and stable. Therefore, there are no concerns related to comparability and thus the quality of the DP used in the pivotal clinical study can be considered comparable to the commercial DP. The rationale for control strategy is clearly presented and is, in general, considered acceptable.

General suitability of the proposed commercial container closure system is sufficiently justified and is

supported by notified body opinion (NBOp).

Extractable studies have been completed and leachable studies to study the container closure components over the course of the product shelf life are still ongoing. Leachable results has been provided and do not give rise to concerns. The leachables testing will be continued and updated results are requested.

FP contains no preservatives and is manufactured using an aseptic process including sterilization by filtration. Sterility and endotoxins are tested as part of FP release and container closure integrity is being monitored as part of the long-term stability program. Based on the information provided, the control strategy for microbiological attributes of the FP is considered adequate.

3.3.2. Manufacture of the product and process controls

Manufacture

The FP manufacturing process is standard for a sterile solution for injection filled into syringes.

A clear flow diagram of the sasanlimab FP manufacturing process and sufficiently detailed manufacturing process description have been provided, including critical process parameters and in-process controls (IPCs) for each manufacturing step.

Process parameters impacting product quality are provided with setpoints or acceptable ranges and are adequately supported by development studies.

Hold times for process intermediates applied in the FP manufacturing process are provided. Hold times are considered adequately validated and are considered acceptable.

Process controls

Process controls with their control limits are provided and are considered appropriate. Information provided on the analytical methods for the IPCs is considered sufficient. Justification of the IPCs and their acceptance criteria is in line with development studies. In general, the control strategy and the acceptance criteria are supported.

Process validation / verification

The validation of FP manufacturing process was performed at the commercial scale using consecutive bulk FP formulation batches. The results of the PPQ demonstrate that the manufacturing process is able to consistently manufacture FP that meets its specifications.

3.3.3. Supportive validation studies has been provided in line with EMA guidance (EMA/CHMP/CVMP/QWP/850374/2015and is considered acceptable. Product specification

Specifications

FP specifications largely overlap with AS specifications and are in line with ICH Q6B and the general monograph for monoclonal antibodies for human use (Ph. Eur. 2031). In general, adequate parameters have been chosen to ensure the quality of FP.

In general, adequate justification is provided for the proposed acceptance criteria for each analytical test of the FP specifications. The approach used to set release and shelf-life acceptance criteria (manufacturing experience, statistical analysis, clinical experience/exposure, relevant development data and non-clinical data) is considered appropriate.

A summary of the risk assessment for elemental impurities in accordance with ICH Q3D has been provided. FP is considered low risk with respect to elemental impurities. This is adequately supported.

A declaration related to the nitrosamine risk assessment and a summary of the nitrosamines risk evaluation and assessment is provided. The Applicant concludes that there is no risk identified for small molecule nitrosamine formation in the active substance, drug product, and primary packaging processes. This is adequately supported.

Analytical procedures and reference standards

The assessment of analytical procedures shared between AS and FP, and their validations are provided in the AS section. FP is tested using a combination of compendial and non-compendial methods. Overall, adequate descriptions of the analytical procedures used in routine control of FP have been provided, including the principle of the method, standard/control/sample preparation, procedure, critical assay conditions, system suitability criteria, calculation methods, representative chromatograms and the way of reporting results for the non-compendial methods.

Compendial methods have been verified to be suitable for their intended purpose according to compendial requirements and the results are presented. Non-compendial methods have been adequately validated according to ICH Q2(R2) and adequate method validation reports have been provided

Information about, and assessment of, the reference standard used for FP are provided in the AS section as the same reference standard is used for AS.

Batch analysis

The batch analysis data indicate that all results comply with specifications in place at time of testing and confirm process and product consistency. In general, the batch data are consistent and do not give rise to concerns.

Container closure

Sufficient information is provided related to the container closure components including drawings, component dimensions, quality control testing, suppliers, and compliance of construction material with relevant compendia.

The choice of the container closure has been adequately justified and is supported with stability data. Container closure integrity has been demonstrated and is verified during stability studies.

A Notified body report and a summary of the human factors use-related risk assessment have been provided. The provided information is considered sufficient and does not give rise to concerns.

3.3.4. Stability of the product

The stability studies are in line with the requirements of ICH Q5E and ICH Q1A. Stability test conditions include the recommended storage condition and stressed storage conditions.

The selected batches are representative of commercial batches and are considered sufficient for the stability studies. All stability results available for the primary stability and supporting stability batches comply with the proposed shelf-life specifications.

Accelerated, stressed and thermal cycling studies support the stability of FP

Photostability was adequately tested in line with ICH Q1B.

3.3.5. Adventitious agents

Sasanlimab is manufactured in accordance with current GMP and adventitious agents are controlled in accordance with the guidelines by the International Conference on Harmonization (ICH) Q5A(R1), Q5D, and Q7A.

The Applicant has addressed both non-viral and viral contaminants.

Viral clearance validation (VCV) studies were performed in line with the requirements in ICH Q5A(R2) to demonstrate the capability of the DS manufacturing process to remove and/or inactivate viruses. Original reports are submitted.

The cumulative inactivation/removal of different types of viruses during the manufacturing process is considered to be sufficiently demonstrated.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

In general, the dossier is of good quality. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The manufacturing processes of both active substance (AS) and finished product (FP) are straightforward and common for a recombinant monoclonal antibody. Several changes have been introduced during the development of the manufacturing process of both AS and FP and comparability has been demonstrated throughout the development programme. The batches used in the pivotal clinical trial are representative of the proposed commercial product. The OCs are mainly related to the specifications of the AS and the FP and the qualification of the assay.

In general, adequate parameters have been chosen to ensure the quality of AS and FP.

Additional questions relate to the manufacturing process description, analytical method descriptions, description of sterilization method of, for which more detailed information should be provided.

For AS, shelf life is sufficiently supported.

before the proposed shelf-life claims are considered sufficiently justified, the Applicant should address the concerns related to shelf-life specifications.

A Notified body report has been provided. The provided information is considered sufficient and does not give rise to concerns.

The issues raised should be properly addressed by the Applicant before a positive opinion can be recommended to the CHMP.

4. Non-clinical aspects

4.1. Introduction

Sasanlimab is a humanized PD-1 blocking IgG4 mAb. *In vitro* assays were conducted to demonstrate the biological function of sasanlimab, including binding to human and cynomolgus monkey PD-1 and blocking the ability of PD-1 to bind to PD-L1 or PD-L2. Functional assessments were performed in activated human and cynomolgus monkey T cells in MLR assays. Superantigen stimulation of cynomolgus monkey whole blood treated with sasanlimab served to test activity following PD-1

blockade in primary cynomolgus monkey T cells. In addition, *in vivo* enhancement of xenogeneic acute Graft-versus-Host Disease (aGvHD) in NOD scid gamma (NSG) mice (transferred with human peripheral blood mononuclear cells (PBMCs)) by sasanlimab was utilized to assess biological activity of this antibody. Secondary pharmacodynamics assessments included investigating the potential for Fc receptor binding and antibody dependent cell-mediated cytotoxicity (ADCC), complement activation, and cytokine release. The nonclinical PK and TK of sasanlimab was characterized in cynomolgus monkeys following single and repeat dosing. The nonclinical safety profile of sasanlimab has been characterized in repeat-dose toxicity studies in cynomolgus monkeys up to 1 month (GLP) in duration by the IV route that supported initial clinical studies and 6 months (GLP) in duration by SC route of exposure supporting the intended route of clinical administration. Monkeys were selected as the sole toxicology species based on similar PD-1 binding affinity and PD-1 tissue distribution as human and the lack of appreciable binding in rodents. Developmental toxicity and carcinogenicity studies of sasanlimab were not performed and the risk assessment was based on a weight-of-evidence approach. A GLP tissue cross-reactivity (TCR) study was conducted to evaluate the potential off-target binding of sasanlimab.

4.2. Analytical methods

Sasanlimab was quantified using a validated electrochemiluminescent (ECLA) ligand binding assay in monkey serum. The GLP-compliant validation report included the evaluation of precision and accuracy (intra- and inter-assay), upper- and lower limits of quantitation, dilution linearity, selectivity, andsample stability. The range of quantification in 100% monkey serum was 27.2 to 926 ng/mL. Incurred sample reanalysis was conducted as part of two GLP repeat-dose toxicity studies (14GR560 and 8391014), and was acceptable.

For the detection of antibodies (ADAs) against sasanlimab in monkey serum, a validated ECLA ligand binding assay was developed. The GLP-compliant validation report included the evaluation of precision (intra- and inter-assay), dilution linearity, and drug tolerance. The anti-sasanlimab ADA assay was selective and the sensitivity was found to be 16.8 ng/mL in monkey serum. Concerning drug tolerance, at 1,000 ng/mL of anti-sasanlimab antibodies, none of the concentrations of drug tested (up to 400 µg/mL) resulted in a negative signal. At 100 ng/mL of anti-sasanlimab antibodies, addition of 200 µg/mL of free drug resulted in a negative signal, indicating interference.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Sasanlimab was characterized *in vitro* and *in vivo* in non-clinical PD studies.

The Applicant first determined the *in vitro* binding affinity and specificity of sasanlimab to recombinant PD-1 proteins and to PD-1 proteins on the surface of T cells from different species. Strong binding was observed for human and cynomolgus monkey PD-1, while little to no binding was observed for mouse and rat PD-1. Sasanlimab exhibited a fast on-rate and slow off-rate, contributing to its strong binding characteristics.

Cell surface binding studies confirmed sasanlimab's ability to bind cell surface PD-1 on activated human and cynomolgus monkey T cells, but not to mouse and rat. Minimal binding was observed on

naïve/resting T cells across all species tested, consistent with PD-1 as a checkpoint receptor mainly expressed on activated and exhausted T cells.

The Applicant further demonstrated that sasanlimab could block the PD-1 receptor/ligand interactions, using both human and cynomolgus PD-1 and PD-L1/2 proteins. These data indicate the first steps in the anticipated mechanism-of-action of sasanlimab, namely binding to PD-1 in order to block the interaction between PD-1 and its ligands on bladder tumour-specific T cells, with the ultimate goal to prevent exhaustion of these cells and enhance the anti-tumour response.

The next step in the anticipated mechanism-of-action of sasanlimab, namely the prevention of PD-1 related inhibitory signalling in T cells, was shown with mixed lymphocyte reaction (MLR) assays. Primary T cells were mixed with allogeneic human dendritic cells (expressing high levels of PD-L1) or with the tumour cell line JeKo-1-PD-L1^{+}. Following PD-1 blockade with 10 µg/mL sasanlimab, human and cynomolgus T cell proliferation and pro-inflammatory cytokine production (primarily IFN-γ and TNF-α) was considerably enhanced.

In vitro, the stimulatory function of the T cell receptor on cells cultured in the presence of sasanlimab was also shown in a *Staphylococcal Enterotoxin B* (SEB) stimulation assay.

The Applicant has also conducted *in vivo* PD studies. Receptor occupancy of sasanlimab on T cells was determined in female cynomolgus monkeys as part of PK study no. 20070482. Single intravenous administration of 0.1 or 1 mg/kg antibody resulted in occupation of all PD-1 receptors on the surface of peripheral T cells (both CD4+ and CD8+), starting at 0.25h after antibody administration. The duration of this occupation was dose-dependent.

The Applicant further conducted an *in vivo* study to show the activity of sasanlimab in a xenogeneic mouse model of graft-versus-host disease (GvHD). On day 0, female NSG mice were transplanted intravenously with 1x10^{7} human healthy donor PBMCs to induce acute GvHD. Subsequently, sasanlimab was administered intraperitoneally on day 2 and day 8 at 0.1, 1 or 10 mg/kg to evaluate the effect on functionality of human T cell and clinical signs. Separate experiments using PBMCs from two different donors were conducted. The results indicate that sasanlimab enhanced the T cell xenogeneic response *in vivo* (measured as increased body weight loss and enhanced infiltration of T cells into target tissues such as liver and spleen).

4.3.1.2. Secondary pharmacodynamics

Sasanlimab was designed with an IgG4 framework to minimize Fc-mediated effector functions and reduce unintended immune activation. The Applicant conducted four experiments to determine binding of sasanlimab to Fc gamma receptors and complement factor 1q, and to determine potential ADCC and cytokine release activity. No increased binding affinity or cytotoxic/cytokine release activity of sasanlimab was observed when compared to the isotype IgG4 control antibody. Thus, as expected with an IgG4-based antibody, sasanlimab will likely not trigger immune functions such as phagocytosis, ADCC, complement activation and pro-inflammatory cytokine release *in vivo*.

4.3.1.3. Safety pharmacology

No dedicated safety PD studies have been conducted with sasanlimab.

4.3.1.4. Pharmacodynamic drug interactions

No non-clinical dedicated pharmacodynamic drug-drug interaction studies with sasanlimab were submitted.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

No dedicated pharmacokinetic studies were performed with sasanlimab. Systemic exposure (AUC and C_{max}) was determined after a single IV dose of 0.1 and 1 mg/kg sasanlimab in female monkeys in a PK-PD study (Study 20070482/111601), and as part of repeat-dose toxicity studies in monkey after weekly SC or IV administration of sasanlimab.

In cynomolgus monkeys dosed intravenously QW for 1 month, the systemic exposure of sasanlimab generally increased dose-proportional from 20-200 mg/kg and was higher after repeat dosing, indicating mild accumulation (2-2.7 fold). In cynomolgus monkeys dosed subcutaneously QW for 6 months, the systemic exposure of sasanlimab generally increased dose proportional from 10 to 100 mg/kg on day 1 and 85, but less than dose-linear at day 176. Mild to moderate accumulation was observed in the pivotal 6-month SC study (2.9-3.9 fold) across the dose groups after d85. There were no sex-related differences in systemic exposure.

The presence of ADAs was observed after repeat SC or IV dosing with similar exposures in ADA-positive compared to ADA-negative monkeys; although high incidences of ADAs were observed in the 6-month study (100% and 63% in the 10 and 100 mg/kg animals).

4.3.2.2. Distribution

Formal tissue distribution and protein binding studies were not conducted with sasanlimab.

4.3.2.3. Metabolism

No metabolism studies were conducted with sasanlimab.

4.3.2.4. Excretion

No excretion studies were conducted with sasanlimab.

4.3.2.5. Pharmacokinetic drug interactions

Please refer to Section 6.2.2.11.

4.3.2.6. Other pharmacokinetic studies

NA

4.4. Toxicology

The non-clinical toxicology programme for sasanlimab (also known as PF-06801591, RN888) consists of a total of five studies. Cynomolgus monkeys were selected as the sole relevant species based on similar PD-1 binding affinity and PD-1 tissue distribution as human and the lack of appreciable binding in rodents. Two pivotal GLP compliant repeat-dose (RD) toxicity studies; 1-month study by the IV route that supported initial clinical studies and 6-months study by SC route supporting the intended clinical route of administration. Local tolerance, immunogenicity and safety pharmacology were

assessed as part of the pivotal RD-toxicity studies. In addition, a GLP compliant TCR study, a GLP compliant RD-toxicity study in sexually mature males and a non-GLP exploratory 15-days RD-toxicity study were included in the dossier. Developmental toxicity and carcinogenicity studies of sasanlimab were not performed and the risk assessment was based on a weight-of-evidence approach. Given the projected prolonged life expectancy of cancer patients indicated for treatment with sasanlimab in combination with BCG, the non-clinical program was conducted in accordance with the recommendations outlined in the ICH S6(R1) guideline and is considered acceptable.

4.4.1. Single-dose toxicity

Single-dose toxicity studies with sasanlimab have not been conducted.

4.4.2. Repeat-dose toxicity

Repeat dose toxicity studies were performed in cynomolgus monkeys for 2 weeks and 1 month followed by a 2-month recovery period by the intravenous (IV) route that supported initial clinical studies. In addition, a 6-month study with subcutaneous (SC) administration was performed, supporting the intended route of clinical administration.

High-doses of 200 mg/kg IV and 100 mg/kg SC were selected for the 1-month and 6-month study, respectively, based on dose volume limits and to achieve >10x expected exposure relative to the clinical dose of 300 mg SC. The weekly dosing interval aligned with the intended clinical regimen. Hence, the dose selection and interval for the pivotal studies is sufficiently justified.

The non-GLP 2-week (two once weekly doses) IV infusion exploratory toxicity study in cynomolgus monkeys was conducted at up to 200 mg/kg/week but did not reveal any unique toxicities.

In the 1-month IV bolus toxicity study, sasanlimab was administered once weekly (5 total doses) to cynomolgus monkeys (3/sex/group) at doses of 0, 20, 60, or 200 mg/kg/week. For the control and 200 mg/kg/week dose levels (2/sex/group), the potential for reversal of toxicity was also evaluated following a 2-month recovery phase. In the 6-month SC injection toxicity study, sasanlimab was administered once weekly (27 total doses) to cynomolgus monkeys (4/sex/group) at doses of 0, 10, or 100 mg/kg/week.

The key findings in both studies were limited to mononuclear cell infiltrates in various organs.

In the one-month study, at the end of the dosing period, no adverse effects were observed. Mononuclear cell infiltrates were either present in both control and treated groups or occurred sporadically in treated animals without a dose-dependent pattern. At the end of the recovery period, infiltrates persisted in most organs in both control and treated animals. However, in the pituitary, pancreas, skeletal muscle, peripheral nerve, brain, and spinal cord, mononuclear cell infiltration was observed only in sasanlimab-treated animals. As there was no associated tissue inflammation or structural damage, and the findings were slight or mild in severity, they were considered non-adverse. In two males at 200 mg/kg/week, mild mononuclear cell infiltration was observed in the meninges and/or choroid plexus, with additional mild multifocal perivascular infiltration in the neuropil. In one male animal, this was accompanied by reactive astrocytes clustering around blood vessels—indicative of local gliosis—and, in one instance, multinucleated syncytial cells adjacent to a vessel wall, suggesting cell fusion or aberrant cellular activity potentially related to inflammation or immune dysregulation. These findings demonstrate a test article–related neuroinflammatory response extending from non-parenchymal structures (meninges/choroid plexus) into the brain parenchyma (neuropil). The presence of gliosis and abnormal syncytial cells indicates a cellular response to injury

or immune activation, supporting an adverse classification. Since lower doses were not evaluated in the recovery phase, a NOAEL could not be established.

In the 6-month SC study, unlike in the 1-month IV study, mononuclear cell infiltration in control animals was limited to the kidney and mandibular salivary gland. At doses ≥10 mg/kg, mononuclear cell infiltrates were observed in multiple organs–including the brain, epididymis, eye, heart, pituitary, thyroid, urinary bladder, and subcutaneous injection sites—with a clear dose-dependent increase in both incidence and severity. Although most infiltrates were graded as minimal or slight and were not associated with overt tissue damage (e.g., necrosis or apoptosis), the systemic and progressive nature of these lesions supports their classification as test article–related adverse effects. Notably, in one female administered 100 mg/kg/week, mononuclear cell infiltration in the pars nervosa of the pituitary, though minimal in severity, extended into the surrounding neuropil. The NOAEL in the 6 month study was 10 mg/kg/week."

In the 1-month study, the Applicant conducted immunophenotyping (prior to dosing and on day 15 and 30) and a Staphylococcal Enterotoxin B stimulation assay (prior to dosing and on day 14, 28 and 43/43) to determine potential safety issues related to the systemic T cell phenotype and functionality following intravenous sasanlimab treatment.

Sasanlimab resulted in increased activated (HLA-DR+) and proliferating (Ki67+) T cells for all dose groups, but only on day 15. In general, numbers of total CD4+ and CD8+ T cells, B cells and NK cells were not changed compared to baseline. These data are in line with the presumed pharmacological activity of sasanlimab, namely retaining or enhancing T cell functionality.

Ex vivo SEB stimulation resulted in considerable IFN-γ secretion from T cells derived from control cynomolgus monkeys and this could be further enhanced by adding sasanlimab to the culture. However, IV sasanlimab administration did not enhance the ability of cynomolgus T cells to respond (via IFN-γ secretion) to *ex vivo* SEB stimulation compared to the control or predose samples, while at all doses the PD-1 receptor of the T cells was blocked by the antibody. Although these data indicate that T cells retain their functionality *in vivo* when PD-1 is occupied by the antibody, the findings are not in agreement with the PD data from cynomolgus T cells stimulated *in vitro* with sasanlimab and SEB (see section 2.1.1.4). Addition of sasanlimab in the SEB culture of the sasanlimab-treated animal samples did even reduced the IFN-γ secretion, which was an unexpected result and could not be explained by the Applicant.

4.4.3. Genotoxicity

It can be agreed in accordance with ICHS6(R1), genotoxicity studies are not generally required for monoclonal antibodies like sasanlimab.

4.4.4. Carcinogenicity

Sasanlimab is a PD-1 inhibitor that enhances immune surveillance and T-cell activation, a mechanism consistent with anti-tumor activity and not suggestive of intrinsic carcinogenic potential. PD-1 expression is restricted to subsets of immune cells and is not present on general somatic cells, thereby minimizing the risk of off-target effects. In repeat-dose toxicity studies of up to six months in cynomolgus monkeys, proliferative responses were limited to immune cell infiltration, with no evidence of hyperplasia or pre-neoplastic changes in tissues. Furthermore, sasanlimab does not cross-react with rodent PD-1, making conventional carcinogenicity studies in mice or rats inappropriate due to lack of pharmacological relevance. Additional support comes from PD-1 knockout mouse models, which do not show increased tumor formation, indicating that chronic PD-1 blockade is not inherently tumorigenic.

Moreover, clinical use of other approved PD-1 inhibitors has not identified safety signals indicative of increased late-onset malignancy risk, further supporting the low carcinogenic potential of this drug class. Overall it can be agreed that the carcinogenic potential is low and carcinogenicity studies are not considered necessary for sasanlimab.

4.4.5. Developmental and reproductive toxicity

The fertility assessment for sasanlimab was based on organ weights and histological examination of male and female reproductive tissues in 1- and 6-month studies using sexually mature monkeys (Males: At least 5 years; Females: At least 4 years). No changes in organ weights were observed in either study. No histopathological effects on female reproductive organs were observed at doses up to 200 mg/kg/week (1-month study) and 100 mg/kg/week (6-month study). Sporadic mononuclear cell infiltrates were noted in male reproductive organs but occurred also in controls without dose dependence and were considered non adverse in one month study. In the 6-month study, minimal perivascular mononuclear cell infiltrates were found in the epididymis at 100 mg/kg/week, with no expected impact on fertility. Additionally, tissue cross-reactivity studies showed no sasanlimab binding in reproductive tissues of monkeys or humans. Overall, the nonclinical data do not indicate any concern for sasanlimab's effects on male or female fertility.

No dedicated developmental toxicity studies have been conducted for sasanlimab due to the known pharmacological mechanism of PD-1 inhibition, which is associated with a significant risk of pregnancy loss. PD-1/PD-L1 signaling plays a critical role in maintaining maternal-fetal immune tolerance; inhibition of this pathway disrupts this balance, leading to increased embryo lethality and adverse pregnancy outcomes, as demonstrated in multiple preclinical models and supported by extensive literature.

Given the immunological basis of the reproductive risk and the variability introduced by paternal antigenic differences, conventional reproductive toxicity studies in pregnant monkeys are of limited value. This is compounded by the high baseline rates of spontaneous abortion and neonatal loss in monkeys, making interpretation difficult and preventing reliable safety margin determinations. *In vivo* pharmacology studies confirm that sasanlimab enhances T-cell activity and pro-inflammatory responses, reinforcing the mechanistic plausibility of fetal loss.

4.4.6. Toxicokinetics and exposure margins

For toxicokinetics please refer to assessor's comment in Section Absorption.

In cynomolgus monkeys, the systemic exposure of sasanlimab generally increased with increasing dose and was higher after repeat dosing. Accumulation in the pivotal 6-month SC study was 2.9-3.9 fold across the dose groups after 3 months. There were no sex-related differences in systemic exposure.

The presence of ADA was observed after repeat SC or IV dosing with exposures generally similar in ADA-positive monkeys compared to ADA-negative monkeys; although high incidences of ADAs were observed. No additional studies to determine the neutralizing capacity of the ADAs were performed, but since pharmacodynamic effects were observed in the pivotal toxicity studies, it can be assumed that sufficient exposure levels were reached.

4.4.7. Local tolerance

Although no dedicated local tolerance studies were conducted with sasanlimab, local tolerability was assessed as part of the repeat-dose toxicity studies. In the 1-month study, after 2 doses on Day 1 and 29, SC injection of sasanlimab did not induce local irritation, as assessed by clinical signs and microscopic observations. In the 6-month study, minimal to moderate mononuclear cell infiltrates were present at SC injection sites, with a dose dependent increase in severity and incidence. The reversibility was unknown. These findings are consistent with a local inflammatory response commonly observed with repeated subcutaneous administration of monoclonal antibodies and they can be associated with tissue damage or clinical signs of intolerance. Overall, the local tolerance of sasanlimab is considered acceptable based on the available data.

4.4.8. Other toxicity studies

The formation of ADA and the associated effects on sasanlimab exposure were measured in the 1- and 6-month monkey toxicity studies.

In the 1-month IV monkey study, sasanlimab was administered once weekly at 20, 60, or 200 mg/kg. ADA was detected in only 1/6 animals (17%) at the 20 mg/kg dose, and not at higher doses (60 and 200 mg/kg). Serum exposure in the ADA-positive animal was comparable to ADA-negative animals, suggesting low immunogenicity and no significant impact on exposure in this short-term IV setting.

In the 6-month SC monkey study, higher ADA incidences were observed. ADA was detected in 50% (4/8) of vehicle control animals, though no sasanlimab was present. In the 10 mg/kg/week group, ADA developed in all animals (8/8) from Day 1, preventing comparison with an ADA-negative group. Notably, three animals (2 males, 1 female) showed marked exposure loss on Days 85 and 176, with AUC values undetectable or ~500-fold lower. In the 100 mg/kg/week group, ADA was detected pre-dose in one animal and developed in 62.5% (5/8) from Day 1. Serum exposure was generally unaffected, except in one female with ~30-fold lower exposure on Day 176. The detection of ADAs already at day 1 in animals dosed 10 and 100 mg/kg/week and in vehicle control animals, suggest some baseline cross-reactivity or assay interference. It is agreed that a dedicated immunotoxicity study such as a T-cell-dependent antibody response (TDAR) assay in monkeys is not warranted in this case. The immunomodulatory risks associated with sasanlimab are adequately addressed through mechanistic understanding, nonclinical toxicity data, and existing clinical experience.

A tissue cross-reactivity (TCR) study was conducted to evaluate the potential off-target binding of sasanlimab, using cryosections of human (up to 3 donors per tissue) and cynomolgus monkey (2 donors per tissue) tissues. The antibody was applied at two concentrations (0.5 and 5 µg/mL), alongside appropriate controls.

Sasanlimab showed specific binding to PD-1–expressing positive control cells with intensity correlating to PD-1 expression levels, and no reactivity with negative control cells, the isotype control, or assay blanks, confirming assay specificity and reproducibility. In tissue panels, sasanlimab stained mononuclear leukocytes within lymphoid tissues of both humans and cynomolgus monkeys, consistent with the known expression pattern of PD-1. No unexpected or non-specific staining was observed in any other tissues. Staining profiles were comparable between species.

These results indicate that sasanlimab exhibits specific, expected tissue binding without evidence of off-target cross-reactivity.

4.4.9. Ecotoxicity/environmental risk assessment

As a recombinant human monoclonal antibody, sasanlimab is made up of amino acids that are readily degraded and not expected to persist or bioaccumulate in the environment. Therefore, an ERA is not warranted.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

Based on the *in vitro* binding affinity data, cynomolgus monkey was considered the most appropriate animal model for further *in vivo* non-clinical testing of sasanlimab. This is endorsed.

The Applicant sufficiently determined the sasanlimab-related binding to and blocking of PD-1 proteins of different species. However, considering the absence of epitope mapping in the Quality or Non-clinical dossier, it is not clear whether this only included full-length PD-1 or also its splice variants. This requires further discussion, substantiated with *in vitro* data, unless otherwise justified (**Rapp OC**). In addition, whether sasanlimab could bind to other members of the immunoglobulin supergene CD28 family (CD28, ICOS, CTLA-4 and BTLA) was not evaluated, while a justification for the absence of such data was requested as post-meeting note in the Presubmission Meeting minutes document. Considering that the (non-)clinical safety data for sasanlimab are in line with those observed with other (marketed) monoclonal antibodies against PD-1, this issue will not be further pursued.

In vitro T cell functionality data indicate that T cells, which are activated in a PD-L1-rich tumour microenvironment and express PD-1 on their cell surface, may be able to maintain their functionality when sasanlimab is also present. However, these data are derived from healthy donor T cells in a culture where sasanlimab was simultaneously present with PD-L1 expressing cells. It is not clear whether sasanlimab can exert the same activity when T cells have already been in contact with PD-L1, thus whether sasanlimab can reverse/dampen the intracellular PD-1 signalling once this has been activated in the T cells. Reference is made to the Clinical AR for further discussion on and assessment of the efficacy data for sasanlimab.

In the *in vitro* SEB stimulation assay, it was not evaluated whether sasanlimab alone (without SEB) could spontaneously activate T cells, thus inducing cytokine secretion without concurrent T cell receptor triggering, but this was evaluated in one of the secondary PD studies. Moreover, the SEB assay only evaluates initial T cell activation, without determining the potential effect of sasanlimab on an antigen-specific recall response (e.g. using a viral antigen like CMV). However, considering that the (non-)clinical safety data for sasanlimab are in line with those observed with other (marketed) monoclonal antibodies against PD-1, no additional non-clinical data on the impact of sasanlimab on the T cell-related antiviral or recall response is warranted.

In their *in vitro* studies, the Applicant used T cells and cell lines with high PD-1 expression. However, it is not clear whether this high expression is physiologically relevant in the context of T cells in the response against bladder tumours and BCG pretreatment, and whether the concentrations of sasanlimab used in the *in vitro* studies (about 10^{-2} to 10^{4} pM and 0.0001-10 µg/mL) are clinically relevant. Nevertheless, as clinical PK data (including receptor occupancy of systemic T cells) and efficacy data are available, the clinical relevance of these non-clinical studies and corresponding data will not be further pursued.

The receptor occupancy data in female cynomolgus indicate that also *in vivo*, sasanlimab can strongly bind to PD-1 protein on (systemic) T cells. Whether the degree of occupancy is similar in patients (with possibly a different level of PD-1 expression on activated tumour-targeting T cells) when using the clinical route of administration and at sites relevant for the indication (e.g. bladder wall) remains unclear. Reference is made to the Clinical AR for assessment of sasanlimab PK and efficacy data.

The Applicant conducted an *in vivo* proof-of-concept study in a xenogeneic mouse model of GvHD. The results of this study indicate that sasanlimab seems to have enhanced the T cell xenogeneic response *in vivo* (measured as increased body weight loss), although it cannot be ruled out that sasanlimab (also) had a direct toxic effect without binding to T cells. In addition, strong evidence for enhanced T cell proliferation and cytokine production by sasanlimab-related blockade of PD-1 signalling is limited.

The Applicant has not performed any primary pharmacodynamic studies in a tumour model system *in vivo*. The provided argumentation is that sasanlimab bound mouse PD-1 only at high, biologically irrelevant concentrations and therefore the function of sasanlimab in syngeneic tumour models could not be evaluated. Further, the Applicant has briefly referred to literature indicating that blockade of the PD-1 pathway is known to accelerate GvHD in mouse models. Therefore, a xeno-aGvHD model in NSG immunocompromised mice, transferred with human PBMCs, was chosen to test the effects of sasanlimab on human T cells *in vivo*. It is agreed that this model could allow to confirm the *in vitro* proof-of-concept of sasanlimab, namely blockade of PD-1 signalling and enhancement of T cell functionality. However, this model does not allow for a proof-of-concept related to the intended clinical indication and target population. Considering the equivocal effects of sasanlimab on T cell proliferation *in vitro* with lack of effects following stimulation with a tumour cell line (in MLR), an *in vivo* study in a tumour model could have provided valuable support for the postulated mechanism-of-action of sasanlimab. Moreover, it is not clear whether the GvHD model is relevant for the location of T cell activation and PD-L1/L2 or anti-PD-1 interactions, thus the location were sasanlimab activity is to be expected. Furthermore, the clinical relevance of the sasanlimab doses (0.1-10 mg/kg), dose regimen (2 times) and route of administration (intraperitoneal) is unclear. The use of a murine homologous anti-PD-1 antibody in a tumour-bearing mouse model might have been more relevant to provide proof for efficacy. The Applicant has not justified the absence of a sasanlimab-related *in vivo* animal study relevant for bladder tumours, while such study would be technically feasible. Therefore, efficacy assessment of this therapeutic antibody should be solely based on clinical data, including impact of sasanlimab on other immune cells than T cells. Still, as mentioned in the Presubmission Meeting, the Applicant is requested to elaborate further on the mechanism-of-action for the expected effects of sasanlimab + BCG on urothelial tumours *in vivo*, by providing a literature-based discussion of the added value of an anti-PD-1 antibody in combination with BCG for the treatment of NMIBC (**Rapp/Co-Rapp OC**).

There is some ambiguity regarding the binding mechanism of sasanlimab, which was already highlighted during the Presubmission Meeting (March 2025). While this antibody is administered subcutaneously and needs to bind to PD-1 on immune cells, it is unclear where in the body this binding occurs. It is not clear whether sasanlimab binds systemically to T cells (and other immune cells), which are subsequently attracted to the bladder by the BCG infection, or whether sasanlimab targets the bladder and binds locally to BCG-attracted T cells. Available data on receptor occupancy (both non-clinically and clinically) seems limited to T cells in the circulation, Whether these circulating cells are the ones that attribute to the anti-tumor response or whether the relevant T cells are attracted from the local tissue and lymph nodes remains to be discussed. The Applicant is therefore asked to discuss the binding mechanism of sasanlimab to substantiate effectiveness and the relevance of biomarkers/phenotypic markers in the (non-)clinical studies. The Applicant should include in this discussion a) where in the body SC-administered sasanlimab will bind to PD-1 on T cells (and/or other immune cells), b) which T cells are attracted to the tumor (in the context of a BCG infection), and thus

c) whether sasanlimab targets the immune cells that are most relevant for the anti-NMIBC response (**Rapp/Co-Rapp OC**).

The absence of dedicated safety PD studies is endorsed. In agreement with ICH S7A, it is considered sufficient that the impact of sasanlimab on the vital organ functions has been evaluated as part of the general toxicity studies in NHP. The Applicant stated that "*no sasanlimab-related effects were observed for cardiovascular endpoints (ECG and heart rate), or respiratory or CNS function in the pivotal IV 1-month and SC 6-month GLP toxicology studies in monkeys (Study No. 14GR560 and 8391014)".* In the study reports, however, there is very limited information on the safety pharmacology endpoints included, and it remains unclear to what extent cardiovascular and respiratory parameters (e.g., respiratory rate and respiratory function; tidal volume, haemoglobin oxygen saturation) and CNS functions (e.g., motor activity, behavioural changes, coordination, sensory/motor reflex responses, and body temperature) were assessed. While behavioural observations appear to have been conducted in the 6-month study, the specific parameters assessed are not explicitly detailed. Similarly, although electrocardiograms and heart rate measurements were included in the 1-month study, it appears that blood pressure evaluations, as recommended by ICH S7A, were not performed. The Applicant should provide a detailed overview of the specific safety parameters assessed in the pivotal non-clinical studies, and justify absence of any endopint to be evaluated according to ICH S7A (**Co-Rapp OC, adapted by Rapp**).

Since sasanlimab is designed to modulate the functional activity of T lymphocytes, there is potential for pharmacodynamic drug-drug interactions of sasanlimab in relation to cytotoxic, immunosuppressive or immunomodulatory therapies. This issue has been raised clinically in section 4.5 of the SmPC.

Pharmacokinetics

Sasanlimab was quantified using a validated electrochemiluminescent (ECLA) ligand binding assay in monkey serum. For the detection of antibodies (ADAs) against sasanlimab in monkey serum, a validated ECLA ligand binding assay was developed. According to validation reports from 2015 (reports no. 135015 and 135235), the initial validations were not conducted in accordance with GLP. The methods were, however, revalidated in 2018 (reports no. 187009 and 187013) in compliance with GLP. The methods are considered adequately validated in accordance with ICH M10 and are found fit for purpose.

No dedicated pharmacokinetic studies were performed with sasanlimab. Systemic exposure (AUC and C_{max}) was determined after a single IV dose of 0.1 and 1 mg/kg sasanlimab in female monkeys in a PK-PD study (Study 20070482/111601), and as part of repeat-dose toxicity studies in monkey after weekly SC or IV administration of sasanlimab. Clearance, V_{ss} and half-life have not been presented, claimed due to variability potentially related to ADA formation. While it is acknowledged that data may indicate some variability in clearance, standard PK parameters (individual and combined clearance, V_{ss} and half-life) should be provided (**Co-Rapp OC**).

In cynomolgus monkeys, the systemic exposure of sasanlimab generally increased with increasing dose and was higher after repeat dosing, indicating mild to moderate accumulation (2-2.7 and 3.9-2.9 following IV and SC dosing, respectively), with a significant delayed T_{max} following SC administration. There were no sex-related differences in systemic exposure.

The presence of ADAs was observed after repeat SC or IV dosing with exposures generally similar in ADA-positive monkeys compared to ADA-negative monkeys; although high incidences of ADAs were observed. Validation data have indicated a risk of analytical interference between plasma levels of sasanlimab and ADAs at higher sasanlimab exposure levels, this is likely the cause for less/no ADA-positive samples at higher exposure levels. No additional studies to determine the neutralizing

capacity of the ADAs were performed, but since pharmacodynamic effects were observed in the pivotal toxicity studies, it can be assumed that sufficient exposure levels were reached.

Distribution, metabolism and excretion studies in non-clinical species were not conducted. This is in line with ICH S6(R1) and agreed.

Excretion of sasanlimab to milk has not been examined. However, as an IgG, sasanlimab would be expected to be present in the first colostrum.

Toxicology

Repeat dose toxicity studies were conducted in monkeys, in both 1-month (IV) and 6-month (SC) studies, mononuclear cell infiltration was observed in multiple organs in sasanlimab-treated monkeys, including the brain, pituitary, spinal cord, and peripheral tissues. These findings are consistent with the mechanism of action of PD-1 inhibition, which promotes immune activation and enhanced immune surveillance. Cynomolgus monkeys were selected as the sole relevant species based on similar PD-1 binding affinity and PD-1 tissue distribution as human and the lack of appreciable binding in rodents. Given the projected prolonged life expectancy of cancer patients indicated for treatment with sasanlimab in combination with BCG, the non-clinical program was conducted in accordance with the recommendations outlined in the ICH S6(R1) guideline and is considered acceptable.

The drug lots utilized in the pivotal non-clinical studies should be representative of the test material used in clinical studies; however, no justification has been provided to substantiate this. According to Module 3.2.S.4.4, the batches used in the pivotal 6-month NHP study and the pivotal phase 3 clinical study (B8011006; CREST) were derived from the same manufacturing process. The Applicant has stated that *the batch analysis results demonstrate consistency of the manufacturing process capabilities (*Module 3.2.S.4.4) and that *in the 6-month study, the test article (API) used was representative of the commercial drug substance* (Module 2.6.6 Toxicology Written Summary). Similar findings were observed in both pivotal toxicology studies, however a question on the batches has been raised in the quality section. Whether the potential batch issue need to be further pursued will depend on the response.

In repeat dose toxicity studies, mononuclear cell infiltration was seen in multiple organs. While most immune cell infiltrates were minimal to mild in severity and not associated with tissue damage (e.g., necrosis or apoptosis), some may be considered adverse due to their localization, persistence, and dose-dependence. Findings in sensitive tissues such as the central nervous system and pituitary raise particular concern. The persistence of certain findings after the recovery period suggests incomplete reversibility. Additionally, in the 6-month study, the infiltrates were dose-dependent in both incidence and severity. Therefore, although mononuclear cell infiltrations are often seen in animals treated with anti-PD-1/PD-L1 monoclonal antibodies and are attributed to the mechanism of action, some are considered adverse including the perivascular mononuclear cell infiltration in the brain neuropil accompanied by increased glial and syncytial cells observed in a single monkey at 200 mg/kg/week in the 1-month study, and the mononuclear cell infiltration in the pars nervosa of the pituitary that extended into the surrounding neuropil, as well as the dose-dependent infiltrates seen in the 6-month study.

NOAEL could not be identified, as findings were present at all tested dose levels in the 6-month study and lower doses were not evaluated in the recovery phase for the 1-month study. Nevertheless, similar findings have been observed with other approved PD-1 inhibitors and immune-related adverse

event (irAE) is a known risks in the clinical setting. The safety margin based on the LOAEL are 15 and 3,6 respectively for the 1 month and 6 month study.

It is agreed that no reproductive or developmental toxicity studies are conducted for sasanlimab. However, it is not agreed that the identified reproductive hazard is not considered a safety concern. Due to its mechanism of action, sasanlimab may increase the risk of abortion and stillbirth if administered during pregnancy. Although the likelihood of exposure during pregnancy is low—given that the proposed indication (non–muscle-invasive bladder cancer, NMIBC) predominantly affects elderly males, with a reported male-to-female incidence ratio of approximately 3:1 to 4:1 and a median age of 70 years—appropriate risk minimisation measures should be proposed. Effective contraception is required for females of childbearing potential during treatment and for a defined period after the last dose. Furthermore, Zumrad is not recommended during pregnancy unless the clinical condition of the woman requires treatment with sasanlimab. The Applicant should revise the SmPC Section 4.6 and the RMP Module SII (Non-clinical part of the safety specification) accordingly, in line with other approved PD-1 inhibitors (**Rapp OC**).

Studies without findings, or with findings that are not relevant, should not be described in SmPC section 5.3. Instead, a general statement should be used. Relevant preclinical safety data should be described here including the repeat dose toxicity and mechanism based reproductive toxicity data. The NOAEL and safety margin should be indicated. A harmonization with other related products are desired (**Rapp/Co-Rapp OC**).

It is not known whether or to what extent sasanlimab is excreted in human milk. However, considering that IgG4 is hardly absorbed in the gastrointestinal tract of a new-born, and only excreted in breastmilk in the first few days after birth (the colostrum), the proposed waiting time of 5 months indicated in SmPC section 4.6 is not sufficiently justified. The Applicant is advised to adjust this section using proposed text, unless it can be justified that this is not appropriate for the current product (**Co-Rapp OC**).

4.5.2. Conclusions

Pharmacology

The Applicant has conducted several *in vitro* and *in vivo* pharmacology studies to determine the mechanism(s)-of-action of sasanlimab and to provide a rationale for clinical treatment. The *in vitro* studies provide a proof-of-concept that sasanlimab can block the PD-1 receptor to prevent interaction with PD-L1/2. However, the clinical relevance of the *in vivo* studies remains unclear. Furthermore, pharmacology studies evaluating sasanlimab in a tumour model and studies evaluating the combination of BCG and a PD-1 inhibitor treatment are lacking non-clinically. In addition, no information on the anticipated mechanism(s)-of-action on the combination treatment and on the location of sasanlimab binding to tumour-relevant T cells is available.

Taken together, although there are *in vitro* proof-of-concept data, there is poor non-clinical support for *in vivo* efficacy and for alleviating clinical efficacy issues (see Clinical discussion).

Pharmacokinetics

The non-clinical pharmacokinetic properties of sasanlimab were sufficiently described to support the MAA of Zumrad. Clarifying OCs are raised.

Toxicology

The primary finding in repeat-dose toxicity studies was mononuclear cell infiltration in various tissues, consistent with the expected class effect of PD-1 inhibition. A weight-of-evidence approach indicates no

carcinogenic potential. However, due to its mechanism of action, sasanlimab may increase the risk of abortion and stillbirth if administered during pregnancy. The Applicant should revise SmPC Section 4.6 and RMP Module SII with respect to pregnancy. Besides, SmPC text for lactation and preclinical safety should be adjusted. Overall, the data support a well-characterized nonclinical safety profile, with one issue regarding SmPC wording that should be addressed prior to approval.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The Applicant indicated that all clinical studies in the current application (thus including the pivotal Study B8011006) were conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the countries of conduct, including the archiving of essential documents.

The below table includes a GCP inspection conducted by a regulatory authority, as indicated by the Applicant:

Site (full address)	**Country**	**Date of inspection**	**Regulatory Agency**
Communal Institution ¨Zaporizhzhya Regional Clinical Oncological Dispensary¨, of Zaporizhzhya Regional Council, Thoracic Department, 177-A, Kulturna St. Zaporizhzhya, Ukraine	Ukraine	May-2019 - 30-May-2019	Ukraine - Ministry of Health

Given the information in Table 1, the above GCP inspection in Ukraine was for the Phase 1 Study B8011001. The report for the above GCP inspection in Ukraine could, however, not be located in the dossier (**Rapp OC**).

A request for routine GCP inspection has been adopted for the pivotal Study B8011006. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181 (see section 2.4.3.). Based on the review of clinical data, there are no specific points the Rapporteurs would like the inspectors to specifically investigate.

Based on the review of clinical data, no need for a further (triggered) GCP inspection of the clinical trials included in this dossier was identified at this time.

5.1.2. Tabular overview of clinical trials

The current submission includes clinical data from a single, pivotal Phase 3 study and three supportive studies, see Table 1.

Table 1: Tabular overview of main clinical studies

Protocol No./Number of Centres (Country)	Study Design and Objective	Treatment Groups	No. of Patients	Demographics (No. of Patients)	Duration of Treatment	Study Initiation Date/Completion Date/Status
Phase 1						
B8011001 55 centres: US, Bulgaria, Poland, Republic of Korea, Malaysia, Russian Federation, Ukraine, and Singapore **Part 1** Johnson et al. JAMA Oncol. 2019 **Part 2** Cho et al. ESMO Open. 2023	A Phase 1, OL, Dose Escalation and Expansion Study of Sasanlimab in Patients with Locally Advanced or Metastatic Melanoma, SCCHN, Ovarian Cancer, Sarcoma, NSCLC, UC or Other Solid Tumours • Phase 1, OL, multi-centre, multiple-dose, dose-escalation and expansion study. • To assess safety and tolerability of increasing dose levels of sasanlimab administered 1) IV or 2) SC in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, UC or other solid tumour types with clinical evidence of response to anti PD-1 or PD-L1 agents to establish the MTD.	**Part 1 (Dose Escalation)** 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg), and 1 SC dose level (300 mg) Q4W of sasanlimab monotherapy in adult patients with select locally advanced or metastatic solid tumours. **Part 2 (Dose Expansion)** 300 mg sasanlimab monotherapy administered SC Q4W in adult patients with locally advanced or metastatic NSCLC or UC.	**Part 1** Enrolled: 147 Treated: 40 patients were treated at dose levels of 0.5, 1, 3, or 10 mg/kg IV Q3W (25 patients) or 300 mg SC Q4W (15 patients). Completed study: 6 **Part 2** Enrolled: 107 Treated: 106 patients were treated with sasanlimab monotherapy 300 mg SC Q4W (68 patients with NSCLC and 38 patients with UC). Completed study: 15	**Part 1** Sex: 12 (30.0%) M 28 (70.0%) F Age (years): Mean (SD): 61.1 (12.5) Range (min, max): (26, 87) Race: White: 32 (80.0%) **Part 2** Sex: 78 (73.6%) M 28 (26.4%) F Age (years): Mean (SD): 65.2 (9.1) Range (min, max): (34, 88) Race: White: 80 (75.5%)	**Part 1** The median (range) duration of treatment: IV dose cohorts: 191.0 (18, 1606) days SC dose cohort: 85.0 (15, 419) days **Part 2** The median (range) duration of treatment: NSCLC cohort: 133.0 (11, 851) days UC cohort: 117.0 (21, 841) days	**Study Initiation Date:** 10-Feb-2016 **Study Completion Date:** 19-Nov-2020 **Study Status:** Completed
Phase 1b/2						
B8011007 38 centres: China, Japan, Taiwan, Republic of Korea, Ukraine, and Russian Federation Penkov et al. Ther Adv Med Oncol. 2024	A Phase 1b/2, OL Study to Evaluate PK, Safety, Efficacy, and PD of Sasanlimab (PD-1 inhibitor) in Patients with Advanced Malignancies. • Phase 1b/2, OL; Phase 1b (dose escalation and expansion) and Phase 2. • Phase 1b: To assess DLT rate of sasanlimab • Phase 2: To compare sasanlimab exposure of 600 mg SC Q6W to 300 mg SC Q4W in terms of area under the concentration-time curve during the dosing interval (τ) (AUC_{τ}) and C_{trough} at steady state	**Phase 1b (Dose Escalation and Dose Expansion)** 2 pre-specified SC dose levels (300 mg Q4W and 600 mg Q6W) of sasanlimab monotherapy in adult Asian patients with advanced solid tumours. **Global Phase 2** Patients with NSCLC were randomized between 2 pre-specified SC dose levels (300 mg Q4W or 600 mg Q6W) of sasanlimab monotherapy to characterize the PK profile.	**Total (Phase 1b and Phase 2)** Enrolled: 155 **Phase 1b Dose Escalation** Enrolled and treated: 300 mg SC Q4W: 4 600 mg SC Q6W: 6 Completed study follow-up phase: 300 mg SC Q4W: 3 600 mg SC Q6W: 4 **Phase 1b Dose Expansion** Enrolled and treated: 300 mg SC Q4W: 12 600 mg SC Q6W: 12 Completed study follow-up phase: 300 mg SC Q4W: 8 600 mg SC Q6W: 2 **Phase 2** Randomized and treated: 300 mg SC Q4W: 41	**Total (Phase 1b and Phase 2)** Sex: 116 (74.8%) M 39 (25.2%) F Age (years): Mean (SD): 62.6 (11.33) Median (range): 63.00 (30, 89) Race: White: 96 (61.9%) Asian: 59 (38.1%)	**Phase 1b (Dose Escalation)** Median (range) duration of treatment: 300 mg SC Q4W: 17.0 (4.0, 35.7) weeks 600 mg SC Q6W: 12.3 (12.0, 71.0) weeks **Phase 1b (Dose Expansion)** Median (range) duration of treatment: 300 mg SC Q4W: 16.0 (4.0, 82.1) weeks 600 mg SC Q6W: 36.4 (12.0, 48.0) weeks **Phase 2** Median (range) duration of treatment: 300 mg SC Q4W: 24.3 (4.0, 115.0) weeks 600 mg SC Q6W: 31.4	**Study Initiation Date:** 18-Mar-2020 **Primary Completion Date:** 03-Mar-2022 **Data Cutoff Date:** 07-Sep-2022 **Study Status:** Ongoing

			600 mg SC Q6W: 80 Completed study follow-up phase: 300 mg SC Q4W: 9 600 mg SC Q6W: 22		(6.0, 106.0) weeks	
Phase 3						
B8011006 (CREST) 149 centres: Australia, Belgium, Canada, China, France, Germany, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, UK, and US Shore et al. Nat Med. 2025	A Phase 3, Multinational, Randomized, OL, 3 Parallel-Arm Study of Sasanlimab, an Anti-PD-1 antibody, in Combination with BCG (IND With or Without MNT) Versus BCG (IND and MNT) in Patients With HR, BCG-Naïve NMIBC or Sasanlimab as a Single Agent in Patients With BCG-Unresponsive NMIBC **Cohort A (BCG-naïve):** Phase 3, OL, 3 parallel-arm study. Primary Objective: To demonstrate that Sasanlimab + BCG (IND+MNT) is superior to BCG (IND+MNT) in prolonging EFS in patients with HR NMIBC. Key Secondary Objectives: - To demonstrate that Sasanlimab + BCG (IND) is superior to BCG (IND+MNT) EFS in patients with HR NMIBC. - Overall survival in all arms **Cohort B (BCG-unresponsive):** Cohort B1 CIS positive, Cohort B2 Ta/T1 disease only. Cohort B study objective no longer required.	**Cohort A** (Cycle=4 weeks) Arm A: Sasanlimab SC 300 mg Day 1 every cycle up to 25 cycles - BCG IND period: 1 intravesical dose QW for 6 consecutive weeks - BCG MNT: D1, D8, D15 during Cycles 4, 7, 13, 19, 25 Arm B: Sasanlimab SC 300 mg Day 1 every cycle up to 25 cycles - BCG IND period: 1 dose QW for 6 consecutive weeks Arm C: BCG IND period: 1 dose QW for 6 consecutive weeks - BCG MNT: D1, D8, D15 during Cycles 4, 7, 13, 19, 25 In all arms of the study, following IND period, patients with CIS at randomization who have persistent disease and patients with recurrence of high-grade Ta disease may receive re-induction with up to 6 additional weekly doses of BCG. **Cohort B1** (Cycle=4 weeks) Sasanlimab SC 300 mg Day 1 every cycle **Cohort B2** (Cycle=6 weeks) Sasanlimab SC 600 mg Day 1 every cycle	**Cohort A** Randomized (N=1055): Arm A: 352 Arm B: 352 Arm C: 351 Treated: Arm A: 350 Arm B: 348 Arm C: 349 Completed study treatment: Arm A: 121 Arm B: 160 Arm C: 203 **Cohorts B1 and B2** (enrolment discontinued by the Sponsor [31 August 2022]) Enrolled: 14 Cohort B1: 6 Cohort B2: 8 Treated: Cohort B1: 5 Cohort B2: 8	**Cohort A (Full Analysis Set)** Sex: 863 (81.8%) M 192 (18.2%) F Age (years): Mean (SD): 66.5 (10.17) Median (range): 67.00 (31, 91) Race: White: 646 (61.2%) Asian: 374 (35.5%)	**Cohort A** Median (range) for overall duration of exposure to study treatment: Arm A: 99.9 (4.0, 12.5,1) weeks Arm B: 84.8 (4.0, 104.4) weeks Arm C: 98.9 (2.0, 110.0) weeks	**Study Initiation Date:** 30-Dec-2019 **Primary Completion Date:** 02-Dec-2024 **Study Status:** Ongoing
Patient Preference Study						
B8011013 NIS No centres. US only.	Patient Preferences in NMIBC: A Discrete Choice Experiment The overall objective of this study was to quantify patient preferences for attribute levels relating to investigational PD-(L)1 regimens used in combination with BCG as alternatives to SOC (BCG alone) to treat patients with HR NMIBC. Attributes of interest in	**Phase 1** Patients with HR NMIBC to participate in a qualitative interview. **Phase 2** Patients with HR NMIBC to participate in the	**Phase 1** Enrolled: 12 Completed Phase 1: 12 **Phase 2** Enrolled: 150 Completed Phase 2: 150	**Phase 1** Sex: 7 (58.3%) M 5 (41.7%) F Age (years): Mean: 64.8 Median (range): 64 (54-78)	NA	**Study Initiation Date:** 17 Oct 2022 **Study Completion Date:** 12 Jun 2024 **Study Status:** Completed

	this study included efficacy/progression outcomes, safety outcomes, and process/administration-related characteristics.	quantitative online survey.		Race: White: 12 **Phase 2** Sex: 76 (50.7%) M 72 (18.0%) F Age (years): Mean: 62.6 Median (range): 63 (49-74) Race: White: 69 Black/African American: 41		

Abbreviations: AUCτ = area under the concentration-time curve during the dosing interval (τ); BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; CSR = clinical study report; Ctrough = concentration at trough; D# = Day #; DLT = dose-limiting toxicity; EFS = event-free survival; F = Female; HR = high-risk; IND = induction; IV = intravenous(ly); M = Male; MNT = maintenance; MTD = maximum tolerated dose; NA = not applicable; NIS = non-interventional study; NMIBC = non-muscle invasive bladder cancer; No. = Number; NSCLC = non-small cell lung cancer; OL = open-label; PCD = primary completion date; PD = pharmacodynamics; PD-1 = programmed cell death protein – 1; PD-L1 = programmed cell death ligand – 1; PK = pharmacokinetics; Q#W = every # week(s); SC = subcutaneous(ly); SCCHN = squamous cell carcinoma of head and neck; SOC = standard of care; T1 = stage of cancer in which the cancer cells are only growing in the most superficial layer of tissues and have not grown into deeper tissues. In bladder cancer, T1 is defined as an invasion into the lamina propria without invasion into the muscularis propria; Ta = stage of bladder cancer defined as a non-invasive papillary carcinoma; UC = urothelial cancer; UK = United Kingdom; US = United States.
Note: Data from the 5 patients with BCG-unresponsive, HR NMIBC with CIS from Study B8011006 Cohort B1 are included in the safety analyses only; no additional data from Cohort B1 are included in the submission.

5.2. Clinical pharmacology

Sasanlimab is a humanised monoclonal antibody indicated in combination with Bacillus Calmette-Guerin (BCG), for the treatment of adult patients with BCG-naïve, high-risk, non-muscle invasive bladder cancer (NMIBC).

Zumrad is formulated as 300 mg solution for injection in pre-filled syringe. The recommended dose is 300 mg every 4 weeks administered as subcutaneous injection.

The pharmacokinetics of sasanlimab was investigated in a phase 1 study, a phase 1b/2 study and an ongoing phase 3 study. In addition, the Applicant has undertaken a population PK analysis, using data from these three studies.

5.2.1. Methods

5.2.1.1. Pharmacokinetics

An electrochemiluminescence (ECL) immunoassay, was developed to quantitatively measure concentrations of sasanlimab in human serum. The PK method was fully validated according to current standards at QPS (Newark, USA) with the analytical range of 48.0 ng/mL to 1250 ng/mL (minimal required dilution (MRD) was 1:10). The same PK method with the same analytical range of 48.0 ng/mL to 1250 ng/mL was transferred to UPP (Beijing, China) to support clinical sample analysis in China after cross-validation. This method was used in all three clinical studies: B8011001, B8011006 and B8011007.

Validation experiments investigated verification of assay range, inter- and intra-assay accuracy and precision, selectivity (matrix effect), specificity, stability, dilutional linearity, parallelism, incurred sample re-analysis and robustness (e.g. incubation time, equipment and analyst) for all labs and showed adequate performance and met the criteria of the relevant guidance.

Accuracy and precision in the study reports was largely similar compared to values reported in the method validation report.

In general, storage periods of PK samples at the clinical sites and bioanalytical labs was covered by the long term stability sufficiently: samples were stable between -20ºC (364 days) and -70ºC (3183 days). All samples were stored at -70ºC analysed within this time period (maximum of 1066 days in study B8011001; 934 days in study B8011006 and 587 days in study B8011007).

ISR results were sufficient with ≤20% deviation for ≥80% of reanalysed samples in all studies.

5.2.1.2. Biomarkers

PD-1 receptor occupancy CD8+ effector and effector memory cells in whole blood

In study B8011001 immune cell phenotypes and PD-1 receptor occupancy (RO) on T-cell subsets was evaluated in whole blood by flow cytometry in Part 1 only. PD-1 RO by sasanlimab was determined by the reduction of free (unbound) receptor on the surface of CD8+ effector cells (CD3+, CD4-, CD8+, CD45RA+, CCR7-, CD279+) and CD8+ effector memory cells (CD3+, CD4-, CD8+, CD45RA-, CCR7-, CD279+) presented in pre- and postdose whole blood samples by flow cytometry.

PD-L1 expression in tumor tissue

In study B8011007 PD-L1 status was considered high if ⩾25% of tumor cells exhibit membrane staining; low if the criteria for PD-L1 high status was not met. Baseline PD-L1 protein expression level was assayed by IHC at central laboratory using Ventana SP263 antibody. In study B8011006 PD-L1 expression was evaluated in pretreatment tumor tissue as follows: PD-L1 expression (high or low), as detected by a pathologist, assisted by image analysis. PD-L1 expression was defined as the number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and immune cells in regions of interest that are defined by tumor cell morphology.

5.2.1.3. Immunogenicity

Collected human ADA samples were analyzed using validated ADA assays based on a tiered approach, where samples were analyzed in a screening ADA assay, positive screened samples were subsequently evaluated in a confirmatory ADA assay, and the confirmed ADA positive samples were then titered. Only confirmed ADA positive samples were then assessed for NAbs using a validated NAb assay.

Detection of anti-sasanlimab (anti-PF-06801591) antibodies in human serum: A quasi-quantitative bridging ECL method with acid dissociation was developed and fully validated (method 15-1543) by QPS.

Detection of neutralizing anti-sasanlimab (anti-PF-06801591) antibodies in human serum: NAbs against sasanlimab were detected in human serum using a fully validated cell-based assay at QPS (Newark USA).

These methods were used in all three studies.

5.2.1.4. Statistical analysis

All PK parameters were calculated using conventional non-compartmental methods using actual times of sampling. The PK parameters were summarized descriptively by dose level and cycle in every study.

In study B8011007 for AUCtau and Ctrough at steady-state, estimates of the adjusted mean differences (sasanlimab 600mg SC Q6W (test) – sasanlimab 300mg SC Q4W (reference)) and the corresponding 90% CIs were obtained. The adjusted mean differences and the 90% CIs for the

differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and the 90% CIs for the ratios.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Pharmacokinetics of sasanlimab were investigated in all three studies, in patients with advanced / metastatic solid tumors, non-small cell lung carcinoma (NSCLC) and non–muscle invasive bladder cancer (NMIBC). No clinical studies with sasanlimab have been conducted in healthy volunteers. Sasanlimab has been administered as monotherapy in two completed studies (B8011001 and B8011007). In the ongoing study B8011006 sasanlimab was administered as monotherapy (cohort B) or in combination with BCG (cohort A).

Conventional non-compartmental data analysis was used for all pharmacokinetic studies with intense sampling (B8011001 and B8011007). Descriptive statistics were used to summarize the Ctrough concentrations in study B8011006. Population PK was used to identify potential covariates which may impact the exposure to sasanlimab and to provide post-hoc predictions for use in exposure-response analyses. (Section 6.2.2.2. Evaluation and qualification of models).

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

Sasanlimab PK were characterized by a 2-compartment model with sequential zero/first-order absorption and allometric scaling of baseline body weight on CL and Vc. The absorption model describes an absorption process for SC administration where sasanlimab enters the absorption compartment through a zero-order process and then is absorbed into Vc through a first-order process. Estimated parameters were CL, Vc, Q, Vp, and first-order absorption rate constant (ka) with bioavailability (F) estimated from IV data. The allometry exponents on CL and Vc were estimated. The covariates included in the model were albumin, alkaline phosphatase, serum creatinine and tumor type, all on CL.

The studies B8011001, B8011007 and B8011006 were included in the pop PK analyses. The pop PK population contained 5360 observations from 1007 cancer patients, among whom 706 with NMIBC. None of the observations were below the limit of quantification. A total of 12 samples were deemed to be outliers and removed.

5.2.2.3. Absorption

The absorption of sasanlimab has been characterized by 2 PK studies: B8011001 (after IV dosing and after SC dosing) and B8011007 (after SC dosing).

Study B8011001 was a phase 1 multiple-dose escalation study to assess MTD in a dose escalation Part 1 (4 IV dosing regimens ranging from 0.5 mg/kg to 10 mg/kg Q3W (up to 229 weeks) and a 300 mg SC Q4W dosing regimen (up to 60 weeks)) followed by an expansion Part 2 (300 mg SC Q4W, up to 122 weeks) in previously treated participants with locally advanced or metastatic solid tumor types that have clinical evidence of response to anti PD-1 or PD-L1 agents.

Study B011007 was a phase 1b/2 study to evaluate 2 SC dose levels of sasanlimab (300 mg Q4W and 600 mg Q6W) in Asian participants with advanced solid tumors (Phase 1b, treatment up to week 82) and global participants with NSCLC in the 1L or 2L treatment setting (Phase 2, treatment up to week 115).

After IV dosing Tmax ranged from 1-3 hours (both after the first dose and at cycle 4). After SC dosing Tmax varied from 51 to 670 hours with a median of 166 hours at steady-state.

Cmax increased dose proportional in the escalating dose study from 0.5 – 10 mg/kg IV sasanlimab dosing. In study B8011007 two different dose regimens of SC sasanlimab dosing were investigated (600mg SC Q6W and 300mg SC Q4W), at steady-state Cmax increased approximately dose proportionally: geometric mean (600mg Q6W:300mg Q4W) ratios (90% CIs) of 183.52% (151.92%, 221.68%).

5.2.2.3.1. Bioavailability

In study B8011001 sasanlimab was administered IV and SC, absolute bioavailability was not reported. The estimated bioavailability in the pop PK analysis was 0.6967.

5.2.2.3.2. Influence of food

Food can affect the pharmacokinetics and bioavailability of orally administered drugs. This application concerns a SC injection of sasanlimab, and therefore studies to assess the effect of food on sasanlimab absorption are not relevant.

5.2.2.4. Bioequivalence

Two different sasanlimab drug product presentations have been used during clinical development: the 100 mg/2 mL vial presentation, used for IV and SC dosing in Study B8011001, and the 300 mg/2 mL PFS, used for SC dosing in Studies B8011006 and B8011007. The 300 mg/2 mL PFS is being proposed as the commercial drug product.

Comparison of PK parameters between Study B8011001 and Study B8011007 indicate similar serum sasanlimab exposures from the 2 product presentations (PFS vs vial). Additionally, drug product presentation was not a significant covariate in the popPK analysis or in the exposure-response safety analysis.

5.2.2.5. Distribution

In the pop PK analysis, geometric mean Vss was estimated to be 6.34 L.

In the non-compartmental analysis Vss was only reported for one subject on 1mg/kg IV dose at cycle 4 and was reported to be 6.85 L (study B8011001), for study B8011007 Vss/F was not reported.

5.2.2.6. Metabolism

Similar to other therapeutic proteins with molecular weights above the glomerular filtration cut-off, sasanlimab is expected to be metabolized primarily by catabolic degradation following endocytosis by the mononuclear phagocytic system.

5.2.2.7. Elimination

In study B8011007 the mean terminal half-life was reported to be 31.27 days for the 300mg SC Q4W regimen (n= 56) and 27.25 days for the 600mg SC Q6W regimen (n=98).

Clearance was reported as PK parameter in the non-compartmental PK analysis of studies B8011001 for a few subjects after IV dosing in study B8011001 and ranged from 0.12 – 0.192 L/day. In study B8011007 CL/F was not reported.

In the pop PK analysis, estimated mean half-life was 29 days. Estimated clearance was 0.142 L/day.

5.2.2.8. Dose proportionality and time dependency

5.2.2.8.1. Dose proportionality

In Study B8011001, following both 1st (Cycle 1) and 4th (Cycle 4, steady state) doses, serum sasanlimab exposures (AUC and Cmax) increased in an approximately dose proportional manner across the evaluated 0.5 to 10 mg/kg IV dose range, with approximately 2-fold accumulation at steady state. See Table 2.

Table 2: Descriptive Summary of Serum Sasanlimab PK Parameters by Dose Level, PK Parameter Set (Protocol B8011001, Part 1)

Parameter, unit[a,b]	0.5 mg/kg (IV) (N=2)	1 mg/kg (IV) (N=8)	3 mg/kg (IV) (N=8)	10 mg/kg (IV) (N=7)	300 mg (SC) (N=15)
Cycle 1					
N2, N4	2, 2	8, 6	7, 6	7, 5	15, 14
C_{avg} (µg/mL)	5.56, 5.88[b]	9.742 (36)	29.40 (28)	105.9 (27)	15.95 (48)
C_{max} (µg/mL)	11.8, 12.0[b]	21.52 (23)	69.63 (28)	217.2 (36)	21.24 (50)
C_{max} (dn) (µg/mL/mg/kg[c])	23.6, 23.8[b]	21.45 (23)	23.29 (28)	21.71 (36)	- (-)
T_{max} (hr)	1.07, 1.70[b]	2.00 (1.08-27.7)	1.17 (1.00-1.25)	1.20 (1.02-2.17)	194 (51.3-673)
AUC_{tau} (µg•hr/mL)	2800, 2970[b]	4907 (36)	14810 (28)	53430 (27)	10720 (48)
AUC_{tau} (dn) (µg•hr/mL/mg/kg[c])	5610, 5880[b]	4901 (36)	4956 (29)	5341 (27)	35.75 (48)
Cycle 4					
N2, N4, N5	2, 2, 2	3, 2, 2	6, 3, 2	5, 4, 4	7, 3, 3
C_{avg} (µg/mL)	9.18, 9.27[b]	15.5, 15.5[b]	65.24 (39)	263.2 (30)	49.91 (26)
C_{max} (µg/mL)	15.5, 10.5[b]	30.10 (16)	86.34 (52)	402.6 (42)	56.48 (29)
C_{max} (dn) (µg/mL/mg/kg[c])	31.2, 20.8[b]	30.10 (16)	29.48 (53)	40.26 (42)	0.1884 (29)
C_{min} (µg/mL)	6.10, 3.45[b]	9.91, 7.95[b]	36.47 (51)	138.0 (42)	25.47 (49)
T_{max} (hr)	1.03, 3.00[b]	2.00 (1.08-2.00)	1.15 (1.00-1.20)	1.17 (1.08-2.15)	166 (164-168)
AUC_{tau} (µg•hr/mL)	4620, 4670[b]	7810, 7790[b]	32850 (39)	132700 (30)	33540 (26)
AUC_{tau} (dn) (µg•hr/mL/mg/kg[c])	9320, 9260[b]	7810, 7790[b]	11480 (32)	13220 (30)	111.6 (25)
R_{ac}	1.66, 1.58[b]	1.23, 1.76[b]	2.09, 2.61[b]	2.360 (12)	2.073 (31)

Source: B8011001 CSR Table 19 and Appendix 2 Table A6.
N = total number of participants in the treatment group in the indicated population; N2 = Number of participants contributing to the summary statistics for C_{max}, C_{max} (dn) and T_{max}; N4 = Number of participants contributing to the summary statistics for AUC_{tau}, AUC_{tau} (dn), C_{avg}, and C_{min} (Cycle 4); N5 = Number of participants contributing to the summary statistics for R_{ac} (Cycle 4).
a. Geometric mean (geometric % coefficient of variation) for all parameters except median (range) for T_{max}.
b. Individual values are listed when there are less than 3 evaluable measurements.
c. In the 300 mg SC treatment group, units for dose-normalized parameters are µg/mL/mg and µg•hr/mL/mg for C_{max} (dn) and AUC_{tau} (dn), respectively.
Participants in IV groups were dosed every 3 weeks. Participants in SC group were dosed every 4 weeks.
'0' values are excluded from calculating the geometric mean and geometric %CV.
Cutoff Date: 19 Nov 2020, Snapshot Date: 23 Dec 2020

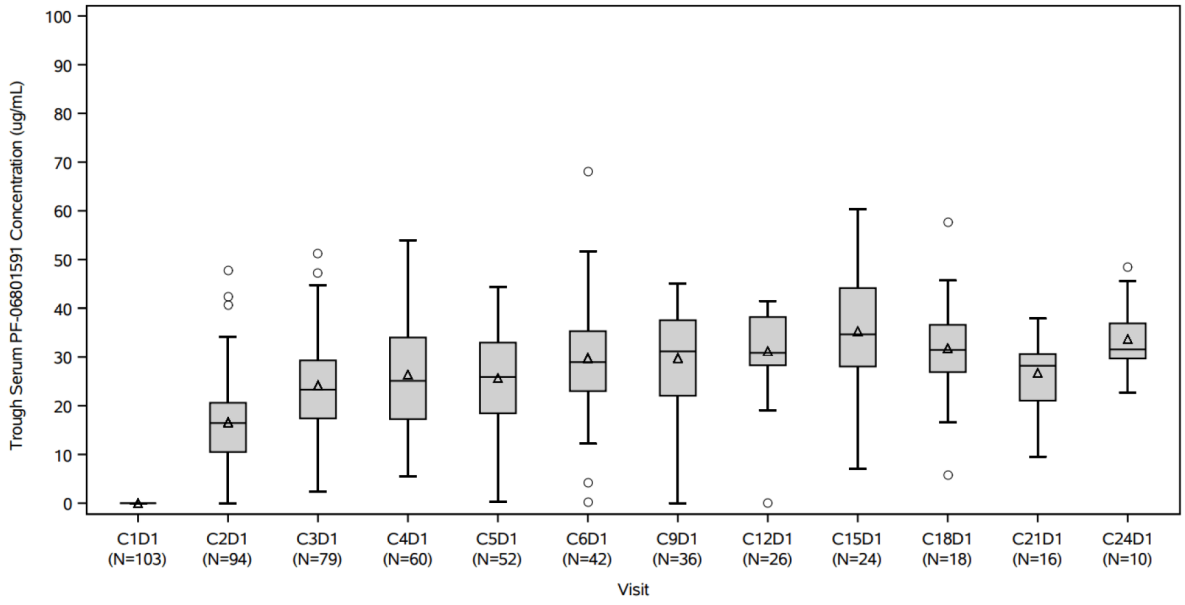
In study B8011007, increasing the dose from 300 mg Q4W SC to 600 mg Q6W SC increased the average (Cavg) and maximum (Cmax) serum sasanlimab steady-state exposure parameters in an approximately dose proportional manner, with the adjusted geometric mean (600mg Q6W:300mg Q4W) ratios (90% CIs) of 154.16% (126.74%, 187.51%) and 183.52% (151.92%, 221.68%), respectively. Ctrough however, remained similar (111.48% [86.31%, 143.99%]).

5.2.2.8.2. Time dependency

Consistent with the estimated thalf, the mean accumulation factor for sasanlimab based on AUC was approximately 2 on Cycle 4 following 300 mg Q4W SC dosing (in both studies: B8011001 and B8011007). Lesser accumulation of sasanlimab was observed on Cycle 3 following 600 mg Q6W SC dosing with a Rac of AUCtau of 1.498. This difference in accumulation between the treatments is expected due to the differences in dosing intervals.

In Figure 1 Ctrough concentrations over time from study B8011006 are shown, indicating that steady-state is reached at approximately cycle 4.

Figure 1: Box and Whisker Plot of Individual Serum Sasanlimab Ctrough Concentrations Following 300 mg SC Q4W Administration, Study B8011001, Part 2, Combined



Symbol in the box interior = Mean.
Box plots provide median and 25% and 75% quartiles with whiskers to the last point within 1.5 times the interquartile range.
Symbols outside the box = measurements outside 1.5 times the interquartile range.

5.2.2.9. Pharmacokinetics in the target population

All studies with PK data were performed in patients with cancer. The Phase 1 monotherapy study (B8011001) was conducted in adult participants with locally advanced or metastatic solid tumor types with clinical evidence of response to anti-PD-1 or anti-PD-L1 agents, who were unresponsive to currently available therapies or for whom no standard therapy was available. In Part 1 40 participants with solid tumors were included. In part 2 106 participants with anti-PD-1 or anti-PD-L1 treatment-naïve NSCLC or UC were included.

In study B8011007 Asian participants with advanced solid tumors (phase 1b) and global participants with the first line and the second line NSCLC were included.

In study B8011006 participants with BCG-naïve, high-risk, NMBIC were included.

The two studies with full PK curve sampling were performed in patients with several different tumors, but not in the target population with NMIBC. In study B8011006 (in patients with NMIBC) only Ctrough sasanlimab concentrations were collected. Variability in Cycle 4 Ctrough across the 3 studies (n = 592) was moderate at 43%. The GM of pooled Cycle 4 Ctrough in Study B8011006 – target population - (30.55 µg/mL) was within 30% of the steady-state Ctrough of the pooled monotherapy studies (24.05 µg/mL). See Table 3.

Table 3: Single-Dose and Steady-State Pharmacokinetic Parameters of SC Administered Sasanlimab

	Study B8011001	Study B8011007	Study B8011006
Parameter, unit	300mg SC Q4W (N=15)	300mg SC Q4W (N=56)	300mg SC Q4W (N=578)
Visit: Cycle 1 / Day 1			
AUCtau, µg*h/mL	10720 (48)	12400 (47)	N-R
Cavg, µg/mL	15.95 (48)	N-R	N-R
Cmax, µg/mL	21.24 (50)	26.39 (41)	N-R
Tmax, h	194 (51.3-673)	168 (142-670)	N-R
Visit: Cycle 4 / week 12			
AUCtau, µg*h/mL	33540 (26)	23480 (57)	N-R
Cavg, µg/mL	49.91 (26)	34.93 (57)	N-R
Cmax, µg/mL	56.48 (29)	47.94 (57)	N-R
Tmax, h	166 (164-168)	166 (95.5-338)	N-R
Ctrough, µg/mL	25.85 (65)	24.48 (58)	30.55 (39)
Thalf. Eff (day)	N-R	31.27 (37)	N-R
Rac	2.073 (31)	2.120 (30)	N-R

Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax.

N = Total number of participants in the treatment group in the indicated population.

N-R=Not reported

In the pop PK analyses, tumor type was a significant covariate on the clearance of sasanlimab.

5.2.2.10. Special populations

No dedicated studies were performed in special populations. Pop PK analysis was used to assess the PK in special populations. In the forest plot below, the influence of tumor type, serum creatinine, body

weight, alkaline phosphatase and albumin on C_{avg} is shown. The reference is the median value for each simulated exposure metric across all participants.

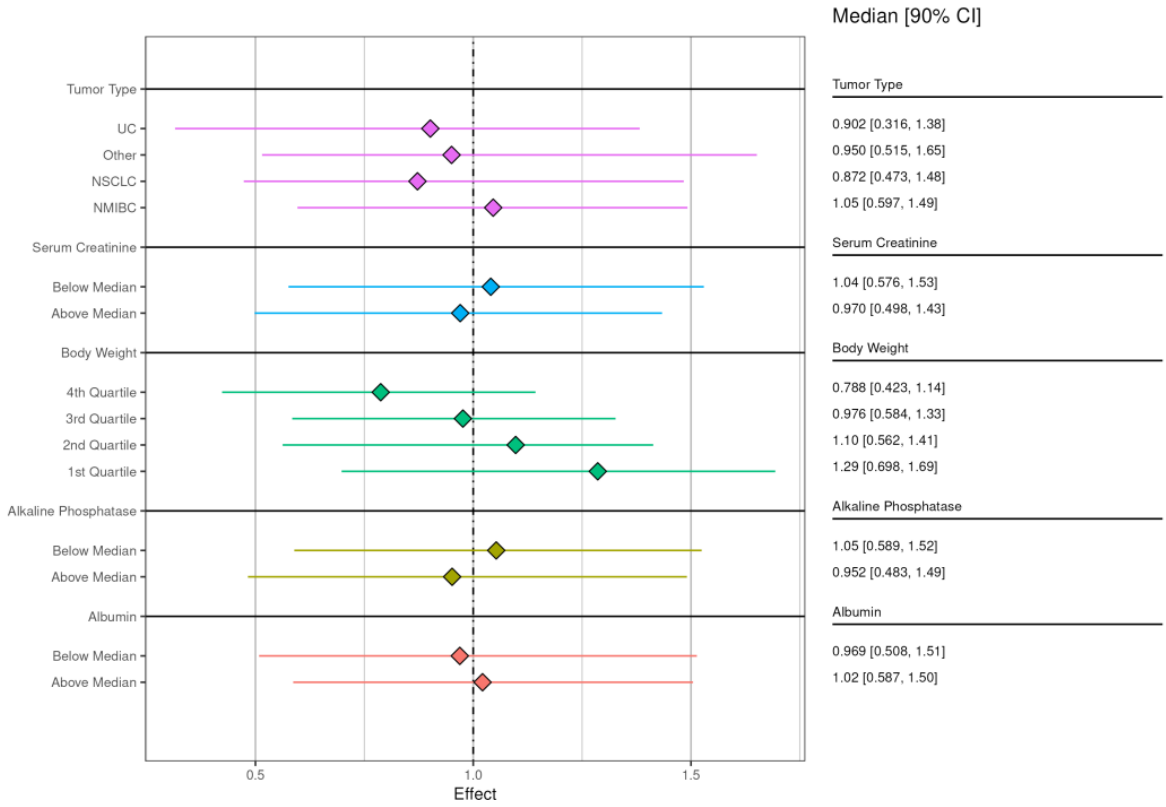


Figure 2: Forest plot for average sasanlimab concentration at steady state

Population PK analysis indicated no significant effect of mild or moderate renal impairment (based on serum creatinine) on sasanlimab clearance (see Figure 3). Sasanlimab clearance in participants with mild renal impairment (CLcr by Cockcroft-Gault formula: 60 to 89 mL/min, N = 420) and with moderate renal impairment (CLcr 30 to 59 mL/min, N = 180) was similar to that in participants with normal renal function (CLcr ⩾90 mL/min, N = 397). There were insufficient data regarding severe renal impairment (N = 3).

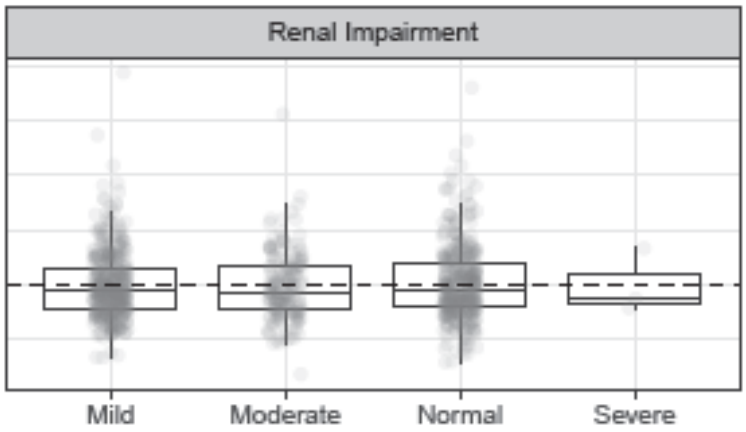


Figure 3: ETA (CL) Versus Categorical Covariate Renal Impairment

Population PK analysis indicated no significant effect of mild hepatic impairment (based on NCI ODWG classification) on sasanlimab clearance. There were insufficient data on moderate hepatic impairment

and no data on severe hepatic impairment.

Gender and ethnicity had no significant effect on the PK of sasanlimab, after correcting for body weight.

In the lowest body weight quartile, estimated Cavg was 29% higher compared to the median and in the highest body weight quartile it was 21% lower (investigated body weight range 38 – 173 kg). Simulation of flat dosing compared to body weight-based dosing showed comparable average concentrations for flat dose and weight-based dose in the two mid-quartiles of body weight, but higher C_{avg} at flat dose compared to weight-based dose in the lowest quartile of body weight, and a lower C_{avg} at the flat dose in the highest quartile.

Studied age range was 26-90 years. Population PK analysis showed that age had no significant effect on the PK of sasanlimab.

Zumrad is not indicated in paediatric patients. A product-specific waiver (EMA decision P/0290/2020 on 12 August 2020) was granted for studies in paediatric patients.

Limited data after SC administration in the thigh indicate that trough concentrations are comparable to those after administration in the abdomen.

Tumor type had not a clinically significant effect on Cavg.

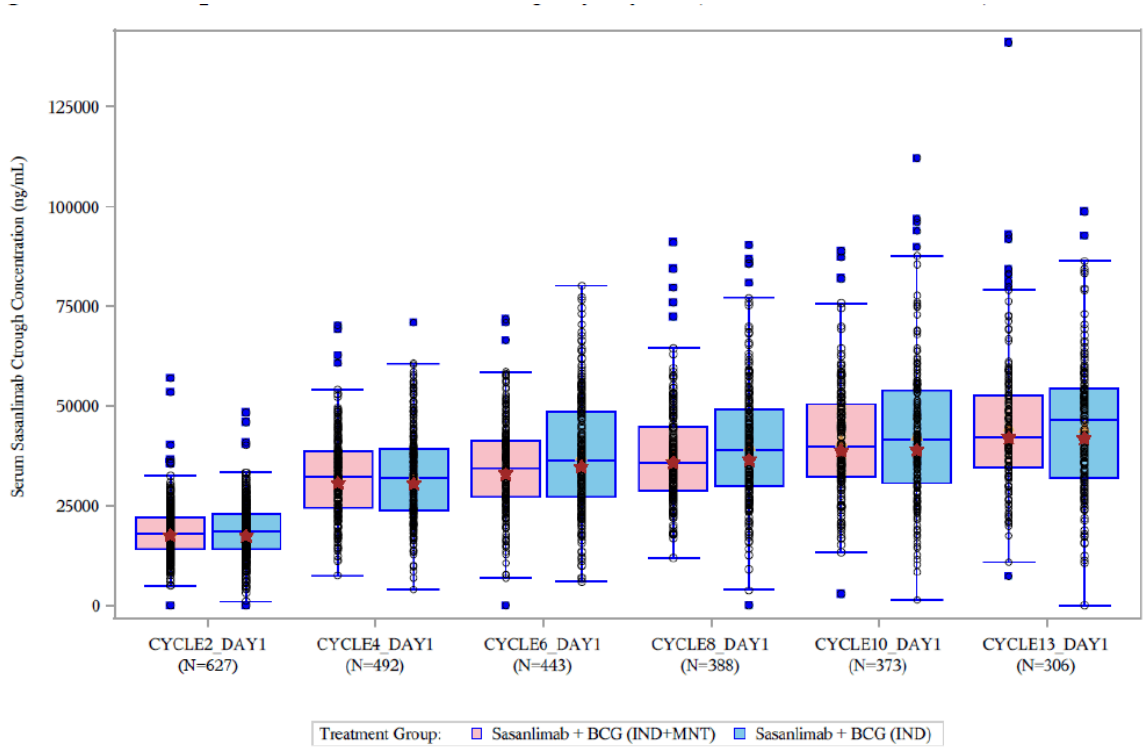
5.2.2.11. Pharmacokinetic interaction studies

No formal DDI studies have been conducted with sasanlimab. Since the elimination of mAbs does not occur through non-catabolic pathways via hepatic metabolic enzymes (ie, CYP enzymes) or via small molecule renal/hepatic drug transporters, direct PK interactions with concomitant medications that are eliminated via these pathways are unlikely.

Therapeutic proteins which are cytokines or have cytokine modulatory properties may have the potential to differentially affect CYP activities, however this interaction generally leads to less than 2-fold changes in the exposure of a co-administered small molecule drug. In non-clinical studies, sasanlimab did not elicit release of cytokines (IFN-, TNF-α, IL-2). Sasanlimab is not considered a cytokine modulator, so it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction.

In Study B8011006 Cohort A, there were no differences in sasanlimab PK between the sasanlimab + BCG (IND+MNT) arm and the sasanlimab + BCG (IND) arm. After cycle 4 the participants in the BCG (IND) arm did not receive BCG anymore. See Figure 4.

Figure 4: Box-plot of Sasanlimab Ctrough by Cycle (Treatment Overlaid) study B8011006



N in the bracket is the number of observations included in the analysis.
Geometric mean analysis on the log scale, '0' values are not included in geometric mean calculation.
Symbol triangle in the box interior = Arithmetic Mean. Symbol star in the box interior = Geometric Mean.
Box plots provide median and 25% and 75% quartiles with whiskers to the last point within 1.5 times the interquartile range.
Symbols outside the box = measurements outside 1.5 times the interquartile range.
PFIZER CONFIDENTIAL SDTM Creation: 10JAN2025 (13:39) Source Data: adpc Table Generation: 14JAN2025 (10:51)
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024) Output File: ./b8011006/B8011006_CSR1/adpp_f101

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Sasanlimab is a humanized hinge region-stabilized IgG4, monoclonal antibody specific for human programmed cell death protein-1 (PD-1) that blocks the interaction between PD-1 and PD-L1/PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.

Increased PD-L1 expression was observed in bladder cancer cells in response to BCG treatment both *in vitro* and *in vivo* preclinical models and the combination of BCG and anti-PD-L1 agent induced an antitumour immune response (Wang et al. Onco Targets Ther. 2018). Moreover anti-PD-1/PD-L1 agents have demonstrated clinical activity in the treatment of advanced UC or BCG-unresponsive CIS (Balar et al. Lancet Oncol. 2021; Bellmunt et al. Cancer Treat Rev. 2017).

5.2.3.2. Primary and secondary pharmacology

See also section 4.3.1. Pharmacodynamics in the non-clinical part of this Overview.

Primary pharmacology

PD-1 Receptor Occupancy – Biomarker

In Study B8011001 whole blood samples for analysis of PD-1 (also known as CD279) receptor occupancy (RO) by sasanlimab were collected in Part 1 of the study at pre dose/Day 1 of Cycles 1, 2, 3, 4 and 5 and at EOT. Additional post-dose samples were collected in Cycle 1 at 24 hours and 168 hours, and in Cycles 1 and 4 at 336 hours and 480 hours (SC dosing only). PD-1 RO by sasanlimab was measured by the reduction of free receptor on the surface of CD8+ effector cells (CD3+, CD4-, CD8+, CD45RA+, CCR7-, CD279+) and CD8+ effector memory cells (CD3+, CD4-, CD8+, CD45RA-, CCR7-, CD279+) presented in pre- and post-dose whole blood samples by flow cytometry.

The mean absolute free receptor rate on the surface of CD8+ effector cells CD3+, CD4-, CD8+, CD45RA+, CCR7-, CD279+ at baseline was 38.5% (SD 19.9, n=39), and the mean free receptor rate on the surface of and CD8+ effector memory cells CD3+, CD4-, CD8+, CD45RA-, CCR7-, CD279+ at baseline was 58.5% (SD 17.4, n=39). These values were similar for both the reanalysis and the original analysis method, i.e., with and without patient-specific gating, respectively (leading to an increased level of variability).

High levels of PD-1 RO (median RO >95%, free receptor <5%) were maintained through the entire dosing interval of each IV and SC dosing regimen, including the lowest, 0.5 mg/kg IV Q3W dosing regimen. This complete or near complete RO was already in effect at the 1st post-dose assessment in Cycle 1 (24 hours) following dosing of every IV and the SC dosing regimens evaluated in this study.

Secondary pharmacology

Effect on QTc Interval

In general, monoclonal antibodies are not expected to have clinically meaningful effect on the QT interval (Jackson et al. Int J Clin Pharmacol Ther. 2015). Given this historical absence of clinically significant QT prolongation for any of the agents in this class of checkpoint inhibitors, coupled with the absence of QT prolongation safety signal across any of the studies in the sasanlimab program, no formal concentration-QTc modelling analysis has been performed to evaluate QT prolongation potential of sasanlimab. Summaries of QT and QTc prolongation (QTcF and/or QTcB, as appropriate) across the three clinical studies (Table 1) were, however, provided in the individual study CSRs (data not shown).

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

No formal drug-drug interaction (DDI) studies have been conducted with sasanlimab.

In Study B8011006, there were no differences in sasanlimab PK between the sasanlimab + BCG (IND+MNT) arm and the sasanlimab + BCG (IND) arm. Additionally, the absence of apparent differences in sasanlimab exposure between the two arms even after patients were no longer receiving BCG in Arm B (sasanlimab + BCG [IND]) indicates that concomitant intravesical administration of BCG does not impact sasanlimab PK (see Figure 4).

5.2.3.4. Genetic differences in PD response

No information could be located in the application dossier.

5.2.3.5. Immunological events

In all three clinical studies immunogenicity (ADA against sasanlimab) was assessed. Overall

development of treatment-induced ADA was low: <10% with <5% NAb+.

In Study B8011001, following IV Q3W dosing, 2/21 (9.5%) patients developed treatment-induced ADA: 1 in the 0.5 mg/kg dose group and 1 in the 1 mg/kg dose group. None of the ADA in the IV-dosed patients were NAb+. Across the 300 mg SC Q4W-dosed patients in Parts 1 and 2 of the study, 9/115 (7.8%) developed treatment-induced ADA, with median (range) time of onset on Day 112 (29 – 329), and with 4 responses (3.5%) being NAb+, three at a single time point, one subject from cycle 6 to 12, and negative again at cycle 15 and 18 (titer 1.06-1.48). In total there were three patients who were positive for ADA at baseline without exhibiting boosted ADA response (3/136 patients).

In Study B8011007, the overall incidence of treatment-emergent ADAs across both study parts and both dose levels was low (7/142 or 4.9% overall; 4/52 [7.7%] following 300 mg SC Q4W and 3/90 [3.3%] following 600 mg SC Q6W), with all 7 patients having treatment-induced responses. There were 4 patients who were ADA positive at baseline (4/142 or 2.8%) not exhibiting boosted ADA response. Within the limited number of Asian (Japan and China) patients, no ADA responses were observed in the Phase 1B Dose Escalation and Expansion arms. Three patients had transient and 4 intermediate ADA durations of response, with median (range) time of onset on Day 30 (27 – 371). None of the ADA+ responses at either dose level were NAb+ (0%).

In Study B8011006, of the 688 ADA-evaluable patients across both sasanlimab combination arms of Cohort A, 38 had ADA against sasanlimab, with an overall low incidence of 5.5%. The majority of ADA were treatment induced (37 out of the 38 ADA positive patients) and only 1 patient was treatment boosted (1/688 [0.1%]). There were 11 patients who were positive for ADA at baseline with most (n = 10) not exhibiting boosted ADA response. Of the 37 patients with treatment-induced ADA responses, 12 (31.6%) were transient, 18 (47.4%) were indeterminate, and 8 (21.1%) were persistent. Median time to first ADA detection was 196 days (range: 25 – 434). The ADA incidence for both sasanlimab arms was 5.5% (19/345 in the sasanlimab + BCG [IND+MNT] arm and 19/343 in the sasanlimab + BCG [IND] arm). One (0.1%) of the ADA+ patients developed a NAb+ response, and it was of indeterminate duration (detected at a single time point; at pre-dose of C8D1, corresponding to day 196 onset). All analysed ADA samples from patients in Cohort B were ADA-negative; however, due to early termination, these immunogenicity data were considered immature and are not included in the summary or analysis.

In the overall pool of 855 ADA-evaluable patients treated with the proposed dose of 300 mg SC Q4W, the ADA incidence was 6.0% (51/855) and the NAb incidence was 0.6% (5/855). The median time to onset of ADA and NAb response was 140 days (range: 25 – 434) for ADA and 85 days (range: 29 – 196) for NAb.

Impact of Immunogenicity on PK, Efficacy and Safety

To assess the potential impact of the presence of ADA on CL of sasanlimab, inter-occasion variance on CL was added to the base popPK model to allow for a different CL estimate before and after ADA positivity. Graphical examination shows no impact of ADA on the CL of sasanlimab. There is substantial overlap of CL estimates before and after ADA positivity for those patients who became ADA positive and when following the patient-level CL estimates before and after ADA positivity, there is no consistent trend in increasing or decreasing estimates. Therefore, given the similarity in CL before and after ADA positivity, there is no anticipated impact of ADA on the PK of sasanlimab.

Given the low immunogenicity incidence, the evaluation of its potential impact on PK, efficacy and safety of sasanlimab is limited. Furthermore, as the overall incidence of ADA response (6.0%) was below the ≥10% pre-specified minimum criterion in popPK and exposure-response modelling analysis plans, formal evaluation of its statistical significance as a covariate impacting PK, efficacy and safety

was limited. Analyses of ADA status using the popPK and exposure-response safety and efficacy models demonstrated no clear association between the emergence of ADA to sasanlimab and its PK, safety, or efficacy.

According to the Applicant, sasanlimab is a humanized IgG4 hinge-stabilized (S228P mutation in hinge) anti-human PD-1 mAb and has shown similar binding affinity to human PD-1 to those observed for pembrolizumab (Keytruda) and nivolumab (Opdivo), both of which are also hinge-stabilized (S228P) human IgG4 PD-1 checkpoint inhibitors with low reported incidences of ADA and NAb and no apparent impact of immunogenicity on PK, safety or efficacy profiles of either agent (Keytruda SmPC; Opdivo SmPC).

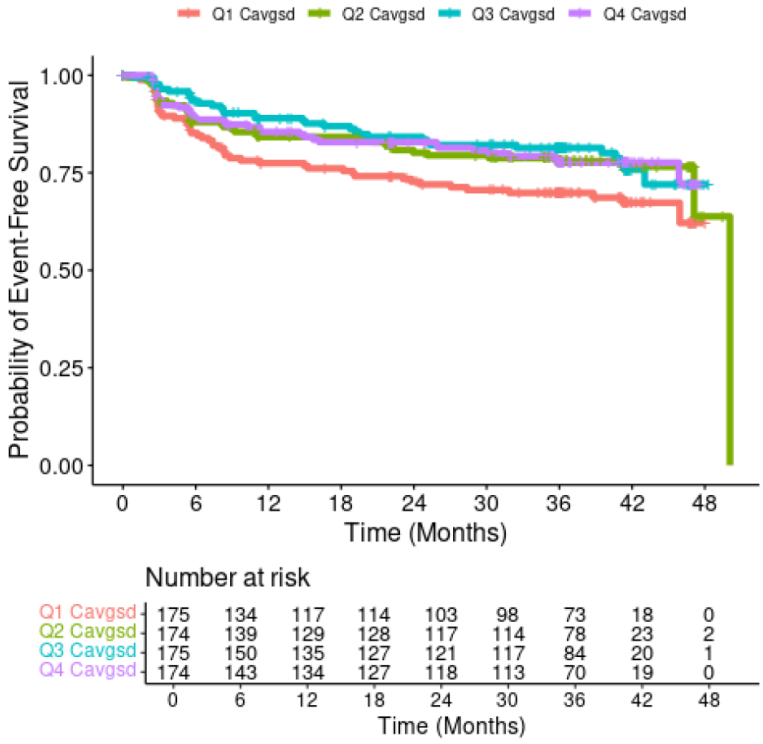
5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure-response analyses for efficacy

The relationships between sasanlimab exposure (estimated Ctrough and Cavg after single dose, derived from the pop PK analysis) and EFS and CR were analysed using data from study B8011006. For the analysis of EFS, data from all patients were used while the analysis of CR was limited to only those patients who had CIS at randomization. EFS was analysed using time-to-event analysis and CR was analysed using a binomial logistic regression modelling approach.

For the analysis of EFS, there were 158 events in 698 total patients (Arm A = 61 events and Arm B = 97 events), with median EFS not reached. Sasanlimab was not a significant covariate (see Figure 5). Significant covariates for EFS were: treatment arm (receipt of BCG maintenance being beneficial to EFS), age (older age being detrimental) and body weight (higher weight being detrimental).

Figure 5: EFS for patients in study B8011006 by sasanlimab exposure quartile (Cavg)



Repository artifact ID FI-60241812.
Kaplan-Meier Curve With Risk Table.
EFS = event-free survival; Q1 = first quartile (median=15.2 µg/mL); Q2 = second quartile (median=19.9 µg/mL); Q3 = third quartile (median=23.7 µg/mL); Q4 = fourth quartile (median=28.6 µg/mL); Cavgsd = average concentration after single dose;

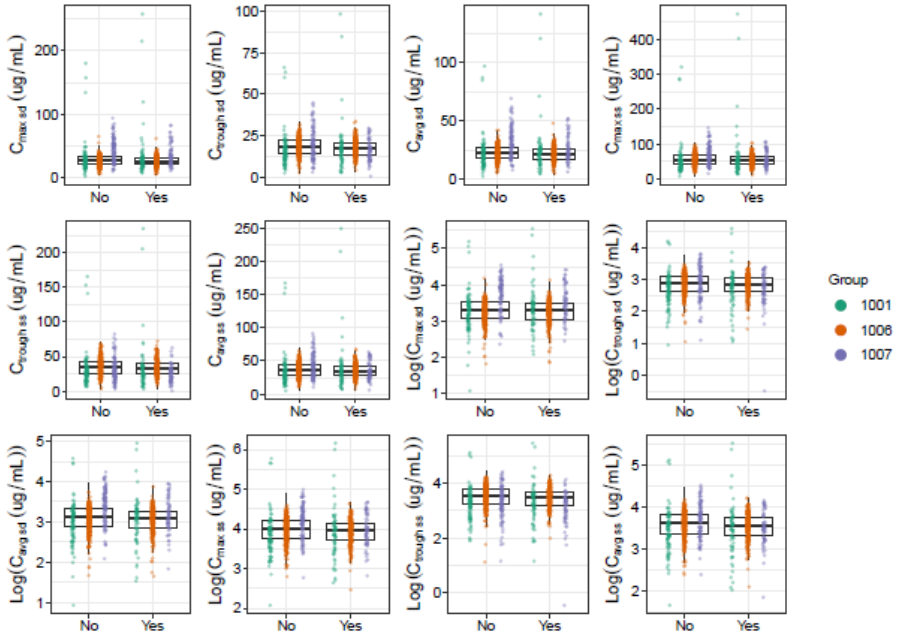
For the analysis of CR in patients with CIS at randomization (179 total patients), the rate of complete response was high (nearly 90%); the CR rate achieved at any time was 90.8% in Arm A (79 out of 87 patients) and 89.1% in Arm B (82 out of 92 patients). Sasanlimab exposure was not a significant covariate. There were no other significant covariates.

Exposure-response analyses for safety

The relationships between sasanlimab exposure (estimated Cmax, Ctrough and Cavg after single dose and at steady state and the logarithm of these values) and the safety parameters were analysed using data from studies B8011001, B8011006 and B011007. Investigated safety parameters were TEAEs Grade ≥2, TEAEs Grade ≥3, immune-related AEs any Grade and immune-related AEs Grade ≥3. Binomial logistic regression was used to describe the exposure-response relationships.

The exposure metrics were not significant covariates for any of the safety endpoints. See for example the relationships with TEAEs Grade ≥3 in Figure 6. Baseline albumin, log of baseline body weight, log of baseline creatinine clearance, log of baseline serum creatinine, log of baseline AST and BCG combination were significant covariates for TEAEs Grade ≥2 (852 events). Treatment duration was the significant covariate for TEAEs Grade ≥3 (437 events). Race Asian and combination with BCG were significant covariates for immune-related adverse events any grade (550 events). Treatment duration and combination with BCG were significant covariates for immune-related adverse events Grade ≥3 (153 events).

Figure 6: Treatment-Emergent Adverse Events Grade 3 or Higher Versus Exposure Metrics



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5.2.5. Dose selection

See section 5.3.1. Dose response study(ies).

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical methods

In general the bioanalytical method validations for sasanlimab serum concentrations and immunogenicity were acceptable and in line with current requirements/guidelines.

Both PK and ADA/NAb assays were fully validated with documented accuracy, precision, sensitivity, dilution linearity, selectivity, and stability. Cross-validation between QPS and UPP met 100% concordance. Use of tiered immunogenicity strategy (screening → confirmatory → titer → NAb) aligns with regulatory requirements. Sample collection and stability management also complies with the corresponding guidelines. Bioanalytical approach is considered acceptable. However, the updated ADA method introduced consolidated cut points (e.g., screening factor 1.09, confirmatory inhibition 8.1%) applicable only to studies starting after Dec 2024, raising concerns about data consistency across study periods (**Co-Rapp OC**). Screening sensitivity improved from 8.4 ng/mL (MRD 1:99) to 0.553 ng/mL, potentially affecting comparability of ADA incidence and titers. Clarification and justification are requested (**Co-Rapp OC**).

Biomarker PD-1 receptor occupancy

The choice for these specific circulating T cell subsets should be substantiated by the Applicant. Are these CD8+ effector memory (EM) and terminally differentiated effector memory CD45+ (TEMRA) cells in whole blood a valid marker for the local anti-tumor effect in the bladder? Do these cells exhibit

the highest PD-1 expression and are they relevant and/or indicative for the anti-carcinogenic effect (**Rapp OC**)?

The Applicant should show or discuss that the presence of sasanlimab does not interfere with the flow cytometry method assessing total PD-1 expression on the T cell population in blood and PD-1 receptor occupancy on the specific CD8+ EM and TEMRA subsets (**Rapp OC**).

The reason for not reporting all biomarkers as indicated the clinical trial protocol should be substantiated. Especially the biomarker evaluation on tumor biopsies (during/after treatment) could be an important biomarker because this is the site of action of the anti-tumor response of sasanlimab (**Rapp OC**).

Population PK analysis

Parameters were in general estimated with acceptable precision. Goodness of fit plots showed an acceptable fit. VPCs over the first 112 days showed an acceptable fit. At later timepoints, some underprediction of the median concentration after IV administration and at SC administration every 6 weeks was observed, which may be related to fewer samples being available at these later timepoints. However this may also be due to a change in the target mediated drug deposition at later time points. A prediction-corrected VPC is stated to have been made, but was not presented in the study report. This should be provided (**Rapp OC**). Shrinkage was acceptable for ω^2CL and ω^2V2 (10 – 29%). Overall, the pop PK model appears fit for purpose, to conclude that the investigated covariates had a low impact on the PK of sasanlimab in cancer patients.

ADME

Apparently, the PK observations, even in the studies with richer PK sampling, were mostly too limited to calculate PK parameters using NCA and limited data on NCA derived PK parameters are presented (CL, Vd, t1/2, CL/F) both from first dose and at steady state. The Applicant should provide reasons for missing samples and reasons for blood sampling not handled/analysed according to protocol, especially with regard to study B8011001 and B8011007 (**Co-Rapp OC**).

Bioavailability

Although in study B8011001 sasanlimab was administered IV and SC, absolute bioavailability was not reported, manual assessment of bioavailability at steady-state was approximately 0.68, which was in line with the estimated bioavailability in the pop PK analysis (0.6967). The observed median Tmax at steady state after sasanlimab subcutaneous administration in study B8011001 is reported as 166 hours. In the SmPC, this number is stated with a range (51 to 673 hours) that originates from Cycle 1 data in the same study. The range is considered of low relevance due to the sampling schedule and the Applicant could consider to only include the median value (**Co-Rapp SmPC comment**).

Distribution

The estimated Vss (6.34 L) is close to plasma volume suggesting that only a limited amount of sasanlimab is distributed extravascular and mainly restricted to the interstitial space, which is consistent with the known limited distribution characteristics of IgG mAbs. The central and peripheral volume estimated in the popPK analysis are 3.67 L and 2.19 L, respectively. The central volume of distribution increases with body weight. PK sampling appears to have been too sparse to generate Vd or Vz based on the observed data and no such values are reported.

Metabolism

The statement by the Applicant that sasanlimab is expected to be metabolized primarily by catabolic degradation following endocytosis by the mononuclear phagocytic system, is reflected in the reported

half-life of 29 days, which is in accordance with the turnover time of IgG4. No additional studies are needed to confirm this.

Elimination

In the pop PK analysis, estimated mean half-life was 29 days. Estimated clearance was 0.142 L/day. Both were in line with the data from the non-compartmental analysis. No renal elimination is expected given the large molecular weight (~149 kDa), and no dedicated metabolism or elimination studies are considered necessary for mAbs.

Dose proportionality/time dependency

The Applicant claims that sasanlimab exposure (measured as AUCtau and Cmax in study B8011001 and study B8011007) increased in an approximately dose proportional manner both for the IV (0.5 to 10 mg/kg) dosing regimen and for the SC (300 mg Q4W and 600 mg Q6W) dosing regimen. However, in study B8011001, this was based on comparison of exposures normalised to dose per body weight across dose levels which is not considered the most appropriate approach. The Applicant should provide analysis of dose proportionality/linearity based on Cycle 1 and 4 data from study B8011001 by using a power model (**Co-Rapp OC**). This analysis should be based on absolute doses, and not weight-adjusted doses. Notably, dose proportionality has been analysed after IV administration, whereas the sought route of administration is SC, which might not show the same pattern. Week 12 exposures following SC administration in phase 2 of study B8011007 were analysed using an ANOVA model with treatment (300 mg Q4W or 600 mg Q6W) as fixed effects and participant as random effect. The ratio of the adjusted geometric means for sasanlimab AUCtau and Cmax was 231.20% and 183.52% indicating that exposures increased in an approximately dose proportional manner following 600 mg Q6W compared to 300 mg Q4W.

Time-dependency was assessed by Pop-PK modelling. The Applicant rightly comments that time-dependent CL is seen for several other immuno-oncology agents, but that the available data did not support incorporating time-varying CL in the Pop-PK model. However, as an example, in study B8011006 Ctrough values are available up until C13D1, and an increase in mean Ctrough values of 39 and 36% is seen from C4D1 to C13D1 for Arm A and Arm B respectively (assessors' calculation, based on Table 14.4.4.1in B8011006 Interim Full Study Report). It is thus not possible to completely rule out time-dependency. However, there is considerable interindividual variability, and no clear indication of a large increase in exposure with time that would warrant dose adjustments. Further, safety data is available from the proposed dose regimen which was used in study B8011006. To verify that there is no evidence of change of CL over time, the applicant should provide details on how time dependency was evaluated in the popPK model (**Co-Rapp OC**).

Special populations

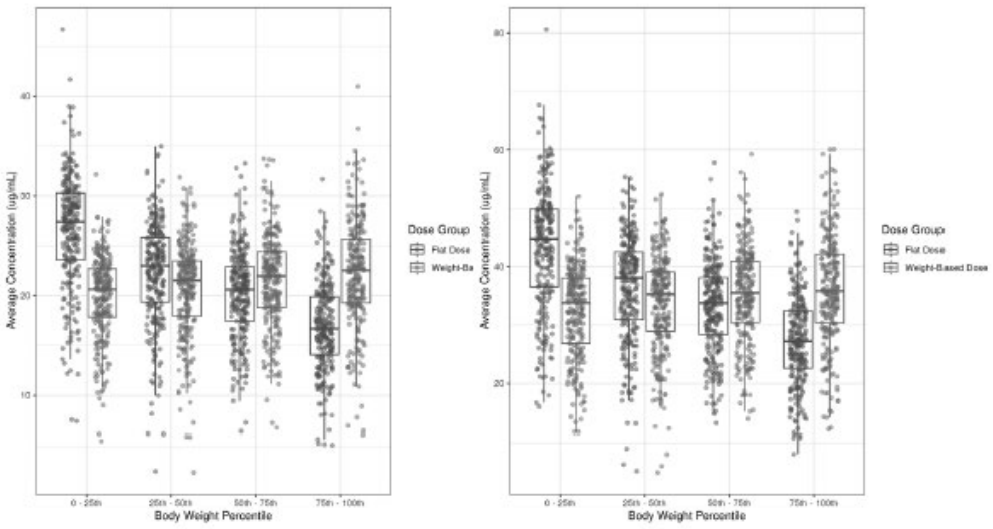
The Applicant has submitted Forest plots showing the impact of the covariates included in the final model on exposure. The Forest plots have not been created using standard methodology as it presents the distributions of individual post-hoc parameters across covariates rather than model-predicted covariate effects on exposure. This is less informative and could under-predict covariate effects because the post-hoc parameters distributions will be affected by parameter shrinkage. To support the evaluation of the effect of significant covariates included in in the final popPK model on the sasanlimab exposure, the Applicant should provide an updated Forest plot (**Co-Rapp OC**).

Body weight

The role played by the weight is of particular importance in this MAA considering the proposed flat dosing regimen. In general, the appropriateness of a flat dose depends on the magnitude of impact of body weight on the PK, and hence whether a flat dose will decrease rather than increase the

interindividual variability in exposure compared to a weight-based dose. The effect of body weight on sasanlimab PK was evaluated by the popPK analysis. The range of body weights investigated (38.2 – 173 kg) appears sufficient for this purpose. Simulations have been conducted based on the final popPK model, comparing Cavg across body weight quartiles following weight-based dosing (4 mg/kg) or flat dosing (300 mg Q4W). Post-hoc parameter estimates and BWTs of participants included in the final model from the popPK analysis were utilized for the simulations. Simulation of flat dosing compared to body weight-based dosing showed comparable average concentrations for flat dose and weight-based dose in the two mid-quartiles of body weight, but higher C_{avg} at flat dose compared to weight-based dose in the lowest quartile of body weight, and a lower C_{avg} at the flat dose in the highest quartile (see Figure 7). The clinical relevance of this should be discussed (**Rapp OC**). To support the rationale for a flat dose, the Applicant is requested to provide a comparison of simulated (with a virtual population including the full range of relevant body weights) sasanlimab PK following a weight-based dose of 4 mg/kg Q3W and the proposed flat dose off 300 mg Q3W at a population level and for body weight stratified sub-groups (**Co-Rapp OC**).

Figure 7: Single dose (a) and steady-state (b) average concentration comparison for weight-based and flat dose



(a) FI-52335198 (b) FI-52335199

Repository artifact IDs are shown in subfigure labels.
Body weight percentiles are calculated based on the observed patient population.

Race and ethnicity were evaluated as covariates in the popPK model but no statistically significant effect on PK was detected. It should however be noted that the vast majority of subject in the study were either of white or Asian race, and a very limited number of black/African American participants were included in the popPK data set.

Age

Age had no significant effect on the PK of sasanlimab after correcting for body weight. There were sufficient subjects in the dataset older than 65 years (568 out of 1007), but the numbers of subjects with age 65-74 years, 75-84 years and 85+ years were not given and should be provided (**Rapp/Co-Rapp OC**).

Gender

Of the 1007 participants included in the three clinical studies, 787 (78.2 %) were male and 220 (21.8

%) were female. Gender was not identified as a significant covariate in the popPK analysis.

Hepatic/renal impairment

As sasanimab is a large protein, elimination is not expected to be affected by renal or hepatic impairment. Based on popPK analysis, sasanlimab clearance is not affected by mild or moderate renal impairment nor by mild hepatic impairment. Very limited or no data are available for patients with severe renal impairment or end stage renal disease. Similarly, very limited or no data are available in patients with moderate or severe hepatic impairment.

Site of SC administration

Sasanlimab is intended for SC administration into the abdominal area (preferred injection site) with the thigh being listed as the alternative injection site. No bioavailability study has been run to compare PK following SC injection at the two sites. It is stated that <1% of patients receiving SC dosing received injecting in the thigh and the total number of individual administrations in the thigh was 47 in study B8011001 and 42 in study B8011006. A plot (Figure 7, 2.7.2 Summary of clinical pharmacology studies) is provided to argue that the Ctrough at steady state did not vary based on site of injection. The thigh group in this plot contains only seven data points and no statistics are provided, which makes the comparison difficult to evaluate. The Applicant refers to a paper that describes that administration dependent PK normally does not apply to the type of IgG that sasanlimab belongs to (Zou et al. 2021).

To better characterise the population of patients that received sasanlimab through administration in the thigh, the Applicant should provide additional information regarding the number of administrations in the thigh and any additional PK data available from these patients (**Co-Rapp OC**). If limited data is available in patients receiving administration through the thigh, this should be reflected in section 4.2 in the SmPC (**Co-Rapp SmPC comment**).

Pharmacokinetic interaction studies

As monoclonal antibodies are primarily cleared via catabolism by proteolytic enzymes and in vitro studies have confirmed the absence of induction of cytokine release with sasanlimab, drug-drug interaction studies were not conducted and are not planned. This approach is consistent with the risk-based recommendations in the EMA guideline titled "Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins" (CHMP/EWP/89249/2004, 2007). Furthermore, sasanlimab is proposed to be administered with intravesical BCG. Absence of a drug-drug interaction was confirmed in study B8011006 (Ctrough levels were similar between the study arms, one with and one without BCG co-administration). It is agreed that no DDI studies with sasanlimab are considered necessary.

Corticosteroids and immunosuppressive drugs may reduce the efficacy of PD-1 inhibitors. In line with previously approved PD-(L)1 inhibitors, the following statement should be included in section 4.5 of the SmPC: "The use of systemic corticosteroids or immunosuppressants before starting sasanlimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting sasanlimab (see section 4.4)" (**Co-Rapp SmPC comment**).

SmPC

The following SmPC text is agreed upon (paragraph 4.5):

Sasanlimab is primarily metabolised through catabolic pathways, therefore, it is not expected that sasanlimab will have pharmacokinetic drug-drug interactions with other medicinal products.

The following SmPC text in paragraph 5.2 is agreed upon regarding its contents, but a textual reformulation is proposed (see **SmPC comment**):

Sasanlimab was shown to exhibit dose-proportional PK across the 0.5 to 10 mg/kg IV Q3W dose range. The maximum, pre-dose, average and overall exposures (Cmax, Ctrough, Cavg, and AUC, respectively) following the 300 mg subcutaneous every 4 weeks dosing regimen fell within those observed following administration of 1 and 3 mg/kg IV every 3 weeks.

The following SmPC text is agreed upon (paragraph 5.2):

Sasanlimab steady-state concentrations are expected to be achieved by approximately 13 weeks of repeated dosing with an every 4-week subcutaneous regimen, with systemic accumulation ratio of ~ 2.1.

Absorption

The population PK estimated absolute bioavailability of sasanlimab following subcutaneous dosing was 70%. The observed median Tmax after sasanlimab subcutaneous administration was 166 hours (range: 51 to 673 hours).

Distribution

The steady-state volume of distribution for sasanlimab is 6.34 L, as estimated by population PK analysis.

Elimination

The terminal half-life of sasanlimab is 29 days, as estimated by population PK analysis. Sasanlimab exhibits low clearance (CV%) of 0.142 L/day (31%) with no evidence of change in clearance over time.

Regarding renal impairment, it is stated in section 4.2 of the SmPC that no dose adjustment is needed for patients with mild or moderate renal impairment and that limited data are available from patients with severe renal impairment. In section 5.2 it is explained that the effect of renal impairment was evaluated by pop PK analysis. This is agreed. However, recommendations should be added for patients with severe renal impairment in section 4.2 (**Rapp/Co-Rapp SmPC comment**).

Regarding hepatic impairment, it is stated in section 4.2 of the SmPC that no dose adjustment is needed for patients with mild hepatic impairment, that limited data are available from patients with moderate hepatic impairment and that no data are available from patients with severe hepatic impairment. In section 5.2 it is explained that the effect of hepatic impairment was evaluated by pop PK analysis. This is agreed. However, recommendations should be added for patients with moderate or severe hepatic impairment in section 4.2 (**Rapp/Co-Rapp SmPC comment**).

Pharmacodynamics

Primary pharmacology

Already at the 1st post-dose assessment in Cycle 1 (24 hours), the lowest dose in Study B8011001 resulted in an almost maximum effect. It is, therefore, not possible to assess a minimal target sasanlimab dose/concentration for effect based on receptor occupancy. This will, however, not be pursued.

Secondary pharmacology

No formal concentration-QTc modelling analysis has been performed to evaluate QT prolongation potential of sasanlimab. It is agreed that monoclonal antibodies have a low likelihood of direct ion

channel interactions and a thorough QT/QTc study is, therefore, not considered necessary.

No pharmacodynamic DDI studies have been conducted with sasanlimab. This is in line with the other approved PD-1 blocking mAbs and acceptable.

No information on genetic differences in PD response could be located in the dossier. This is acceptable, as no such differences are expected.

Immunogenicity

The incidence of ADA in patients treated with sasanlimab was <10%. The analysis of CL (based on popPK) and Ctrough values of ADA+ versus ADA- patients over time suggest that ADA has minimal to no effect on exposures to sasanlimab. However, it is difficult to draw conclusions due to the small number of ADA positive patients.

Exposure-response relationships

No clear association between sasanlimab exposure and EFS or between sasanlimab exposure and CR was found. The E-R analysis is hampered with uncertainties, thus limiting the interpretation. The PK measurements are based on sparse sampling, providing only Ctrough values, which could limit the reliability of the model-estimated individual PK parameters. In addition, all patients in study B8011006 received the same starting dose, resulting in less span in exposure, which is a weakness for the E-R analysis. Furthermore, median EFS was not reached, thus the ER relationship for this endpoint should be interpreted with caution. To provide some more information regarding E-R for efficacy, the Applicant should submit E-R analyses for efficacy from study B8011007, although is it acknowledged that this study is based on patients with a different tumour diagnosis (**Co-Rapp OC**). No statistically significant relationship was observed between sasanlimab exposure (measured as Cmax sd, Cmax ss, and Ctrough ss) and the incidence of Grade ⩾3 TEAEs, Grade ⩾2 TEAEs, Grade ⩾ 3 irAEs or any Grade irAEs in the final model.

Dose selection

See section 5.3.10.1. 'Discussion' on clinical efficacy.

5.2.6.2. Conclusions

The pharmacokinetics of sasanlimab have overall been adequately investigated. However, before approval a number of other concerns should be addressed by the Applicant regarding the bioanalytical methods, the population PK analysis and special populations, in particular the appropriateness of a flat dose.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

Sasanlimab Selection of Dose

Pharmacokinetic and receptor occupancy considerations

The sasanlimab non-clinical C_{eff} range, estimated based on *in vivo* receptor occupancy (RO) data in cynomolgus monkeys and *in vitro* mixed lymphocyte reaction assay results, was determined to be 0.1210 µg/mL, which saturated the responses in all 3 *in vitro* markers (T-cell proliferation, IFN-g, and TNF secretion) and resulted in >90% RO in CD4+ and CD8+ cells at 21 days post dose. Based on

these data and the utilization of PK/PD modelling, a dose of 1 mg/kg Q3W was projected to be the clinical IV dose that would provide sasanlimab serum concentrations above the nonclinical C_{eff} range. See the Rapp D80 Non-clinical AR, also for discussion on these data/results and conclusions.

PD-1 RO by sasanlimab, measured in Part 1 (dose escalation) of Study B8011001 by the reduction of free receptor on the surface of CD8+ effector cells and CD8+ effector memory cells, demonstrated similarly high levels of PD-1 RO (>95%) after sasanlimab treatment at all dose levels and methods of administration (0.5 – 10 mg/kg IV Q3W and 300 mg SC Q4W). This complete or near complete RO was already in effect at the 1st post-dose assessment in Cycle 1 (24 hours) following dosing of every IV and the SC dosing regimens evaluated in this study (see also section 5.2.3.2. Primary and secondary pharmacology' and/or Figure 3C and D in Johnson et al. JAMA Oncol. 2019). Sasanlimab PK were linear over the 0.5 – 10 mg/kg IV dosing regimen, with exposure parameters following the fixed 300 mg SC Q4W dosing regimen falling between those from the 1 mg/kg IV Q3W dosing regimen (the projected nonclinical C_{eff} range) and the 3 mg/kg IV Q3W dosing regimen (see also section 5.2.2.8. 'Dose proportionality and time dependency'). The steady-state exposures from the 300 mg SC Q4W sasanlimab dosing regimen were comparable to those from therapeutic dose levels of pembrolizumab and nivolumab, both also S228P hinge-stabilized human IgG4 PD-1 checkpoint inhibitors (Keytruda; Opdivo).

Safety considerations

No DLTs were reported in any of the four evaluated dosing regimens in Part 1 of Study B8011001 and the 300 mg SC Q4W dosing regimen was generally well-tolerated (data not shown). In addition, a higher sasanlimab dose of 600 mg Q6W has been administered to 80 patients in Phase 2 portion of Study B8011007. The overall safety profile was consistent between the 300 mg SC Q4W and 600 mg SC Q6W group with no increased incidence of any Grade TEAEs and Grade ≥3 AEs or immune-related AEs observed at the higher dose level tested (data not shown). Thus, while the MTD was not formally reached, sasanlimab was considered tolerable at the 300 mg SC Q4W dose.

Exposure-Response Relationship for Efficacy and Safety Endpoints

See also section 5.2.4. 'Pharmacokinetics/pharmacodynamics (PK/PD)'.

E-R Analyses for Sasanlimab Efficacy – Analyses were performed using data from the pivotal Phase 3 Study B8011006 (Cohort A - Arm A and Arm B) to explore the E-R relationship for investigator-assessed EFS, as well as complete response (CR; for patients with CIS at randomization).
There was no association between sasanlimab exposure and EFS (Figure 5). For the analysis of EFS, there were 158 events in 698 total patients, with median EFS not reached. Therefore, a thorough evaluation of an E-R relationship for this endpoint is limited. Of the evaluated hazard distributions, the Log-Normal distribution best fit the observed data.
The rate of CR was high (nearly 90%) in the 179 patients with CIS at time of randomization, therefore a thorough evaluation of an E-R relationship for this endpoint is limited considering the relatively low number of non-responders. Sasanlimab exposure ($C_{avg,sd}$) was retained, per analysis plan, in the final model but was not significant and displayed a slightly negative relationship (see figure 'Simulations of final model for CR (patients with CIS)' in the Rapp D80 Clinical AR). Therefore, there was no association between sasanlimab exposure and CR.

E-R Analyses for Sasanlimab Safety – Analyses were performed using data from Studies B8011001, B8011006, and B8011007 (Table 1) to explore the E-R relationship for TEAEs Grade ≥2, TEAEs Grade ≥3, irAEs any Grade and irAEs Grade ≥3. All analyses indicated no significant relationship with increasing sasanlimab exposure. The flat exposure-safety relationship indicates a similar probability of experiencing these events with the 300 mg SC Q4W dose vs lower doses evaluated in Study B8011001.

In conclusion, according to the Applicant the E-R analyses results for both efficacy and safety endpoints support the proposed sasanlimab posology of 300 mg SC Q4W for patients with BCG-naïve, HR NMIBC.

5.3.2. Main study

5.3.2.1. Study B8011006 (CREST)

5.3.2.1.1. Study title

Study title: A Phase 3, Multinational, Randomized, Open-Label, Three Parallel-Arm Study of Sasanlimab, an Anti-PD-1 Antibody, in Combination With Bacillus Calmette-Guérin (BCG Induction With or Without BCG Maintenance) Versus BCG (Induction and Maintenance) in Participants With High-Risk, BCG-Naïve Non-Muscle Invasive Bladder Cancer or Sasanlimab as a Single Agent in Participants With BCG-Unresponsive NMIBC.

Acronym: CREST: Combination of sasanlimab and alternative BCG Regimens to Evaluate outcomes with Subcutaneous anti-PD-1 Treatment.

5.3.2.1.2. Study design

In short, Study B8011006 (CREST; Shore et al. Nat Med. 2025) is a randomized, open-label Phase 3 study of sasanlimab (300 mg SC Q4W) in combination with intravesical BCG in patients with BCG-naïve, HR NMIBC (Cohort A) or sasanlimab as a single agent in patients with BCG-unresponsive NMIBC (Cohorts B1 and B2).
Due to a business strategy decision, however, enrolment to Cohorts B1 and B2 was closed/stopped early. Efficacy data from Cohorts B1 and B2 were not analysed and are, therefore, not included in this report.
For Cohort A, 'HR NMIBC' was defined as HG Ta and/or T1 papillary tumours and/or CIS. 'BCG-naïve' was defined as no prior treatment with BCG or prior BCG treatment >2 years from randomisation. Prior to randomisation, all patients had undergone transurethral resection of bladder tumour (TURBT) to remove all resectable papillary disease (Ta and T1). Residual CIS not amenable to complete resection was allowed. Randomisation was stratified by presence of CIS at randomisation (CIS vs no CIS) and geography (US vs Western Europe + Canada vs Rest of World). In Cohort A, patients were randomised (1:1:1) to one of the following treatment arms:

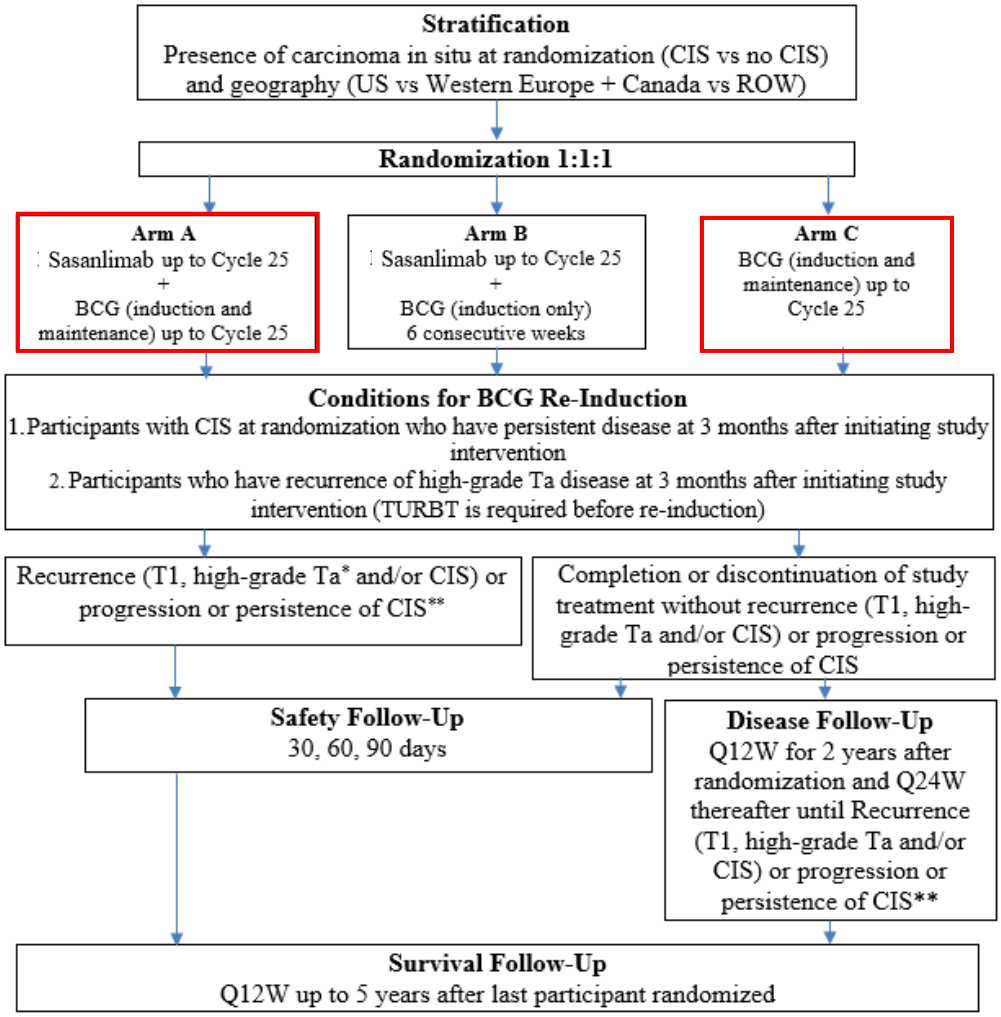
- Arm A: sasanlimab in combination with BCG induction and maintenance;
- Arm B (depicted in grey): sasanlimab in combination with BCG induction; or
- Arm C: BCG induction and maintenance.

The BCG induction period included 6 weekly doses of BCG. BCG re-induction was allowed for patients with CIS at randomisation who had persistent disease and patients who had recurrence of HG Ta disease after induction. Following the induction period, the BCG maintenance period included 5 cycles of 3 weekly doses of BCG at 3, 6, 12, 18, and 24 months. Treatment with sasanlimab continued until recurrence of HG disease, disease progression, persistence of CIS, unacceptable toxicity, or a maximum of 24 months.
Assessment of disease – by cytology and cystoscopy, followed by biopsy and imaging (CT/MRI) when needed – was performed at baseline and then every 12 weeks for 2 years from randomisation and then every 24 weeks thereafter.
The primary endpoint for Cohort A was investigator-assessed event-free survival (EFS) for the

comparison of Arm A vs Arm C. Key secondary endpoints were investigator-assessed EFS for Arm B vs Arm C, and overall survival (OS) for Arm A vs Arm C and Arm B vs Arm C.

See Figure 8 for a schematic representation of the study design.

Figure 8: CREST study schematic Cohort A – BCG-naïve patients



Note: The primary endpoint for Cohort A was investigator-assessed EFS for the comparison of Arm A vs Arm C (shown in red boxes).
Abbreviations: BCG: Bacillus Calmette-Guérin; CIS: carcinoma in situ, EFS: event-free survival; ROW: rest of world; US: United States.
* See below section 'Study assessments' for additional details.
** For patients with CIS at randomization.

Study population

Patients were enrolled across 149 centres in Europe, North America, Asia, and Australia (Table 1).

Key Inclusion Criteria

- Patients must be ≥18 years of age, at the time of signing the informed consent (except in Japan, where patients must be ≥20 years).
- Histological confirmed diagnosis of HR, non-muscle invasive transitional cell carcinoma (TCC) of the urothelium of the urinary bladder (tumours of mixed transitional/non-transitional cell histology are allowed, but TCC must be the predominant histology) defined as any of the following per WHO grading system.
    - T1 tumour

- HG Ta tumour
- CIS

- Complete resection of all Ta/T1 papillary disease (including patients with concurrent CIS), with most recent positive TURBT occurring within 12 weeks prior to randomization for patients. A second TURBT must have been performed if indicated according to the current locally applicable guidelines, e.g., EAU guidelines.
- Availability of the tumour tissue from the most recent TURBT for the assessment of the PD-L1 expression. If a second TURBT was performed, as indicated according to the current locally applicable guidelines, the tumour tissue from the TURBT procedure that supports the primary diagnosis for study eligibility should be the tumour tissue used for the PD-L1 expression testing.
- ECOG PS ≤2.
- Adequate bone marrow function (without hematopoietic growth factor or transfusion support within 14 days prior to study randomization for patients, including:
  - ANC ≥1,500/mm^3 or ≥1.5 x 10^9/L
  - Platelets ≥100,000/mm^3 or 100 x 10^9/L
  - Haemoglobin ≥9 g/dL (≥5.6 mmol/L)
- Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min according to the Cockcroft Gault formula or by 24-hour urine collection for creatinine clearance, or according to local institutional standard method.
- Adequate liver function, including:
  - Total serum bilirubin ≤1.5 × the ULN. Patients with Gilbert syndrome should have total serum bilirubin <3 x ULN;
  - Aspartate and alanine aminotransferase (AST and ALT) ≤2.5 × ULN.

Key Exclusion Criteria

- Evidence of muscle-invasive, locally advanced or metastatic UC or concurrent extravesical, non-muscle invasive TCC of the urothelium.
- Active or prior autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
- Intravesical BCG therapy within 2 years prior to randomization. Prior intravesical chemotherapy for NMIBC is allowed.
- Prior immunotherapy with anti PD-1, anti PD-L1, anti PD-L2, or anti cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
- Prior treatment with immunostimulatory agents including interleukin (IL)-2, IL-15, interferon (INF)-γ.
- Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

Randomisation and blinding

Patients were randomized 1:1:1 to one of the treatment arms, see Figure 8. Randomization was stratified by the presence of CIS (yes vs no) and geography (US vs Western Europe and Canada vs ROW).

CREST is an open-label study; however, the specific intervention to be taken by a patient was assigned centrally via interactive response technology (interactive voice/website response system).

According to the protocol – as this is an open-label study – the Applicant was allowed to conduct unblinded reviews of the data during the course of the study for the purpose of data cleaning at the patient level. According to the CSR, however, the study team remained fully blinded to aggregate/cumulative data summaries by treatment arm until the primary completion date (PCD).

Description of trial intervention

Sasanlimab Dosing

- Q4W 300 mg SC in a pre-filled syringe, up to Cycle 25 (a cycle is 4 weeks and is defined as the time from Day 1 dose to the next Day 1 dose).

BCG Dosing

- The intravesical dose for BCG was 1 therapeutic dose per the product label for the strain given (see below).
    - Induction period: one dose every week for 6 consecutive weeks (QWx6: Cycle [C]1Day [D]1, C1D8, C1D15, C1D22, C2D1, C2D8)
    - Re-induction period: Following first induction period, patients with CIS at randomization who have persistent disease and patients with recurrence of HG Ta disease may receive re-induction with one dose every week via intravesical instillation for up to 6 consecutive weeks. Suggested schedule was C4D1, C4D8, C4D15, C4D22, C5D1, C5D8. Maintenance began on C7D1. If TURBT was performed, the schedule for BCG re-induction was modified according to the product label.
    - Maintenance period: Doses on D1, D8, D15 during Cycles C4, C7, C13, C19 and C25. For patients that had a re-induction period, the maintenance period began at C7D1.

Several BCG strains are approved for treatment as SOC in the different countries where this study is conducted, e.g. TICE, RIVM, TOKYO172, IMURON-VAC (BCG-1), BCG China Strain (D2PB302). If BCG is sourced locally by the study site, the site should ensure that sufficient quantities of BCG are available to support the patient for the study treatment duration, prior to randomization. It is recommended that a patient receive the same strain of BCG for the duration of study treatment. In the event that there is a shortage of the BCG strain that a site typically uses, the investigator may be allowed to use a different BCG strain during re-induction or maintenance only, provided that it is permissible for use in these circumstances under the auspices of the relevant local authority.

On cycles when sasanlimab and BCG are both administered for Arms A and B of Cohort A, BCG will be administered first. SC injections to the abdomen are preferred.

Dose Modifications

For sasanlimab, no dose reductions were permitted, but the next dosing could be skipped for the cycle based on persisting toxicity. See Table 4 for the recommended treatment modifications for drug-related toxicity (excluding immune-related AEs). Algorithms for the clinical management of

immune-related AEs were also provided in the study protocol (see section 10.13 of the final protocol, i.e., pages 326-334 of the supplementary information to Shore et al. Nat Med. 2025). These are, however, not included in this report, for brevity.

Table 4: Sasanlimab recommended treatment modifications for drug-related toxicity (excluding immune-related AEs)

Haematologic toxicities	
Grade 1 and Grade 2	Continue as per schedule.
Anemia Grade ≥3 (hemoglobin <8 g/dL)	Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue sasanlimab if anemia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Neutropenia Grade ≥3 (ANC <1000/µL)	Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue sasanlimab if neutropenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Thrombocytopenia Grade ≥3 (platelets <50,000/µL)	Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue sasanlimab if thrombocytopenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Non-haematologic toxicities	
Grade 1 and Grade 2	Continue as per schedule.
Grade 3	Hold sasanlimab. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. **Exceptions are:** laboratory values that do not have any clinical correlate.
Grade 4	Permanently discontinue sasanlimab. **Exceptions are**: laboratory values that do not have any clinical correlate.

For BCG, dosing could be skipped or delayed according to the product label.

Discontinuation of Study Intervention

If a patient permanently discontinued one of the two study interventions, i.e., sasanlimab and BCG, the patient was allowed to continue with the other study intervention. If a patient permanently discontinued both study interventions, the patients was to remain in the study and move into the post-treatment follow-up period to allow for an adequate evaluation of the study objectives based on the prespecified estimands.

Reasons for withdrawal of study treatment include:

- Patient request
- Completion of study treatment (25 cycles)
- Patients with CIS at baseline who do not achieve a CR within 6 months of initiating study intervention will be withdrawn from study treatment
- Recurrence of HG disease or progression of disease
- Global deterioration of health status requiring discontinuation of study treatment
- Unacceptable toxicity
- Pregnancy
- Significant protocol violation
- Lost to follow-up
- Patient refused further treatment
- Study terminated by sponsor
- Death

Reasons for discontinuation from the study include:

- Patient request
- Refused further follow-up
- Lost to follow-up
- Death
- Study terminated by sponsor

A patient is considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Concomitant and rescue therapies

Concomitant treatment considered necessary for the patient's wellbeing may be given at discretion of the treating physician. Chronic, systemic corticosteroid use (prednisone >10 mg/day or equivalents) is, however, not permitted.

Additional anticancer treatment including chemotherapy, hormonal therapy, radiotherapy, and experimental anticancer medications are not permitted while patients are receiving study treatment.

Radiation therapy is not allowed during the study.

Study assessments

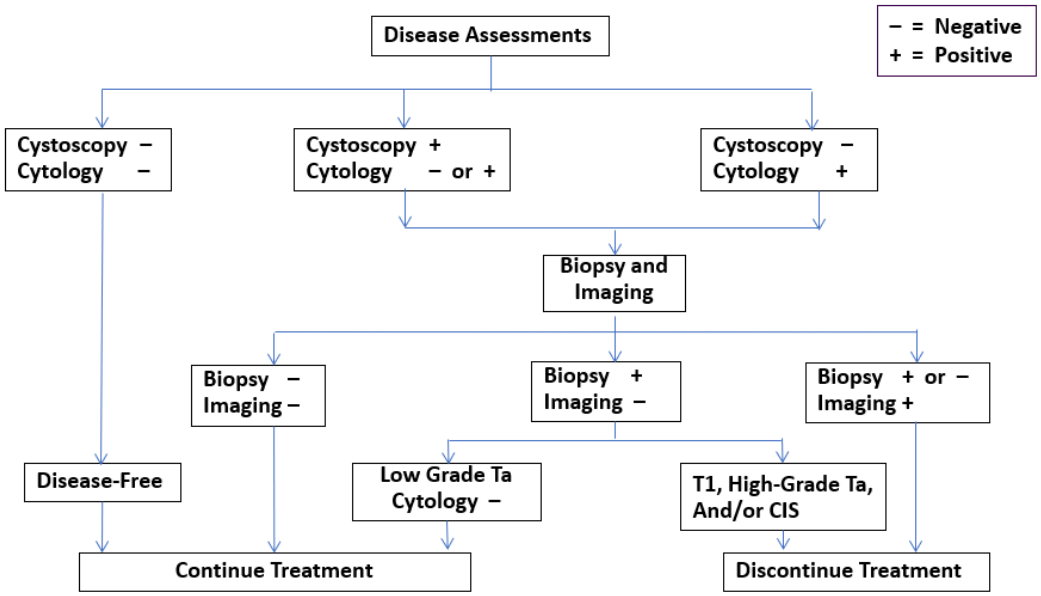
Clinical Efficacy Assessments

Assessment of disease – by cytology and cystoscopy, followed by biopsy and imaging (CT/MRI) when needed – was performed at baseline and then every 12 weeks for 2 years from randomisation and then every 24 weeks thereafter, plus when clinically indicated.

Cytology and cystoscopy results were read locally. Data obtained from cystoscopy, cytology, biopsy and imaging were read locally. Data obtained from cystoscopy, cytology, biopsy and imaging were evaluated locally during the course of the study according to the disease assessment decision algorithm shown in below Figure 9.

Independent reviewers provided retrospective central assessment of imaging and tumour tissue samples taken during the study. This includes the tumour tissue sample(s) taken from the TURBT supporting the primary diagnosis for the study during the screening period, biopsies or TURBT samples collected at the time of recurrence of HG disease, disease progression, persistence of CIS (applicable only to patients with CIS at randomization), or CR (applicable only to patients with CIS at randomization), and done after a positive cystoscopy or cytology.
Cystoscopy results and cytology results provided by the investigator were also included in the retrospective blinded independent central review (BICR) assessment.

Figure 9: Decision algorithm for disease assessment



The above diagram illustrates how cystoscopy, urine cytology, biopsy and imaging should be integrated to assess achievement of CR for patients with CIS at baseline, recurrence of HG disease, persistence of CIS or progression of disease. Patients enrolled with CIS with persistent disease and patients with recurrence of HG Ta disease following first induction period are eligible for a re-induction period of up to 6 additional weekly doses of BCG treatments (see Figure 8). Below, definitions are provided for no evidence of disease, CR, persistence of CIS, recurrence of HG/LG disease, and progression of disease.

Cystoscopy

Cystoscopy should be performed and assessed using the same method and equipment by the same study staff (whenever possible), for the duration of the study. White light, blue light or narrow-band imaging are allowed in this study and blue light is preferred.

Biopsy for confirmation of CR for patients with CIS should be performed at the 24 week disease assessment, unless collection at the 12 week disease assessment is routinely performed at the given institution. If the bladder biopsy collection at the Week 12 disease assessment fails to confirm CR, the biopsy collection must be repeated at the Week 24 disease assessment. If it is not possible to perform the bladder biopsy collection by the Week 24 disease assessment, biopsies should be collected as soon as possible at the next scheduled disease assessment.

Cytology

Cytology results are defined as the following:

1. Positive - if indicative or suggestive of malignant cells:
- HG UC
- Suspicious for HG UC

2. Negative if NOT indicative or suggestive of malignant cells:
- Negative for HG UC cells
- Presence of low-grade (LG) UC cells
- Atypical urothelial cell not abnormal enough to be considered as cancerous

3. Indeterminate: unsatisfactory sample.

Imaging

Imaging is done as clinically indicated, with CT or MRI or urogram of the abdomen and pelvis/urinary tract being the recommended imaging modalities. Other areas may be scanned as clinically indicated. Imaging should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used at screening will be employed in the tumour assessments conducted on study. Guidance for integration of imaging in the disease assessment is provided in the disease assessment decision algorithm in Figure 9.

Definitions

No evidence of disease only applies to patients without CIS at baseline and is defined as disease that was completely resected prior to randomization and does not meet the criteria of progression of disease, recurrence of HG disease, or recurrence of LG disease while on study. The date of imaging, biopsy, cystoscopy, or cytology (whichever result of the available assessments is earliest) that supports no evidence of disease will be used as the date of no evidence of disease.

CR, in patients with CIS at randomization, is defined as:
- histologic disappearance of malignancy on bladder biopsy with negative cytology and cystoscopy; or
- negative cytology and positive cystoscopy with biopsy-proven LG Ta lesion or non-malignant tissue.

The date of biopsy, cystoscopy, or cytology (whichever is earliest) will be used as the date of CR.

Persistence of CIS, in patients with CIS at baseline, is defined as persistence of CIS after induction or re-induction (if re-induction is administered). This will require a cystoscopy or cytology positive result with biopsy positive for CIS. The date of positive biopsy, cystoscopy, or cytology (whichever positive result is earliest) will be used as the date of persistence of CIS.

Recurrence of HG disease is defined as re-appearance of HG disease (HG Ta, T1 or CIS) after randomization for the following: 1) patients without CIS at baseline; 2) after CR for patients with CIS at baseline; or 3) before CR for patients with CIS and concurrent papillary disease at baseline. This will require a cystoscopy or cytology positive result, with biopsy positive for T1, HG Ta and/or CIS. The date of positive biopsy, cystoscopy, or cytology (whichever positive result is earliest) will be used as the date of recurrence of HG disease. If recurrence of HG disease occurs at the time of progression, progression should be the event. For patients with CIS at randomization, appearance of HG disease after a CR is considered recurrence of HG disease, while appearance of HG disease before a CR is progression.

Recurrence of LG disease is defined as re-appearance of LG disease (LG Ta) after randomization. This will require a cystoscopy or cytology positive result, with biopsy positive for LG Ta. The date of positive biopsy, cystoscopy, or cytology (whichever positive result is earliest) will be used as the date of recurrence of LG disease.

Progression of disease is defined as any of the following:
- lamina propria invasion (e.g., increase from Ta to T1 or CIS to T1);
- muscle-invasive disease (stage ≥T2);
- lymph node positive disease (N+);
- metastatic disease (M1); and/or
- appearance of HG Ta or T1 in patients with CIS only at baseline before achieving a CR.

This will require a cystoscopy or cytology positive result with imaging positive and/or biopsy positive for disease progression as described above. The date of positive biopsy, imaging for new lesion, positive cystoscopy, or positive cytology (whichever result is earliest) will be used as the date of progression.

5.3.2.1.3. Objectives, endpoints and estimands

Table 5 shows the CREST efficacy objectives and endpoints.

Table 5: Study efficacy objectives and endpoints

Type	Objectives	Endpoints
Primary		
Efficacy	• To demonstrate that sasanlimab + BCG (IND+MNT) is superior to BCG (IND+MNT) in prolonging EFS in patients with HR NMIBC.	**EFS** as assessed by the investigator (Arm A vs Arm C)
Key Secondary		
Efficacy	• To demonstrate that sasanlimab + BCG (IND) is superior to BCG (IND+MNT) in prolonging EFS in patients with HR NMIBC.	EFS as assessed by the investigator (Arm B vs Arm C)
Efficacy	• To demonstrate that sasanlimab + BCG (IND+MNT) is superior to BCG (IND+MNT) in prolonging OS in patients with HR NMIBC.	**OS** (Arm A vs Arm C)
Efficacy	• To demonstrate that sasanlimab + BCG (IND) is superior to BCG (IND+MNT) in prolonging OS in patients with HR NMIBC.	OS (Arm B vs Arm C)
Secondary		
Efficacy	• To evaluate the CR rate of sasanlimab + BCG (IND+MNT or IND) and BCG (IND+MNT) in patients with CIS at randomization.	**CR** as assessed by the investigator (**in patients with CIS** at randomization) (Arm A or Arm B vs Arm C)
Efficacy	• To evaluate the duration of CR (DoCR) of sasanlimab + BCG (IND+MNT or IND) and BCG (IND+MNT) in patients with CIS at randomization	**DoCR** for patients with CR as assessed by the investigator (**in patients with CIS** at randomization) (Arm A or Arm B vs Arm C)
Efficacy	• To evaluate the time to recurrence of LG disease of sasanlimab + BCG (IND+MNT or IND) and BCG (IND+MNT) in patients with HR NMIBC.	Time to recurrence of LG disease as assessed by the investigator (Arm A or Arm B vs Arm C)
Efficacy	• To evaluate the time to cystectomy of sasanlimab + BCG (IND+MNT or IND) and BCG (IND+MNT) in patients with HR NMIBC.	**Time to cystectomy** (Arm A or Arm B vs Arm C)
Efficacy	• To evaluate the DSS of sasanlimab + BCG (IND+MNT or IND) and BCG (IND+MNT) in patients with HR NMIBC.	DSS as assessed by the investigator (Arm A or Arm B vs Arm C)
PROs	• To assess the effects of sasanlimab + BCG (IND+MNT or IND) and BCG (IND+MNT) on patient-reported HRQoL in patients with HR NMIBC.	HRQoL as measured by: EORTC QLQ-C30; EORTC QLQ-NMIBC24; and PTAB. (Arm A or Arm B vs Arm C)
Biomarkers	• To evaluate PD-L1 expression in pre-treatment tumour tissue that may aid in the identification of a patient subpopulation most likely to benefit from treatment with sasanlimab + BCG (IND+MNT or IND).	Tumour sample biomarker status based on PD-L1 expression (high or low) (Arm A or Arm B vs Arm C)

Note: The table is limited to the primary and secondary efficacy objectives and endpoints, for brevity, and objectives and endpoints for the comparison of Arm B vs Arm C which are not relevant for the proposed indication and posology are shaded grey.

Abbreviations: AEs: adverse events; CR: complete response; CIS: carcinoma in situ; DoCR: duration of complete response; DSS: disease-specific survival; EFS: event-free survival; EORTC QLQ: European Organization for Treatment of Cancer Quality of Life Questionnaire; HG: high-grade; HR: high-risk; HRQoL: health-related quality of life: IND: induction; LG: low-grade; MNT: maintenance; OS: overall survival; PK: pharmacokinetics; PRO: patient-reported outcome; PTAB: Patient Treatment Administration Burden questionnaire.

Biomarkers

PD-L1 status was assessed by the VENTANA PD-L1 immunohistochemistry SP263 assay and used the VENTANA OptiView PD-L1 detection kit (Shore et al. Nat Med. 2025).

PD-L1 expression was evaluated in pre-treatment tumour tissue as follows: PD-L1 expression (high or low), as detected by a pathologist, assisted by image analysis. PD-L1 expression was defined as the number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumour and immune cells in regions of interest that are defined by tumour cell morphology.

PD-L1 status was defined as high if ≥25% tumour cells (TCs) or >1% immune cells present in the tumour area (ICP) and ≥25% PD-L1-positive immune cells (IC+) or (ICP = 1% and IC+ = 100%), and low if <25% TC and [(ICP >1% and IC+ <25%) or (ICP = 1% and IC+< 100%) or ICP = 0].

Primary objective

The CREST primary objective is to demonstrate that sasanlimab + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging EFS in patients with HR NMIBC (Table 5).

The following statistical hypothesis will be tested to address the primary objective:

H_{01}: $HR_{EFS(AvsC)} \geq 1$ vs. H_{11}: $HR_{EFS(AvsC)} < 1$

where $HR_{EFS(AvsC)}$ is the hazard ratio (HR) for EFS for Arm A vs Arm C.

Estimands for the primary objective

Primary Estimand (EFS for Arm A vs Arm C): treatment effect, estimated based on data from all randomized patients, of Arm A on EFS compared to Arm C from randomization to the earliest of recurrence of HG disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anticancer therapy. The date of the event (event as defined in Table 6) is the date of disease assessment documenting recurrence of HG disease, progression of disease, persistence of CIS (applicable only to patients with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of HG disease, progression of disease, persistence of CIS or death due to any cause, whichever occurs first.
- Censoring: see Table 7.
- Population-level summary measure: HR for EFS including all randomized patients.

Definitions for no evidence of disease, CR, persistence of CIS, recurrence of HG/LG disease, and progression of disease are provided above in the section 'Study assessments'.

Table 6: Possible clinical outcomes for patients with or without CIS at randomization and EFS evaluation

Population	Disease Assessment	EFS Event Y/N
Patients with CIS at randomization	Progressive disease [a] before achieving a CR for patients with CIS only at randomization	Y
	Progressive disease after achieving a CR	Y
	Recurrence of HG disease before achieving a CR for patients with CIS and concurrent papillary disease at randomization	Y
	Recurrence of HG grade disease after achieving a CR	Y
	Persistence of CIS (non-CR) [b]	Y
	Recurrence of LG disease	N
Patients without CIS at randomization	Progressive disease	Y
	Recurrence of HG disease	Y
	Recurrence of LG disease	N

[a] Including appearance of new HG Ta or T1 disease for patients with CIS only at randomization.
[b] Persistence of CIS after induction, with CR after re-induction is not considered an event.

Table 7: Outcome and event dates for the primary analysis of EFS

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of randomization [a]	Censored [a]
Event • After at most one missing or inadequate post-baseline disease assessment, OR • ≤ 24 weeks after the date of randomization	Date of event	Event
Event • After 2 or more missing or inadequate post-baseline disease assessments	Date of last adequate disease assessment documenting no event	Censored
No event	Date of last adequate disease assessment documenting no event	Censored

[a] However, if the patient dies ≤24 weeks after the date of randomization the death is an event with date on death date

Supportive Estimand 1 (EFS): treatment effect, estimated based on data from all randomized patients, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of HG disease, progression of disease, persistence of CIS, or death, regardless of tolerability, duration of study treatment or initiation of subsequent anticancer therapy. The date of the event (event as defined in Table 6) is the date of disease assessment documenting recurrence of HG disease, progression of disease, date of randomization for patients with persistent CIS (applicable only to patients with CIS at randomization), or death, whichever occurs earlier.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.
- Censoring: see Table 7.
- Population-level summary measure: HR for EFS including all randomized patients.

Supportive Estimand 2 (EFS): treatment effect of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of HG disease, progression of

disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anticancer therapy. Data from randomized patients who do not meet per-protocol criteria as defined below are excluded. The date of the event (event as defined in Table 6) is the date of disease assessment documenting recurrence of HG disease, progression of disease, persistence of CIS (applicable only to patients with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of HG disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.
- Censoring: see Table 7.
- Population-level summary measure: HR for EFS excluding randomized patients who did not receive at least 1 dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.

The primary aim of the trial was to estimate the treatment effect presented as hazard ratio estimated based on data from all randomized patients, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anticancer therapy. ICEs defined in the clinical question are tolerability, duration of study treatment, or initiation of subsequent anticancer therapy.

Key secondary objectives

The CREST key secondary objectives are (Table 5):

- to demonstrate that sasanlimab + BCG (induction) is superior to BCG (induction and maintenance) in prolonging EFS in patients with HR NMIBC;
- to demonstrate that sasanlimab + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging OS in patients with HR NMIBC; and
- to demonstrate that sasanlimab + BCG (induction) is superior to BCG (induction and maintenance) in prolonging OS in patients with HR NMIBC.

Similar as in Table 5, the objectives for the comparison of Arm B vs Arm C which are not relevant for the proposed indication and posology are shaded grey.

The following statistical hypotheses will be tested to address the key secondary objectives:

H_{02}: $HR_{EFS(BvsC)} \geq 1$ vs. H_{12}: $HR_{EFS(BvsC)} < 1$

H_{03}: $HR_{OS(AvsC)} \geq 1$ vs. H_{13}: $HR_{OS(AvsC)} < 1$

H_{04}: $HR_{OS(BvsC)} \geq 1$ vs. H_{14}: $HR_{OS(BvsC)} < 1$

where $HR_{EFS(BvsC)}$ is the HR for EFS for Arm B vs Arm C, $HR_{OS(AvsC)}$ is the HR for OS for Arm A vs Arm C, and $HR_{OS(BvsC)}$ is the HR for OS for Arm B vs Arm C.

The hypotheses for the comparison of Arm B vs Arm C which are not relevant for the proposed indication and posology are shaded grey.

Estimands for the key secondary objectives

Similar to above, the estimands pertaining to the comparison of Arm B vs Arm C which is not relevant for the proposed indication and posology are shaded grey. Plus, for these estimands no table is included.

Key Secondary Estimand (EFS for Arm B vs Arm C): treatment effect, estimated based on data from all randomized patients, of Arm B on EFS compared to Arm C from randomization to the earliest of recurrence of HG disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anticancer therapy. The date of the event (event as defined in Table 6) is the date of disease assessment documenting recurrence of HG grade disease, progression of disease, persistence of CIS (applicable only to patients with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of HG disease, progression of disease, persistence of CIS or death due to any cause, whichever occurs first.
- Censoring: see Table 7.
- Population-level summary measure: HR for EFS including all randomized patients.

Key Secondary Estimand (OS): treatment effect, estimated based on data from all randomized patients, of each experimental arm (Arm A and Arm B) on OS compared to Arm C regardless of tolerability, duration of study treatment, initiation of subsequent anticancer therapy or patient's request to discontinue study procedures.

- Variable: OS
- Censoring: data for patients not known to have died are censored at the time of last contact.
- Population-level summary measure: HR for OS, including all randomized patients.

For OS, the treatment effect is based on all randomised subjects of each experimental arm (arm A or B) compared to arm C regardless of tolerability, duration of study treatment, initiation of subsequent anticancer therapy or patient's request to discontinue study procedures.

No estimand table for OS was provided.

Statistical methods for estimation and sensitivity analysis on primary estimands

The efficacy analysis sets are shown in Table 8.

Table 8: Efficacy analysis sets

Population	Description
Enrolled	All patients who sign the informed consent document
Randomly Assigned to Study treatment (Full Analysis Set [FAS])	All patients who are randomized. Patients will be classified according to the study treatment assigned at randomization.
Per Protocol (PP)	Patients randomized A excluding those who did not receive at least one dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.

Table 9 summarizes the use of the analysis sets for efficacy.

Table 9: Statistical analyses by efficacy analysis set

Endpoints	Full Analysis Set	Per Protocol Analysis Set
Efficacy: Primary	√	√ (EFS for Arm A vs Arm C)
Efficacy: Secondary	√	√ (EFS for Arm B vs Arm C, OS)
PRO	√	

Note: The EFS comparison of Arm B vs Arm C which is not relevant for the proposed indication and posology is shaded grey.

Primary Endpoint – EFS as assessed by investigator – Primary analysis (Arm A vs Arm C)

The primary efficacy analysis will compare the EFS time based on the investigator assessment between Arm A and Arm C and will be performed using a 1-sided stratified log-rank test.

The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata to calculate the hazard ratio along with 95% CIs. Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG), i.e., for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the treatment arm (0=control arm, 1=experimental arm) and β is the unknown regression parameter. Ties will be handled using the Exact option in SAS (Ties=Exact option in SAS PROC PHREG).

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median EFS time with 2-sided 95% CIs. In particular, the EFS rate at 6, 12, 18, 24, 30, 36, 42, and 48 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula. A Kaplan-Meier plot for EFS will be generated.

Frequency (number and percentage) of patients with each event type (progression of disease, recurrence of HG disease, persistence of CIS, or death) or censoring will be presented by treatment arm. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10: EFS censoring reasons and hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment[a]
2	Event after 2 or more missing or inadequate post-baseline disease assessments	Event after 2 or more missing assessments
3	No event and [withdrawal of consent date ≥ date of randomization]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost-to-follow-up
5	No event and [EOS][b] present OR all EOT disposition pages of all drugs in the treatment arm say patient will not continue into any subsequent phase of the study] and no adequate post-baseline disease assessment	No adequate post-baseline disease assessment

6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] However, if the patient dies ≤24 weeks after the date of randomization the death is an event with date on death date
[b] EOS here refers to completion of follow-up disposition page.

For the patients with a progressive disease event for EFS as assessed by the investigator, the number and percentage of patients with the following types of progressive disease (defined hierarchically) will be presented:

- Progression to metastatic disease (defined as N+, M+);
- Progression to muscle-invasive disease (defined as ≥T2 disease); and
- Stage progression (defined as HG Ta or T1 disease)

The EFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for EFS

A Kaplan-Meier plot for EFS follow-up duration will also be generated to assess the follow-up time in the treatment arms reversing the EFS censoring and event indicators.

Primary Endpoint – EFS as assessed by investigator – Sensitivity analyses

The following analyses will be performed to explore the robustness of the primary analysis results. The sensitivity analyses will repeat the primary analysis (p-value, HR and 95% CIs) described above with the modifications below:

1. EFS based on BICR results following the definitions in Table 6 and the censoring rules outlined in Table 7 and Table 10.
2. EFS based on investigator assessment where the date of the event for patients with persistence of CIS is the date of randomization (refer to Supportive Estimand 1)
3. EFS based on investigator assessment following the definitions in Table 6 and the censoring rules outlined in Table 7 and Table 10 for patients in the per-protocol analysis set (refer to Supportive Estimand 2)
4. EFS based on investigator assessment following the definitions in Table 6 and the censoring rules outlined in Table 7 and Table 10 and using an unstratified analysis.
5. EFS based on investigator assessment following the definitions in Table 6 and modifying the censoring rules in Table 7 (update footnote 'a' to "*If the patient dies ≤24 weeks after the date of randomization and did not initiate new anticancer therapy, the death is an event with date on death date*") and Table 10 to include initiation of subsequent anticancer therapies as a censoring reason after "no adequate baseline assessment".
6. EFS based on investigator assessment following the definitions in Table 6 and the censoring rules outlined in Table 7 and Table 10 and using CIS stratification factor derived based on the data entered by the investigator in the "Oncology Biopsy" electronic case report form (CRF) at Screening.
7. EFS based on investigator assessment following the definitions in Table 6 and modifying the censoring rules in Table 7 and Table 10 to not censor events after 2 or more missing or inadequate post-baseline disease assessments (i.e., all events will be counted).
8. If >10% of deaths are due to COVID-19, an analysis will be performed for EFS (primary definition excluding COVID-19 related deaths) by treating COVID-19 related deaths as a competing risk event.

9. If there are >10% of patients with missed visits resulting in 2 or more missing assessments or inadequate post-baseline disease assessments due to COVID-19 before EFS events, censoring for event after 2 or more missing or inadequate disease assessment will not occur per Table 7 and Table 10 and the EFS event will be counted (i.e., not censored per Table 7 and Table 10).

To assess the impact of informative censoring due to potentially imbalanced dropout on the primary analysis of EFS by the investigator, a reference based multiple imputation method based on Bayes Gibbs sampling as outlined by Lu, Liu and Koch (2015) will also be implemented if imbalanced dropouts are observed between treatment arms.

If proportional hazards assumption is seriously violated, then EFS based on central pathology assessment of biopsies and independent review of imaging scans will also be analysed based on restricted mean survival time (RMST) differences.

Exploratory analyses to investigate the impact of potential prognostic or effect modifying (predictive) factors

Multivariable Cox's regression analysis will be carried out to assess and adjust the treatment effect for relevant baseline factors of potential prognostic impact. A stepwise selection procedure will serve to identify explanatory variables of potential prognostic values additional to the randomization strata which will be included in all models during the selection procedure. In the stepwise selection procedure, variables are entered into and removed from the model in such a way that each forward selection step can be followed by one or more backward elimination steps. The stepwise selection process terminates if no further variable can be added to the model or if the variable just entered into the model is the only variable removed in the subsequent backward elimination. The level of significance for an explanatory variable to enter the model is set to 0.15 (p-value of Score test) and the significance level for removing it is set to 0.40 (p-value of Wald test). This analysis will be performed using the stepwise selection method in SAS (Proc PHREG). Once this procedure stops, the factor "treatment arm" will be added to the last selected model in order to evaluate the effect of treatment on EFS time when adjusted for the selected explanatory variables. The hazard ratios of all selected explanatory variables and of treatment effects will be reported including 2-sided 95% CIs. No interactions will be considered. Post-baseline factors will not be considered for the model.

Statistical methods for estimation and sensitivity analysis on the key secondary estimand

Key Secondary Endpoint – OS – Primary analysis (Arm A vs Arm C)

The primary analysis of OS will compare the OS time between Arm A and Arm C and will be performed using the same approach as the primary parameter, EFS time based on the investigator assessment.

In order to account for the group sequential design in this study, the repeated CI (RCI) method (Jennison and Turnbull, 2000), will be used to construct the 2-sided RCIs for the hazard ratio at the interim and the final analyses of OS.

In addition, the unadjusted 95% CIs for the hazard ratio will also be reported at the interim and the final analyses for OS.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm along with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rate at 12, 24, 36, 48, 60, 72, and 84 months will be estimated with corresponding 2-sided 95% CIs.

Frequency (number and percentage) of patients with an event (death) or censoring will be presented by treatment arm.

Reasons for censoring will be summarized according to the categories in Table 11 following the hierarchy shown.

Table 11: OS censoring reasons and hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ 'start date']	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR (data cut-off date – last contact date > 365 days)]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment arms reversing the OS censoring and event indicators.

Key Secondary Endpoint – OS – Sensitivity analyses

The following sensitivity analyses will be performed to explore the robustness of the primary analysis results for OS. These analyses are regarded as purely exploratory. The sensitivity analyses will repeat the primary analysis (p-value, HR and 95% CIs) described above with the modifications below:

- Per-protocol analysis set;
- Unstratified;
- If >10% of deaths are due to COVID-19, an analysis will be performed for non-COVID-19 related deaths by treating COVID-19 related deaths as a competing risk event.

The same methodology described for EFS will be used for OS for evaluating the model assumptions and impact of potential prognostic factors or effect modifying factors.

Other Key Secondary Endpoints

The analyses for the comparison of Arm B vs Arm C which is not relevant for the proposed indication and posology are not described in this report, for brevity.

Statistical methods for non-key secondary endpoints

CR rate for patients with CIS at randomization will be calculated with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option) for each treatment arm.

The difference in CR rates between Arm A and Arm C will be tested with a nominal 2-sided p-value using a stratified analysis stratified by the randomization stratum of geographic region. The Mantel-Haenszel (MH) test and MH confidence limits will be obtained through PROC FREQ using the option of COMMONRISKDIFF(CL=MH Test=MH), which tests the null hypothesis that the common risk difference is 0.

BICR biopsy evaluation of investigator-assessed CR

For the patients with CIS at randomization by the investigator, the following will be presented:

- Number of patients achieved CR as assessed by the investigator.
  - Number of patients achieved CR as assessed by the investigator which was confirmed by investigator biopsy assessment.
    - BICR agreed (investigator-assessed CR confirmed by BICR biopsy assessment).
    - BICR disagreed (investigator-assessed CR not confirmed by BICR biopsy assessment).
    - No BICR biopsy assessment (biopsy not available/evaluable for BICR assessment).

If there are >5% of patients who discontinued treatment due to COVID-19 prior to achieving CR, a sensitivity analysis based on cumulative incidence curve will be performed for CR to estimate the CR rate by treating COVID-19 related discontinuation as censoring.

DoCR will be censored for patients without an EFS event according to rules similar as shown for EFS in Table 7.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median DoCR time with 2-sided 95% CIs. In particular, the DoCR rates at 6, 12, 18, 24, 30, 36, 42, and 48 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (progression of disease, recurrence of HG disease, or death) and censoring reasons will be presented by treatment arm. Reasons for censoring will be summarized according to categories similar to those shown for EFS in Table 10 following the hierarchy shown.

The DoCR time or censoring time and the reasons for censoring will also be presented in a patient listing.

For **time to cystectomy**, patients without a cystectomy will be censored at death date or last date known to be alive.

The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio for time to cystectomy between Arm A and Arm C.

The analyses of time to cystectomy will be performed using the analysis approach for EFS.

Reasons for censoring will be summarized according to the categories in Table 12 following the hierarchy shown.

Table 12: Time to cystectomy censoring reasons and hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and patient died	Death prior to event
2	No event and [withdrawal of consent date ≥ 'start date']	Withdrawal of consent
3	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 365 days]	Lost to follow-up
4	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

A listing for time to cystectomy will be provided.

The information on the **PRO endpoints** is limited to the ones included in Table 5.

PRO instruments

PROs will be collected using the following instruments: European Organization for Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), NMIBC symptoms (NMIBC24), and treatment administration burden (PTAB).

PRO scoring

The EORTC QLQ-C30 and NMIBC24 will be scored according to their respective user guides. For the EORTC QLQ-C30 and EORTC QLQ NMIBC24, missing items will be handled per the respective scoring manuals of each questionnaire. For the PTAB there will be no adjustments for missing data.

Instrument completion rates

For each treatment arm, at each time point the number and percentage of patients who complete each of the EORTC QLQ-C30, NMIBC24, and PTAB will be summarized.

Descriptive Summary

Separate tables for each questionnaire will be used to summarize the mean, SD, median, range and 95% CI of absolute scores and change from baseline of the total, all subscales of the EORTC QLQ-C30 and NMIBC24 at each time point. A line chart depicting the means along with 95% CI bars over time will be provided for each scale in each treatment arm.

For the PTAB, summary statistics (number and percentage) will be provided for each item, by treatment arm at each time point.

A figure will be provided for the cumulative patient disposition by treatment arm in Cohort A per PRO assessment window for all scheduled assessments using the following categories:

- PRO assessment expected;
- PRO assessment not expected due to lack of efficacy;
- PRO assessment not expected due to death; and
- PRO assessment not expected due to other reasons.

Random Coefficient Models

Random coefficient models will be carried out in Cohort A for the EORTC QLQ-C30 and NMIBC24 (all domains, subscales and symptoms) using PROC MIXED. Outcomes are post-baseline scores and change scores and the predictors are the corresponding baseline PRO score, treatment, time (treated as a continuous variable), and treatment-by-time interaction. Intercept and time are considered as random effects particular to each patient. All available data for each patient prior to the end of therapy should be used in the analyses. All parameter estimates should be obtained using restricted maximum likelihood. The unstructured covariance structure should be used to define covariance between random effects (using option "Type=UN" as a part of the RANDOM statement in PROC MIXED). For the degrees-of-freedom calculations the Kenward and Roger algorithm should be used (using option ddfm = kr") as a part of the MODEL statement in PROC MIXED).

Planned subgroup analyses

Subset analyses, if applicable, will be performed for OS, EFS, and CR per investigator assessment as noted below, based on the FAS for the subgroups defined below.

The following subgroups will be defined and used for analyses:

- Randomization stratification factors
    - Presence of CIS per IRT (EFS per investigator, and OS): Yes (Reference); No
    - Geography: US (Reference); Western Europe and Canada; ROW
- Presence of CIS per CRF (EFS per investigator and OS only): Yes (Reference); No
- Age: Age <65 years (Reference); Age ≥65 years
- Sex: Male (Reference); Female
- Race: White (Reference); Asian; Black or African American; Other
- Ethnicity: Hispanic or Latino or of Spanish origin; Not Hispanic or Latino or of Spanish origin (Reference)
- TICE Strain: TICE (Reference); No TICE
- BCG strain at induction: TICE (Reference); RIVM; TOKYO172; BCG-1; CHINA D2PB302
- T1 disease at baseline per CRF (EFS per investigator and OS only): Yes; No (Reference)

Subset analyses for EFS and OS will use the censoring rules described above.

Treatment arms will be compared for each endpoint using a 2-sided unstratified log-rank test for each subgroup level and the unstratified HR and its corresponding 95% CI will be computed per subgroup level.

Subset analyses for difference in CR rates will be performed and the 2-sided 95% CI will be provided.

All the subset analyses will be unstratified and exploratory; no adjustment for multiplicity will be performed. In the case of a low number of patients within a category (<5% of the FAS) and low number of events within the category (<10 events) the categories will be pooled or in cases where no meaningful pooling can be performed, the category may not be summarized.

To assess the heterogeneity of treatment effects for EFS and OS across the subgroup levels, a Cox's regression models will be fitted with EFS and OS as the dependent variable, respectively, and subgroup, treatment, and the treatment-by-subgroup interaction as explanatory variables.

- Model: treatment + subgroup + treatment×subgroup-variable

A p-value for the interaction test (Wald's test) will be provided together with the HR and corresponding 95% CI for the interaction model parameter.

The HR for EFS and OS and corresponding 95% CIs for each subgroup will be presented in a forest plot.

The difference in CR rates and corresponding 95% CIs for each subgroup will be presented in a forest plot.

Sample size determination

Approximately 999 patients (including a minimum of 250 patients with CIS) were planned to be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms (A, B, or C; Figure 8) with approximately 333 patients randomized to each treatment arm.

The sample size was determined based on the following assumptions:

- median EFS for patients receiving BCG (induction and maintenance) is 24 months.
- treatment with sasanlimab in combination with BCG (induction and maintenance) or BCG (induction only) is expected to increase the median EFS to 34.8 months, corresponding to a HR of 0.69 under the exponential model assumption.
- 20% drop-out rate for EFS within each arm.

- non-uniform patient accrual over 22 months.
- follow-up of approximately 33 months after the last patient is randomized.

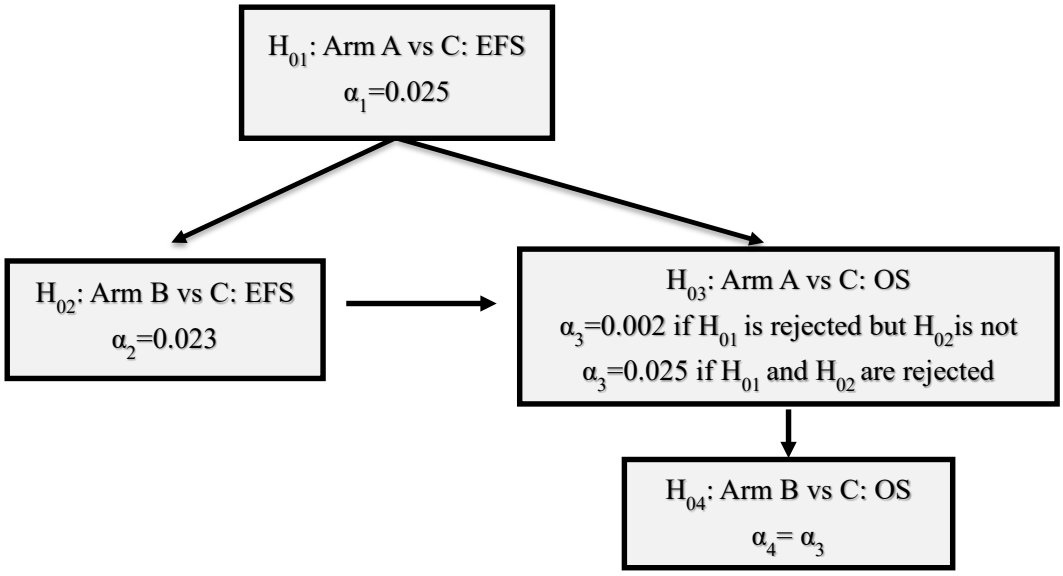
Error probabilities, adjustment for multiplicity and interim analyses

See above sections for the primary objective/hypothesis and the key secondary objectives/hypotheses. See also below section 'Changes in the planned conduct of the study'.

A graphical approach with group sequential testing outlined in Bretz *et al.* (2009) was used to control the family-wise type I error rate at a 1-sided 0.025 level as shown in Figure 10. The initial 1-sided alpha allocated to H_{01} was 0.025. If H_{01} is statistically significant, H_{02} and H_{03} were formally tested at initial 1-sided alpha of 0.023 and 0.002, respectively. If H_{02} was statistically significant, alpha recycling will be applied to evaluate H_{03} at 1-sided 0.025 level. If H_{03} was statistically significant, all the alpha will be recycled to formally test H_{04}. One interim analysis on the OS endpoint is planned at the time of the EFS primary analysis. A Haybittle-Peto α-spending function will be used to determine the efficacy boundary.

Based on Protocol Amendment 5 (PA5), the Interim Analysis 2 (IA2) was removed, and the Final Analysis (FA) for EFS based on a calendar-based data cut-off (DCO) date was conducted. Randomization was completed on 16-Nov-2021 and the EFS FA DCO date was set to allow for approximately 3 years of follow-up after last randomized patient. The treatment period was completed on 16-Nov-2023. Based on the observed pooled blinded data of EFS accrual rate, approximately 261 EFS events were expected to have occurred across all three arms. Assuming equal event rate across three arms, approximately 174 events for each two-arm comparison were expected by the EFS FA DCO date.

Figure 10: Testing strategy



For the primary endpoint, if the true HR was 0.69, 174 EFS events in Arm A and Arm C combined would provide 68.7% power to detect a difference using a 1-sided log-rank test at a significance level of 0.025.

Based on PA5, the FA for OS will be performed at the end of the study, which is approximately 5 years after the last patient has been randomized in Cohort A. Approximately 150 OS events are expected to

have occurred across the three study arms assuming equal event rate across three arms (approximately 100 OS events for each two-arm comparison) by the OS FA DCO date.

If the primary objective was met, a gatekeeping approach was used to allow further testing of the key secondary endpoints of EFS for Arm B vs Arm C, OS for Arm A vs Arm C, and OS for Arm B vs Arm C as shown in Figure 10.

- For the key secondary endpoint of EFS for Arm B vs Arm C (H_{02}), if the true HR was 0.69 under the alternative hypothesis, 174 EFS events would provide 67.4% power to detect a difference using a 1-sided log-rank test at a significance level of 0.023.
- If both H_{01} and H_{02} were rejected, 100 OS events for Arm A vs C would provide 96.3% power to detect a HR of 0.472 using a 1-sided log-rank test at the 0.025 significance level and a 2-look group sequential design with Haybittle-Peto α spending function to determine the efficacy boundary. The HR of 0.472 corresponds to an increase in the 5-year Kaplan-Meier rate for OS from 0.8013 in Arm C to 0.90 in Arm A, under the exponential model assumption.
- If H_{01} was rejected but H_{02} was not rejected, 100 OS events for Arm A vs C would provide 80.8% power to detect a HR of 0.472 using a 1-sided log-rank test at the 0.002 significance level and a 2-look group sequential design with Haybittle-Peto α spending function to determine the efficacy boundary.
- If H_{03} was rejected, H_{04} would be tested with the same power as H_{03} under the same assumptions.

Decision rules

Prior to PA5, two interim (IA1 (futility only) and IA2) and final (FA) analyses were planned for the primary endpoint.

IA1 for EFS was conducted after 658 patients were randomized to Cohort A for all 3 arms combined. As IA1 was for futility only, no alpha was spent at IA1.

Based on PA5, the IA2 was removed, and the FA for EFS based on a calendar-based DCO date was conducted. Randomization to Cohort A was completed on 16-Nov-2021 and the EFS FA DCO date was set to allow for approximately 3 years of follow-up after last randomized patient.

Cohort A of the study was to be considered positive if the primary objective was met.

One interim and one final efficacy analyses were planned for OS. The IA for OS was performed at the time of the FA for EFS. The FA for OS will be performed at the end of the study, which is approximately 5 years after the last patient has been randomized:

- IA: at the time of the FA for EFS; approximately 64 OS events (64% of the 100 OS events expected for each comparison) were expected to have occurred for each comparison.
- FA: this will occur at the end of the study, approximately 5 years after last patient randomized; approximately 100 OS events are expected to have occurred for each comparison.

Table 13: OS efficacy boundaries

OS Comparison	**Arm A vs Arm C**		**Arm B vs Arm C**	
Analysis	**Interim Analysis**	**Final Analysis**	**Interim Analysis**	**Final Analysis**
Analysis cutoff trigger	EFS final analysis	5 years after last patient randomized	EFS final analysis	5 years after last patient randomized

Number of events (information fraction)[a]	64 (64%)	100 (100%)	64 (64%)	100 (100%)
p-value (z-value) for efficacy if H01 is rejected but H02 is not rejected	<0.0001 (<-3.719)	<0.00197 (<-2.883)	<0.0001 (<-3.719)	<0.00197 (<-2.883)
p-value (z-value) for efficacy if both H01 and H02 are rejected	<0.0001 (<-3.719)	<0.025 (<-1.96)	<0.0001 (<-3.719)	<0.025 (<-1.96)

Note: The column with the comparison of Arm B vs Arm C which is not relevant for the proposed indication and posology is shaded grey.
a. For IA, the number of events was that expected under the alternative hypotheses (for EFS and OS) at the time of final EFS analysis; for FA, the number of events is that expected under the alternative hypothesis for OS at 5 years after last patient randomized.

The efficacy boundary for OS will be updated based on the actual number of observed OS events for each comparison using the pre-specified α-spending function. Therefore, the observed Z-test statistic at the IA for OS will be compared with the updated efficacy boundary. If OS was not met at the IA, the study for Cohort A will continue to the final analyses of OS, and the p-value that will be used to declare statistical significance at the FA for each comparison of OS will be based on the actual number of events documented at the cut-off date for the FA and the α already spent at the IA. Further details are provided below.

Interim analyses

The goals of the IAs were to allow early stopping of treatment arm(s) for futility or efficacy.

Prior to PA5, two interim (IA1 [futility only] and IA2) and final (FA) analyses were planned for the primary endpoint. IA1 for EFS was conducted after 658 patients were randomized. As IA1 was for futility only, no alpha was spent at IA1.

Based on PA5, IA2 was removed, and the FA for EFS based on a calendar-based DCO date was conducted. Randomization was completed on 16-Nov-2021 and the EFS FA DCO date was set to allow for approximately 3 years of follow-up after last randomized patient.

The interim efficacy analysis of OS was performed as described above.

As this is an open-label randomized study, the treatment is unblinded on patient level. However, the aggregate/cumulative data summaries by treatment arm were unavailable to the study team and the external investigators until the database snapshot for the primary analysis according to the Applicant.

Unblinded results from the interim futility analysis for EFS were not communicated to the Applicant's clinical team or to any party involved in the study conduct (apart from the independent statistician and external data monitoring committee [EDMC] members) until the EDMC determined that either (i) EFS analysis has crossed the pre-specified boundary for efficacy; or (ii) the study needed to be terminated due to any cause, including futility or safety reasons.

At the time of final EFS analyses, all patients continue to be followed for OS until the final OS analysis (approximately 5 years after the last patient is randomized).

Based on PA5, since EDMC review of interim efficacy data (IA2) is no longer applicable, the study team will be unblinded to aggregate/cumulative data summaries by treatment arm at the time of FA for EFS. No additional EDMC activities are foreseen after the FA for EFS.

Interim Analyses and Summaries (OS)

At each OS efficacy analysis time point, the critical boundaries for the group sequential test will be derived from the predefined spending function(s). The calculations of boundaries will be performed using EAST.

Let $u(t_1)$ and $u(t_F)$ denote the upper critical boundaries based on the test statistics Z_1 and Z_F for efficacy at the IA and the FA, respectively.

The critical value $u(t_1)$ for the interim analysis of OS is determined such as $P_0(Z_1 \geq u(t_1)) = \alpha(t_1)$, where P_0 denotes the probability under the null hypothesis and $\alpha(t_1)$ denotes the α spent based on the predefined spending function at information fraction t_1 (t_1 is calculated as the ratio of the number of OS events observed at the time of the cut-off for the IA and the total number of OS events targeted for the FA).

The boundary for the final efficacy analysis will be calculated such that $\alpha(t_1) + P_0(Z_1 < u(t_1), Z_F \geq u_F) = \alpha'$ where α'=0.002 or 0.025 for the analysis of OS determined according to the testing strategy described above.

As described above, if the number of OS events in the FA deviates from the target number of OS events, the FA criteria will be determined as above taking into account the actual α spent at the AI and the actual correlation between the two test statistics Z_1 and Z_F, so that the overall 1-sided significance level across all analyses and comparisons is preserved at 0.025.

OS Update at the '120-Day Safety Update'

OS update at the time of '120-Day safety update' for FDA submission will be conducted with a DCO date to allow for an approximately 6 months of additional follow-up for safety from the PCD. This OS update will not be a formal IA; hence no alpha will be spent at this update.

Descriptive statistics will be provided to summarize OS. The treatment effect will be estimated using the same statistical methods as described above for the OS primary analysis.

As part of the '120-Day safety update', DSS will also be updated using the same methods as described above.

Changes from protocol-specified analyses

The original version of the Statistical Analysis Plan (SAP) is dated 11-Dec-2019 and the final version 9 is dated 27-Mar-2025. See also below section 'Changes in the planned conduct of the study'.

As of 17-Jun-2024, PA5 revised the study analysis plan for the primary and key secondary objectives. The rationale for this change was based on the observation from pooled treatment groups that EFS events were accumulating at a much slower rate than originally projected, together with an increasing rate of patients dropping out from EFS observation. IA2 was removed, and the FA for EFS based on a calendar-based DCO date was to be conducted. Randomization was completed on 16-Nov-2021 and the EFS FA DCO date was set to allow for approximately 3 years of follow-up after the last patient was randomized. The treatment period was completed on 16-Nov-2023. Based on the blinded observed EFS events accrual rate and assuming equal event rate across three arms, approximately 261 EFS events were expected to have occurred across all three arms (approximately 174 events for each two-arm comparison) by the EFS FA DCO date.

Table 14 shows modification to the analysis plan described in the protocol (following PA5, dated 17-Jun-2024).

Table 14: Modifications to the analysis plan described in the protocol

Changes	Protocol	SAP
Complete response as assessed by BICR	Specified in protocol	Removed from SAP
Duration of CR as assessed by BICR	Specified in protocol	Removed from SAP

The removal of the analysis of CR and DoCR by BICR described in the protocol was based on the infeasibility of these analyses without large amount of data imputations based on investigator assessment. As per protocol, on-study biopsy was not required at each disease assessment visit, therefore central pathology assessment of CR could not be performed at each visit, and independent oncology review of CR is not feasible.

In addition, to adhere to the requirements from the FDA with reference to independent evaluation of EFS events and CR, the following summaries were added:

- BICR oncology evaluation of investigator-assessed EFS events.
- BICR biopsy evaluation of investigator-assessed CR.

5.3.2.1.4. Results

Changes in the planned conduct of the study

Protocol amendments

See above section 'Changes from protocol-specified analyses' for changes to the SAP not specified in the protocol.

The original protocol was dated 15-Oct-2019 and there were five (5) protocol amendments. Below, the amendments pertaining to the Cohorts B1 and B2 (not to Cohort A) which are not relevant for the proposed indication and posology are shaded grey.

For reference, the CREST initiation date (first patient first visit) was 30-Dec-2019 (Table 1), randomization was completed on 16-Nov-2021 (see e.g., above section 'Changes from protocol-specified analyses'), and the PCD/DCO date was 02-Dec-2024.

Amendment 1 dated 26-Jun-2020

The following PROs will now be completed during safety follow-up in addition to the timepoints specified in the original protocol: EORTC QLQ-C30 and EORTC QLQNMIBC24 (others not shown, for brevity).

Amendment 2 dated 21-Sep-2021

Addition of non-randomized Cohorts B1 and B2 to enrol patients with BCG-unresponsive NMIBC and evaluate single-agent sasanlimab in this population. Data from Cohort B1 and Cohort B2 were to be analysed separately from the data of the randomized Cohort A in BCG-naïve, HR NMIBC. The study design of Cohort A (Figure 8) was not modified.

Amendment 3 dated 12-Jan-2022

Modification of dose level and schedule of sasanlimab for patients in Cohort B2 in order to explore possibility of reducing dosing frequency burden for patients, their caregivers and the healthcare system.

Amendment 4 dated 10-Nov-2022

As of 31-Aug-2022, enrolment in Cohorts B1 and B2 was closed by the Applicant for business strategy reasons. This decision was not made due to any safety concerns, new emerging data, or regulatory interaction. Patients who had already been enrolled into Cohorts B1 and B2 were allowed to continue treatment (and study procedures and assessments).

Amendment 5 dated 17-Jun-2024

Applicant revised the Cohort A study analysis plan for primary and key secondary study objectives. The rationale for this change was based on the observation that EFS events were accumulating at a much slower rate than originally projected, together with an increasing rate of patients dropping out from EFS observation. IA2 was removed, and the FA for EFS was to be conducted based on a calendar-based data cut-off date.

Protocol deviations

All protocol deviations were systematically reviewed by the study team to identify important protocol deviations (IPDs). See Table 15 for important protocol deviations.

Table 15: Important protocol deviations – FAS

	Sasanlimab+BCG (IND+MNT) (N=352) n (%)	Sasanlimab+BCG (IND) (N=352) n (%)	BCG (IND+MNT) (N=351) n (%)	Total (N=1055) n (%)
Patients with any important deviations	181 (51.4)	154 (43.8)	155 (44.2)	490 (46.4)
Concomitant Medications	11 (3.1)	10 (2.8)	7 (2.0)	28 (2.7)
Took prohibited concomitant medication/vaccine	10 (2.8)	10 (2.8)	7 (2.0)	27 (2.6)
Inclusion/Exclusion	21 (6.0)	26 (7.4)	10 (2.8)	57 (5.4)
Complete resection of Ta/T1 papillary disease with most recent TURBT within 12 weeks of randomization	9 (2.6)	6 (1.7)	6 (1.7)	21 (2.0)
Patient dosed even though a procedure/lab/assessment required for eligibility determination was not done or results were not available.	5 (1.4)	8 (2.3)	0	13 (1.2)
Available tumor tissue from most recent TURBT	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)
Evidence of muscle-invasive bladder cancer	2 (0.6)	3 (0.9)	0	5 (0.5)
Cohort A: Intravesical BCG therapy within 2 years prior to randomization	1 (0.3)	1 (0.3)	0	2 (0.2)
High-risk, non-muscle invasive bladder cancer	1 (0.3)	1 (0.3)	0	2 (0.2)
Informed Consent	80 (22.7)	64 (18.2)	82 (23.4)	226 (21.4)
Subsequent (revised, updated) ICD not signed or not signed at the first patient visit after the revised/approved ICD was available at site	73 (20.7)	59 (16.8)	74 (21.1)	206 (19.5)
Investigational Product	26 (7.4)	5 (1.4)	15 (4.3)	46 (4.4)
Dosing error	7 (2.0)	2 (0.6)	9 (2.6)	18 (1.7)
BCG dose missed due to shortage	4 (1.1)	1 (0.3)	4 (1.1)	9 (0.9)
Laboratory	1 (0.3)	5 (1.4)	0	6 (0.6)

	Sasanlimab+BCG (IND+MNT) (N=352) n (%)	Sasanlimab+BCG (IND) (N=352) n (%)	BCG (IND+MNT) (N=351) n (%)	Total (N=1055) n (%)
Abnormal lab result not followed up appropriately	0	4 (1.1)	0	4 (0.4)
Procedures/Tests	79 (22.4)	74 (21.0)	82 (23.4)	235 (22.3)
Abnormal procedure/test result not followed up per protocol	61 (17.3)	61 (17.3)	69 (19.7)	191 (18.1)
Protocol Specific Discontinuation Criteria	2 (0.6)	1 (0.3)	3 (0.9)	6 (0.6)
Patient met any of the protocol specified study treatment discontinuation criteria, but was not discontinued from study treatment appropriately.	1 (0.3)	1 (0.3)	3 (0.9)	5 (0.5)
Randomization	12 (3.4)	11 (3.1)	13 (3.7)	36 (3.4)
Randomized under wrong stratification	10 (2.8)	7 (2.0)	11 (3.1)	28 (2.7)
Randomized and not treated	2 (0.6)	4 (1.1)	2 (0.6)	8 (0.8)
Visit Schedule	4 (1.1)	2 (0.6)	1 (0.3)	7 (0.7)
Visit not done	4 (1.1)	2 (0.6)	1 (0.3)	7 (0.7)

Notes: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey. For brevity, not all subcategories are shown.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

GCP aspects

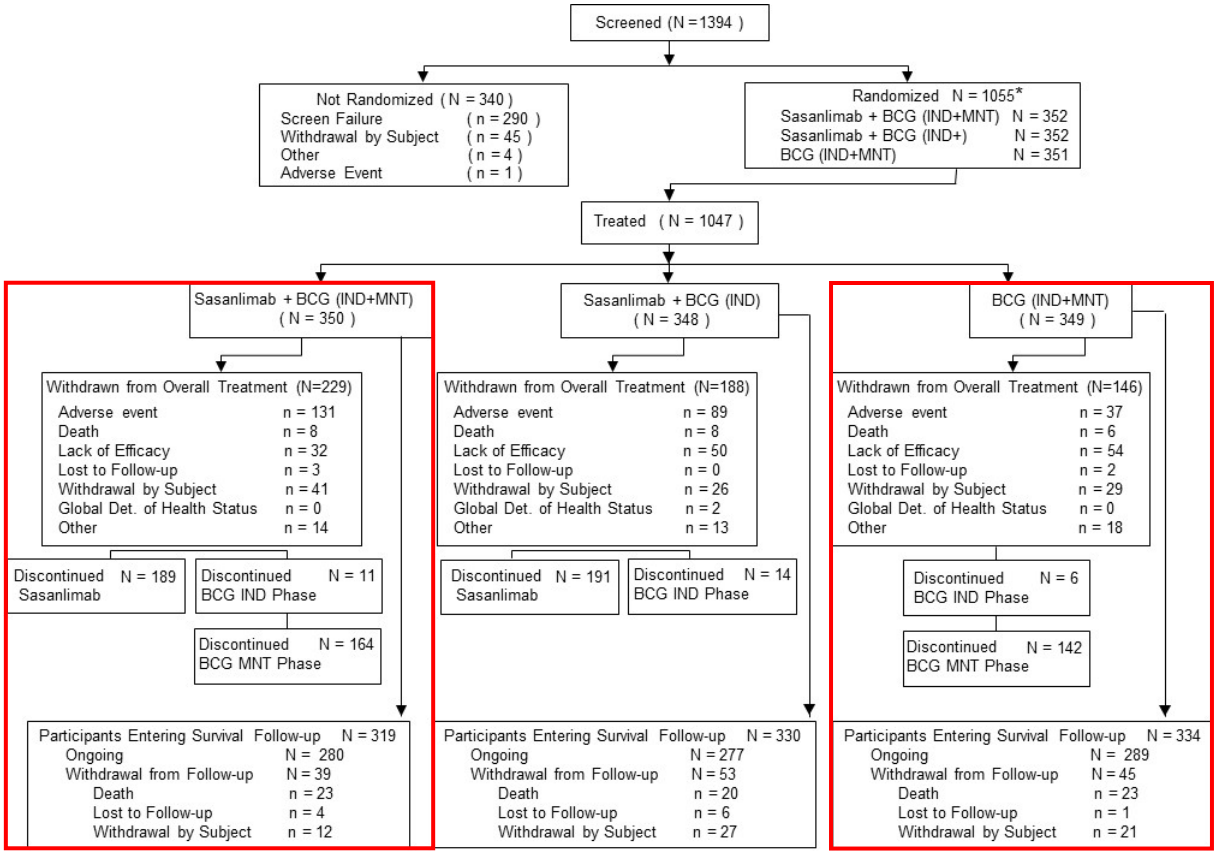
See section 5.1.1.

Participant flow and numbers analysed

The CREST initiation date (first patient first visit) was 30-Dec-2019. The study was conducted at 149 centres in 14 countries across Europe, North America, Asia, and Australia (Table 1). The first patient was randomized on 20-Jan-2020 (Shore et al. Nat Med. 2025), and randomization was completed on 16-Nov-2021. The PCD/DCO date was 02-Dec-2024 and the study is ongoing.

See Figure 11 for the participant flow.

Figure 11: Participant flow



* 1 participant was a Screen Failure but randomized in error.

Note: Arm A and Arm C relevant for the proposed indication and posology are shown in red boxes.
For the sasanlimab + BCG (IND+MNT) and sasanlimab + BCG (IND) arms, participants are considered to have completed the overall treatment if they fulfill the requirement of completing both planned sasanlimab and BCG treatments; the reason for discontinuation from overall treatment is the latest discontinuation reason from BCG and sasanlimab. In cases where sasanlimab and BCG were discontinued on the same date, the reason for discontinuation from overall treatment is the reason of discontinuation from Sasanlimab.

The number of screened patients and patient numbers by efficacy analysis data sets is provided in Table 16 (see also Table 8).

Table 16: Efficacy analysis data sets

	Sasanlimab+BCG (IND + MNT) n (%)	Sasanlimab+BCG (IND) n (%)	BCG (IND + MNT) n (%)	Total n (%)
Screened				1394
Full analysis set[a]	352 (100.0)	352 (100.0)	351 (100.0)	1055 (100.0)
Per protocol analysis set[b]	339 (96.3)	338 (96.0)	343 (97.7)	1020 (96.7)

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.
a. Full analysis set: all randomized patients.
b. Per protocol analysis set: patients randomized excluding those who did not receive at least one dose of study drug, or did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.

Baseline data

See Table 17 for demographic and baseline characteristics and Table 18 for disease characteristics (primary diagnosis and substance use).

Table 17: Demographic characteristics and baseline characteristics - FAS

	Sasanlimab+BCG (IND+MNT) (N=352)	Sasanlimab+BCG (IND) (N=352)	BCG (IND+MNT) (N=351)	Total (N=1055)
Age (years), n (%)				
<65	142 (40.3%)	141 (40.1%)	133 (37.9%)	416 (39.4%)
≥65	210 (59.7%)	211 (59.9%)	218 (62.1%)	639 (60.6%)
65 - <75	135 (38.4%)	141 (40.1%)	142 (40.5%)	418 (39.6%)
75 - <85	71 (20.2%)	62 (17.6%)	66 (18.8%)	199 (18.9%)
≥85	4 (1.1%)	8 (2.3%)	10 (2.8%)	22 (2.1%)
Mean (SD)	66.6 (10.09)	66.2 (10.06)	66.6 (10.37)	66.5 (10.17)
Median	67.00	67.00	67.00	67.00
Range (min, max)	(31, 85)	(34, 90)	(31, 91)	(31, 91)
Gender, n (%)				
Male	280 (79.5%)	299 (84.9%)	284 (80.9%)	863 (81.8%)
Female	72 (20.5%)	53 (15.1%)	67 (19.1%)	192 (18.2%)
Race, n (%)				
White	225 (63.9%)	211 (59.9%)	210 (59.8%)	646 (61.2%)
Black or African American	3 (0.9%)	2 (0.6%)	5 (1.4%)	10 (0.9%)
Asian	115 (32.7%)	133 (37.8%)	126 (35.9%)	374 (35.5%)
Not Reported	9 (2.6%)	6 (1.7%)	10 (2.8%)	25 (2.4%)
Ethnicity, n (%)				
Hispanic or Latino or of Spanish origin	22 (6.3%)	25 (7.1%)	24 (6.8%)	71 (6.7%)
Not Hispanic or Latino or of Spanish origin	315 (89.5%)	314 (89.2%)	310 (88.3%)	939 (89.0%)
Not Reported	15 (4.3%)	13 (3.7%)	17 (4.8%)	45 (4.3%)
Geographic Region, n (%)				
North America	57 (16.2%)	55 (15.6%)	53 (15.1%)	165 (15.6%)
Western Europe	77 (21.9%)	79 (22.4%)	80 (22.8%)	236 (22.4%)
Eastern Europe	104 (29.5%)	87 (24.7%)	94 (26.8%)	285 (27.0%)
Australasia	3 (0.9%)	1 (0.3%)	1 (0.3%)	5 (0.5%)
Asia	111 (31.5%)	130 (36.9%)	123 (35.0%)	364 (34.5%)
ECOG Performance Status at Baseline, n (%)				
0	298 (84.7%)	293 (83.2%)	291 (82.9%)	882 (83.6%)
1	54 (15.3%)	57 (16.2%)	59 (16.8%)	170 (16.1%)
2	0	2 (0.6%)	1 (0.3%)	3 (0.3%)
Stratification factor 1 - Presence of carcinoma in situ at randomization per IRT, n (%)				
Yes	94 (26.7%)	94 (26.7%)	93 (26.5%)	281 (26.6%)
No	258 (73.3%)	258 (73.3%)	258 (73.5%)	774 (73.4%)
Stratification factor 2 - Geographic Region per IRT, n (%)				
United States	49 (13.9%)	47 (13.4%)	47 (13.4%)	143 (13.6%)
Western Europe and Canada	85 (24.1%)	87 (24.7%)	86 (24.5%)	258 (24.5%)
Rest of World	218 (61.9%)	218 (61.9%)	218 (62.1%)	654 (62.0%)

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
Age at Screening (years) = year of given informed consent - year of birth.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.
a. n is the number of patients with non-missing age.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Table 18: Disease characteristics: primary diagnosis and substance use - FAS

	Sasanlimab+BCG (IND+MNT) (N=352)	Sasanlimab+BCG (IND) (N=352)	BCG (IND+MNT) (N=351)	Total (N=1055)
	n (%)	n (%)	n (%)	n (%)
Histopathological classification				
Urothelial (transitional cell) carcinoma	339 (96.3)	346 (98.3)	332 (94.6)	1017 (96.4)
Urothelial (transitional cell) carcinoma with squamous differentiation	6 (1.7)	2 (0.6)	8 (2.3)	16 (1.5)
Urothelial (transitional cell) carcinoma with glandular differentiation	2 (0.6)	4 (1.1)	3 (0.9)	9 (0.9)
Urothelial (transitional cell) carcinoma with variant histology (specify)	4 (1.1)	0	6 (1.7)	10 (0.9)
Other	1 (0.3)	0	2 (0.6)	3 (0.3)
Disease Recurrence Type				
Recurrence	90 (25.6)	93 (26.4)	91 (25.9)	274 (26.0)
Newly diagnosed	262 (74.4)	259 (73.6)	260 (74.1)	781 (74.0)
CIS at baseline per CRF				
Yes	88 (25.0)	93 (26.4)	88 (25.1)	269 (25.5)
No	264 (75.0)	259 (73.6)	263 (74.9)	786 (74.5)
Number of tumors identified by cystoscopy				
Single	199 (56.5)	174 (49.4)	182 (51.9)	555 (52.6)
Multiple	136 (38.6)	163 (46.3)	146 (41.6)	445 (42.2)
Unknown	17 (4.8)	15 (4.3)	23 (6.6)	55 (5.2)
Size of largest tumor identified by cystoscopy				
<3cm	193 (54.8)	189 (53.7)	190 (54.1)	572 (54.2)
≥3cm	94 (26.7)	105 (29.8)	95 (27.1)	294 (27.9)
Unknown	65 (18.5)	58 (16.5)	66 (18.8)	189 (17.9)
Highest grade of tumor identified by biopsy (2004/2016 WHO grading system)				
High	319 (90.6)	322 (91.5)	316 (90.0)	957 (90.7)
Low	33 (9.4)	30 (8.5)	35 (10.0)	98 (9.3)
Worst T stage				
CIS	52 (14.8)	42 (11.9)	50 (14.2)	144 (13.6)
Ta	96 (27.3)	136 (38.6)	107 (30.5)	339 (32.1)
T1	204 (58.0)	174 (49.4)	194 (55.3)	572 (54.2)
Smoking history:				
Never smoker	127 (36.1)	108 (30.7)	126 (35.9)	361 (34.2)
Current smoker	71 (20.2)	70 (19.9)	54 (15.4)	195 (18.5)
Former smoker	154 (43.8)	174 (49.4)	171 (48.7)	499 (47.3)

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Prior Therapy

See Table 19 for a summary of prior anticancer therapies.

Table 19: Summary of prior anticancer therapies - FAS

	Sasanlimab+BCG (IND+MNT) (N=352)	Sasanlimab+BCG (IND) (N=352)	BCG (IND+MNT) (N=351)	Total (N=1055)
	n (%)	n (%)	n (%)	n (%)
Patients with at least one type of prior anticancer therapy				
Yes	352 (100.0)	352 (100.0)	351 (100.0)	1055 (100.0)
No/ Not Reported	0	0	0	0
Patients with at least one prior anticancer drug therapy				
Yes	110 (31.3)	109 (31.0)	115 (32.8)	334 (31.7)
No/ Not Reported	242 (68.8)	243 (69.0)	236 (67.2)	721 (68.3)
Patients with at least one prior anticancer surgery				
Yes	352 (100.0)	352 (100.0)	351 (100.0)	1055 (100.0)
No/ Not Reported	0	0	0	0
Number of prior anticancer drug therapy regimens				
0 Regimens	242 (68.8)	243 (69.0)	236 (67.2)	721 (68.3)
1 Regimen	86 (24.4)	80 (22.7)	89 (25.4)	255 (24.2)
2 Regimens	16 (4.5)	20 (5.7)	18 (5.1)	54 (5.1)
3 Regimens	5 (1.4)	3 (0.9)	5 (1.4)	13 (1.2)
≥4 Regimens	3 (0.9)	6 (1.7)	3 (0.9)	12 (1.1)

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Concomitant Therapy

During the study, concomitant medications were administered in 96.9% and 95.1% of patients in the sasanlimab + BCG (IND+MNT) and BCG (IND+MNT) arms, respectively.

Overall, concomitant medication use was reported (by ATC2 code) at a higher frequency in the sasanlimab + BCG combination arm than in the BCG arm. Concomitant medications in the sasanlimab + BCG (IND+MNT) and BCG (IND+MNT) treatment arms, respectively, included corticosteroids for systemic use in 47.4% (including high dose corticosteroids, i.e., ≥40 mg daily prednisolone or equivalent) and 16.0%; immunosuppressants in 4.3% and 0.6%; pituitary and hypothalamic hormones and analogues in 3.4% and 0.9%; thyroid therapy in 22.6% and 4.3%; and antimycotics for systemic use in 8.6% and 0.6%. Antimycobacterial drugs used in tuberculosis were reported at similar frequencies in both treatment arms.

Post-intervention Therapy

See Table 20 for a summary of follow-up anticancer therapies and Table 21 for the subsequent anticancer drug therapies (by preferred term).

Table 20: Summary of follow-up anticancer therapies - FAS

	Sasanlimab + BCG (IND+MNT) (N=352)	Sasanlimab + BCG (IND) (N=352)	BCG (IND+MNT) (N=351)
	n (%)	n (%)	n (%)
Participants with at least one type of follow-up anti-cancer therapy			
Yes	91 (25.9)	113 (32.1)	113 (32.2)
No/ Not Reported	261 (74.1)	239 (67.9)	238 (67.8)
Participants with at least one follow-up anti-cancer drug therapy			
Yes	26 (7.4)	47 (13.4)	47 (13.4)
No/ Not Reported	326 (92.6)	305 (86.6)	304 (86.6)
Participants with at least one follow-up anti-cancer radiotherapy			
Yes	2 (0.6)	0	5 (1.4)
No/ Not Reported	350 (99.4)	352 (100.0)	346 (98.6)
Participants with at least one follow-up anti-cancer surgery			
Yes	75 (21.3)	95 (27.0)	91 (25.9)
No/ Not Reported	277 (78.7)	257 (73.0)	260 (74.1)

Table 21: Follow-up anticancer drug therapies by preferred term - FAS

Preferred Term	Sasanlimab+BCG (IND+MNT) (N=352) n (%)	Sasanlimab+BCG (IND) (N=352) n (%)	BCG (IND+MNT) (N=351) n (%)
Patients with any follow-up anticancer drug therapies	26 (7.4)	47 (13.4)	47 (13.4)
BCG VACCINE	12 (3.4)	27 (7.7)	18 (5.1)
GEMCITABINE	5 (1.4)	7 (2.0)	17 (4.8)
GEMCITABINE HYDROCHLORIDE	4 (1.1)	7 (2.0)	4 (1.1)
PACLITAXEL	2 (0.6)	0	0
TORIPALIMAB	2 (0.6)	0	0
BCG VACCINE LIVE INTRAVESICAL (TICE)	1 (0.3)	3 (0.9)	1 (0.3)
CARBOPLATIN	1 (0.3)	1 (0.3)	5 (1.4)
CARBOPLATIN;GEMCITABINE	1 (0.3)	1 (0.3)	0
CHEMOTHERAPY NOS	1 (0.3)	0	2 (0.6)
CISPLATIN	1 (0.3)	3 (0.9)	7 (2.0)
DISITAMAB VEDOTIN	1 (0.3)	0	0
DOCETAXEL	1 (0.3)	1 (0.3)	0
DOCETAXEL;GEMCITABINE	1 (0.3)	2 (0.6)	2 (0.6)
EPIRUBICIN HYDROCHLORIDE	1 (0.3)	0	1 (0.3)
ERDAFITINIB	1 (0.3)	0	0
PIRARUBICIN HYDROCHLORIDE	1 (0.3)	3 (0.9)	1 (0.3)
T 3011	1 (0.3)	0	0
ATEZOLIZUMAB	0	0	1 (0.3)
AVELUMAB	0	1 (0.3)	3 (0.9)
BCG VACCINE LIVE INTRAVESICAL	0	0	1 (0.3)
BOSWELLIA SACRA;COMMIPHORA MYRRHA RESIN;COW BEZOAR;MUSK	0	0	1 (0.3)
CARBOPLATIN;GEMCITABINE HYDROCHLORIDE	0	0	1 (0.3)
CISPLATIN;GEMCITABINE	0	1 (0.3)	2 (0.6)
DOXORUBICIN	0	2 (0.6)	0
ENFORTUMAB VEDOTIN	0	0	2 (0.6)
FOSFOMYCIN TROMETAMOL	0	0	1 (0.3)
HERBAL PREPARATION	0	0	1 (0.3)
INVESTIGATIONAL DRUG	0	0	1 (0.3)
MITOMYCIN	0	5 (1.4)	0
NADOFARAGENE FIRADENOVEC VNCG	0	0	1 (0.3)
PACLITAXEL NANOPARTICLE ALBUMIN-BOUND	0	0	1 (0.3)

Preferred Term	Sasanlimab+BCG (IND+MNT) (N=352) n (%)	Sasanlimab+BCG (IND) (N=352) n (%)	BCG (IND+MNT) (N=351) n (%)
PEMBROLIZUMAB	0	1 (0.3)	5 (1.4)
PIRARUBICIN	0	1 (0.3)	0
SACITUZUMAB GOVITECAN	0	0	1 (0.3)
SASANLIMAB	0	0	1 (0.3)
TISLELIZUMAB	0	0	1 (0.3)

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.
WHODDG B3 v MAR2024 coding dictionary applied.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Secondary objective (non-key) – biomarkers – PD-L1 expression in pre-treatment tumour tissue (is considered baseline data)

Table 22 shows a summary of PD-L1 expression in pre-treatment tumour tissue (at baseline) in the Biomarker Analysis Set, i.e., the patients in the Safety Analysis Set who had at least one of the biomarkers evaluated at pre and/or post dose.

Table 22: PD-L1 expression at baseline - Biomarker Analysis Set

	Sasanlimab + BCG (IND+MNT) (N=340)	Sasanlimab + BCG (IND) (N=337)	BCG (IND+MNT) (N=337)	Total (N=1014)
Baseline PD-L1 expression, n (%)				
High	77 (22.6)	68 (20.2)	73 (21.7)	218 (21.5)
Low	252 (74.1)	256 (76.0)	253 (75.1)	761 (75.0)
Unknown	11 (3.2)	13 (3.9)	11 (3.3)	35 (3.5)

The denominator to calculate percentages is N, the number of patients in the biomarker analysis set within each treatment group.
PD-L1 status is defined as High if ≥25% TC or (ICP >1% and IC+ ≥25%) or (ICP = 1% and IC+ = 100%), and Low if <25% TC and [(ICP >1% and IC+ <25%) or (ICP = 1% and IC+<100%) or ICP = 0].
TC = tumor cell, IC+ = PD-L1-positive immune cells , ICP = immune cells present in the tumor area.

Of the 329 and 326 patients evaluable for PD-L1 tumor expression in each arm, respectively, the mean percentage of immune cells in the tumour that were positive (IC+) was 17.13% (SD: 19.646) in the sasanlimab + BCG (IND+MNT) arm and 16.59% (SD: 19.392) in the BCG (IND+MNT) arm.

The mean percentage of tumour cells (TCs) that were positive was 1.29% (SD: 6.234) in the sasanlimab + BCG (IND+MNT) arm and 0.99% (SD: 6.466) in the BCG (IND+MNT) arm.

Outcomes and estimation

Primary objective – investigator-assessed EFS (Arm A vs Arm C)

Primary analysis

The study met its primary objective; a statistically significant improvement in EFS per investigator assessment was observed in the sasanlimab + BCG (IND+MNT) arm compared with the BCG (IND+MNT) arm. See Table 23 and Figure 12 for EFS in Arm A vs Arm C.

The median (95% CI) time of follow-up for investigator-assessed EFS was 36.4 (36.1, 37.7) months in Arm A and 36.7 (36.1, 41.2) months in Arm C.

Table 23: Summary of investigator-assessed EFS (primary analysis) - FAS

	Sasanlimab + BCG (IND+MNT) (N=352)	BCG (IND+MNT) (N=351)
Patients with event, n (%)	61 (17.3)	89 (25.4)
Type of event, n (%)		
Progressive disease	18 (5.1)	22 (6.3)
Recurrence of high-grade disease	26 (7.4)	53 (15.1)
Persistence of CIS	1 (0.3)	1 (0.3)
Death	16 (4.5)	13 (3.7)
Patients censored, n (%)	291 (82.7)	262 (74.6)
Reason for censoring, n (%)		
No adequate baseline assessment	2 (0.6)	3 (0.9)
Event after 2 or more missing assessments	10 (2.8)	2 (0.6)
Withdrawal of consent	29 (8.2)	26 (7.4)
Lost to follow-up	5 (1.4)	2 (0.6)
No adequate post-baseline disease assessment	1 (0.3)	0
Ongoing without an event	244 (69.3)	229 (65.2)
Probability of being event-free (95% CI) [a]		
at 6 months	0.909 (0.872, 0.935)	0.890 (0.851, 0.919)
at 12 months	0.870 (0.828, 0.902)	0.853 (0.810, 0.887)
at 18 months	0.860 (0.817, 0.894)	0.828 (0.783, 0.865)
at 24 months	0.847 (0.802, 0.882)	0.799 (0.752, 0.839)
at 36 months	0.821 (0.774, 0.859)	0.748 (0.697, 0.792)
at 48 months	0.735 (0.634, 0.813)	0.691 (0.625, 0.747)
Kaplan-Meier estimates of Time to Event (months)		
Quartiles (95% CI) [b]		
Q1	45.9 (43.0, NE)	35.8 (24.9, NE)
Median	NE (NE, NE)	NE (NE, NE)
Q3	NE (NE, NE)	NE (NE, NE)
Stratified analysis [c]		
Comparison vs BCG (IND+MNT)		
Hazard Ratio [d]	0.68	
95% CI [d]	0.489, 0.941	
1-sided p-value [e]	0.0095	
2-sided p-value [e]	0.0191	

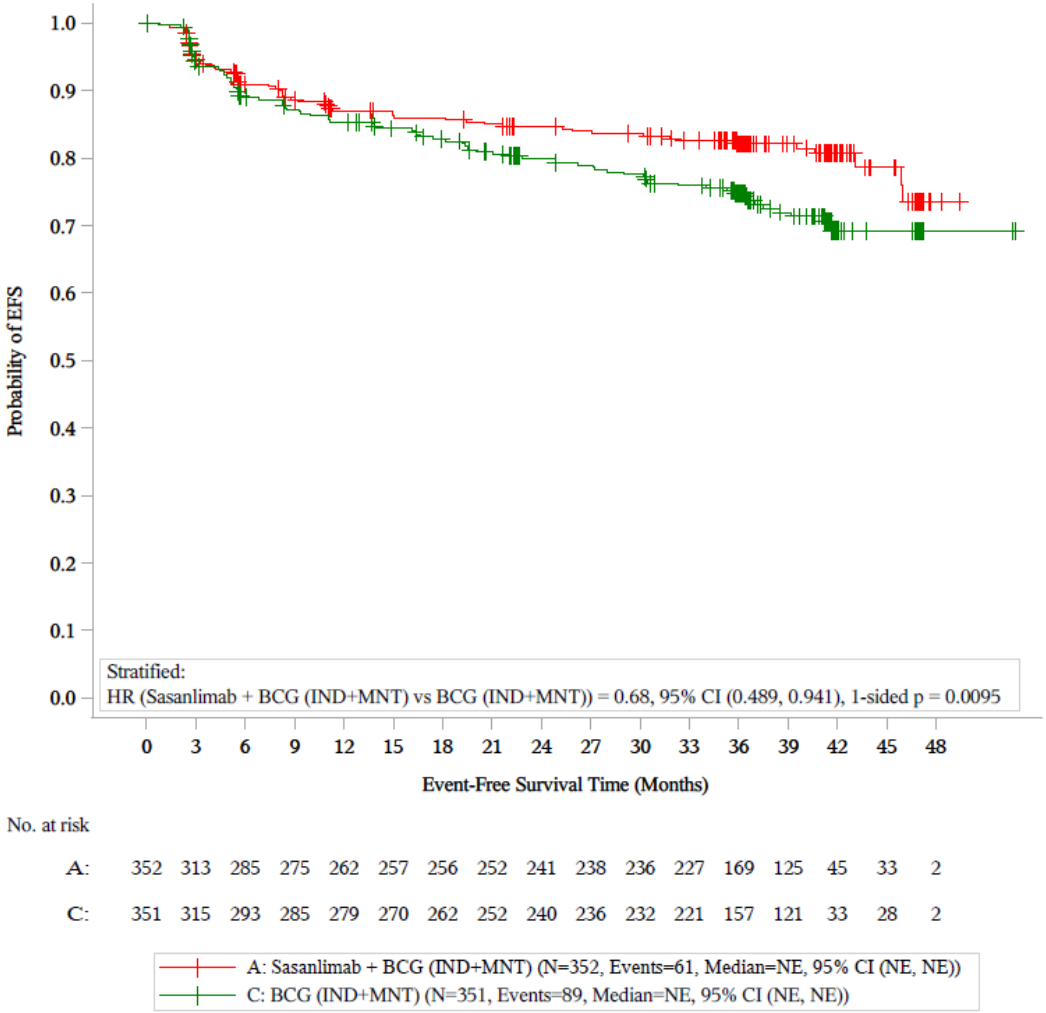
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group. NE = Not Estimable.
Progression of disease: Lamina propria invasion (e.g., increase from Ta/CIS to T1); Muscle invasive disease; Lymph node positive disease; Metastatic disease; high-grade Ta/T1 in patients with CIS only at baseline before achieving a CR.
a. CIs are derived using the log-log transformation with back transformation to untransformed scale.
b. CIs are calculated using the Brookmeyer and Crowley method.
c. Stratified by randomization stratification factors: CIS and geographic region. IRT stratification values used.
d. Hazard ratio is based on stratified Cox proportional hazards model.
e. p-value based on stratified log-rank test.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Table 24 summarizes the type of progressive disease (PD) event for investigator-assessed EFS.

Table 24: Summary of type of PD event for investigator-assessed EFS (primary analysis)

	Sasanlimab + BCG (IND+MNT) (N=352) n (%)	Sasanlimab + BCG (IND) (N=352) n (%)	BCG (IND+MNT) (N=351) n (%)
Investigator Assessment PD for EFS Primary Analysis	18	14	22
Progression to Metastatic Disease (N+, M+)	3 (16.67%)	2 (14.29%)	7 (31.82%)
Progression to Muscle Invasive (>= T2)	7 (38.89%)	3 (21.43%)	7 (31.82%)
Stage Progression (TaHG, T1)	7 (38.89%)	9 (64.29%)	7 (31.82%)
Unknown	1 (5.56%)	0	1 (4.55%)

Figure 12: Kaplan-Meier plot of investigator-assessed EFS (primary analysis) – FAS



Sensitivity analyses

For brevity, not all (results of the) sensitivity analyses are included in this report.

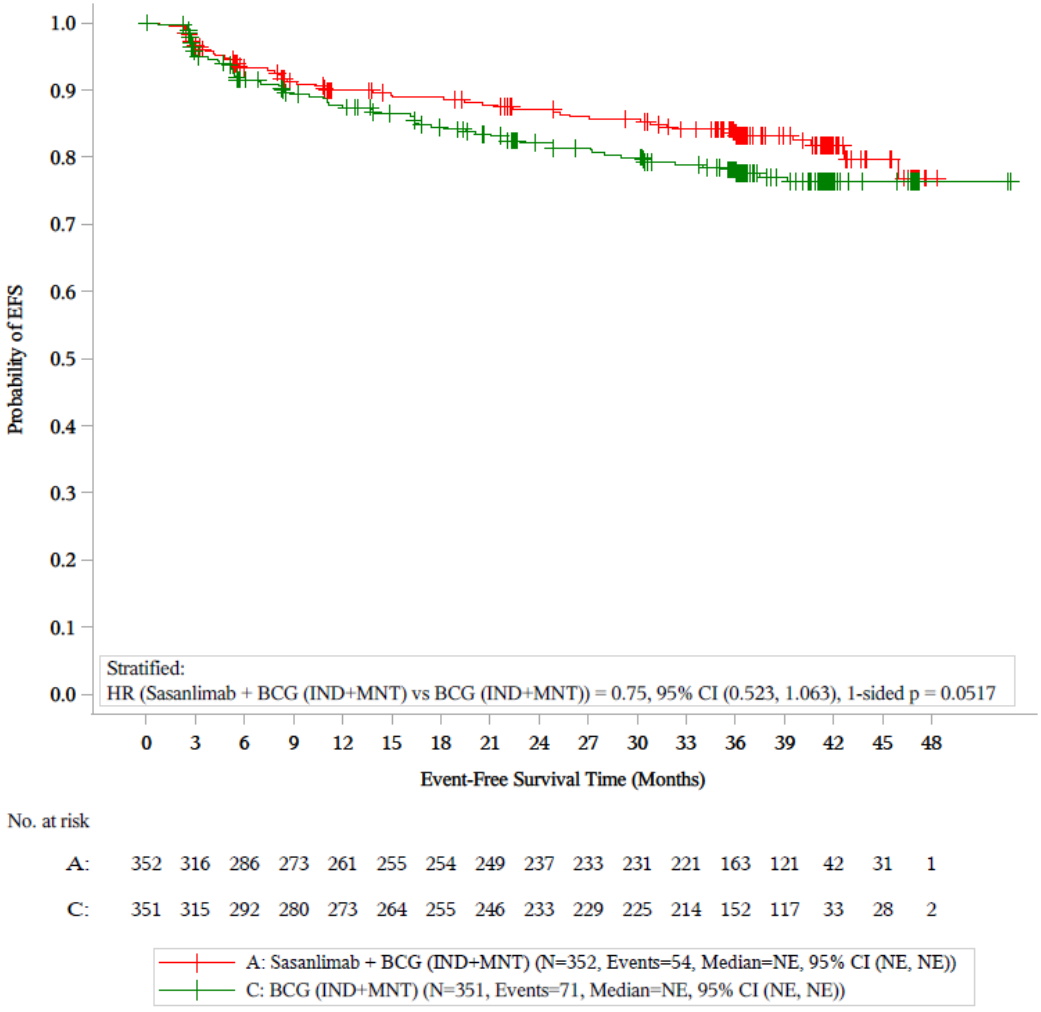
<u>EFS based on BICR Assessment</u>

For this sensitivity analysis, the observed stratified HR was 0.75 (95% CI: 0.523, 1.063; 2-sided p=0.1035) (Table 25 and Figure 13).

Table 25: Summary of BICR-assessed EFS (sensitivity analysis) - FAS

	Sasanlimab + BCG (IND+MNT) (N=352)	BCG (IND+MNT) (N=351)
Participants with event, n (%)	54 (15.3)	71 (20.2)
Type of event, n (%)		
Progressive disease	11 (3.1)	15 (4.3)
Recurrence of high-grade disease	25 (7.1)	40 (11.4)
Persistence of CIS	2 (0.6)	3 (0.9)
Death	16 (4.5)	13 (3.7)
Participants censored, n (%)	298 (84.7)	280 (79.8)
Reason for censoring, n (%)		
No adequate baseline assessment	2 (0.6)	3 (0.9)
Event after 2 or more missing assessments	10 (2.8)	3 (0.9)
Withdrawal of consent	30 (8.5)	27 (7.7)
Lost to follow-up	6 (1.7)	2 (0.6)
No adequate post-baseline disease assessment	1 (0.3)	0
Ongoing without an event	249 (70.7)	245 (69.8)

Figure 13: Kaplan-Meier Plot of BICR-assessed EFS (sensitivity analysis) - FAS



EFS based on Investigator Assessment for Patients in the Per-Protocol Analysis Set

For this sensitivity analysis, the observed stratified HR was 0.64 (95% CI: 0.459, 0.899; 2-sided p=0.0092).

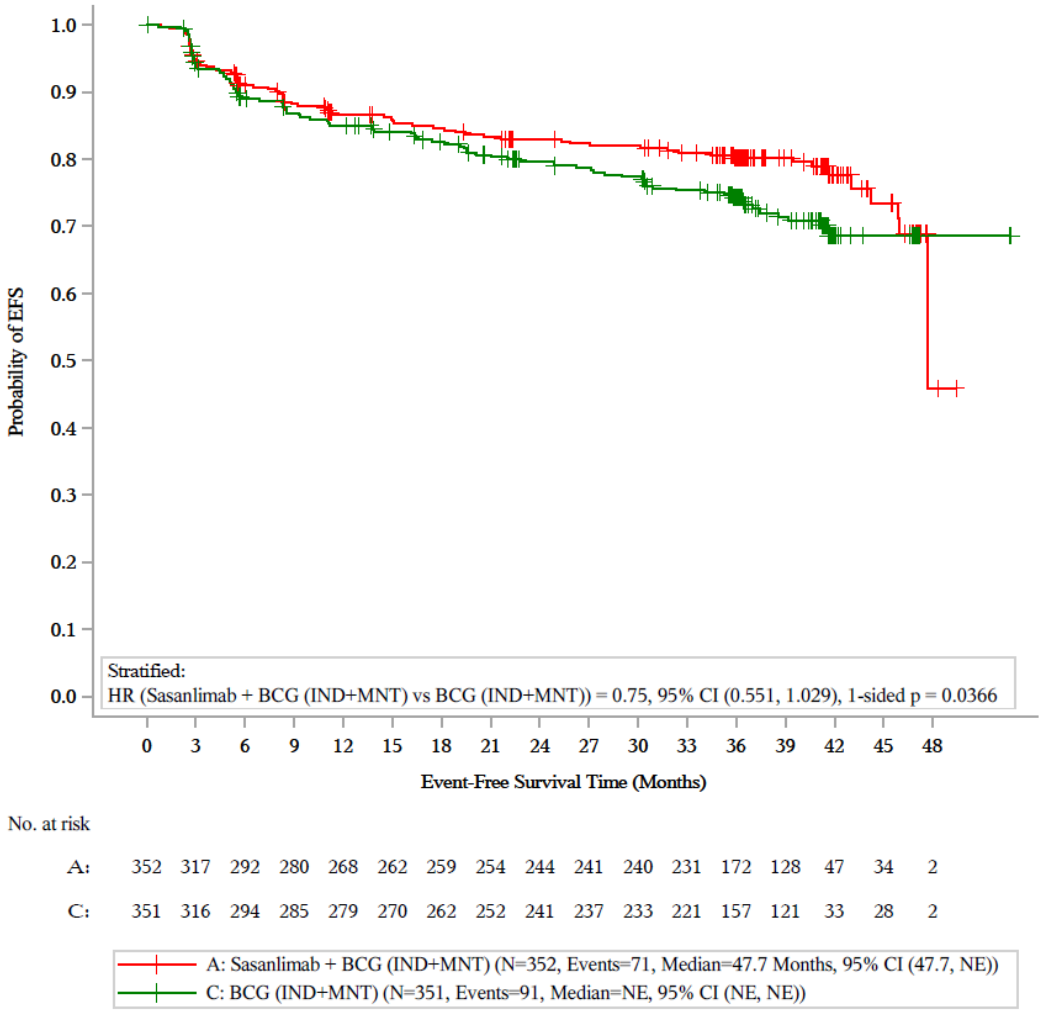
EFS When Events are Not Censored After 2 Missing Disease Assessments (i.e., counting all events)

For this sensitivity analysis, the observed stratified HR was 0.75 (95% CI: 0.551, 1.029; 2-sided p=0.0732) (Table 26 and Figure 14).

Table 26: Summary of investigator-assessed EFS not censoring events after ≥2 missing or inadequate post-baseline disease assessments (i.e., counting all events; sensitivity analysis) - FAS

	Sasanlimab + BCG (IND+MNT) (N=352)	BCG (IND+MNT) (N=351)
Participants with event, n (%)	71 (20.2)	91 (25.9)
Type of event, n (%)		
Progressive disease	21 (6.0)	22 (6.3)
Recurrence of high-grade disease	27 (7.7)	55 (15.7)
Persistence of CIS	1 (0.3)	1 (0.3)
Death	22 (6.3)	13 (3.7)
Participants censored, n (%)	281 (79.8)	260 (74.1)
Reason for censoring, n (%)		
No adequate baseline assessment	2 (0.6)	3 (0.9)
Withdrawal of consent	29 (8.2)	26 (7.4)
Lost to follow-up	5 (1.4)	2 (0.6)
No adequate post-baseline disease assessment	1 (0.3)	0
Ongoing without an event	244 (69.3)	229 (65.2)

Figure 14: Kaplan-Meier plot of investigator-assessed EFS not censoring events after ≥2 missing or inadequate post-baseline disease assessments (i.e., counting all events; sensitivity analysis) - FAS



The study was not significantly impacted by the consequences of the COVID-19 global pandemic. Due to low numbers of patients reported with COVID-19 (<20% in any arm), the reporting criteria were not met to perform sensitivity analyses for efficacy endpoints, as described in the section 'Statistical methods for estimation and sensitivity analysis'.

Key secondary objective – investigator-assessed EFS (Arm B vs Arm C)

The study did not meet this key secondary objective; sasanlimab + BCG (IND) did not result in prolongation of EFS when compared with BCG (IND+MNT). The observed stratified HR was 1.16 (95% CI: (0.870, 1.552); 2-sided p-value: 0.3121).

This subsection is shaded grey since the comparison of Arm B vs Arm C is not relevant for the proposed indication and posology. For the same reason, (further) results for this key secondary objective are not included in this report.

Key secondary objective – OS (Arm A vs Arm C)

Primary analysis

At the time of FA for EFS, an IA of OS was performed. **The study did not meet this key secondary objective**; no (statistically significant) improvement in OS was observed in the sasanlimab + BCG (IND+MNT) arm compared with the BCG (IND+MNT) arm.

Few deaths were considered treatment-related; refer to Table 39 and Table 40 for additional details about causes of death, and below subsection on disease-specific survival (DSS). OS is summarized in Table 27 and Figure 15.

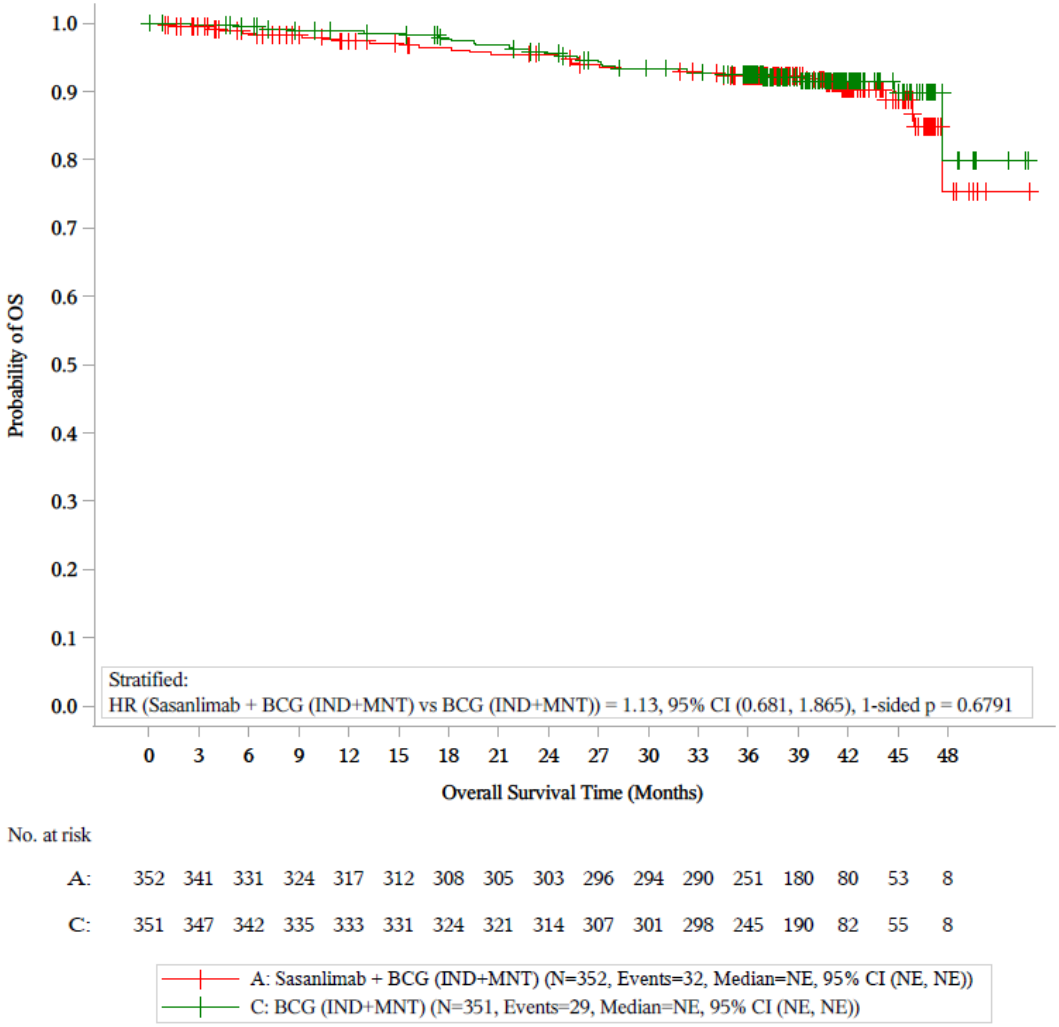
The median (95% CI) time of follow-up for OS was 40.8 (39.1, 41.3) months in Arm A and 41.2 (39.8, 41.3) months in Arm C.

Table 27: Summary of OS (primary analysis) - FAS

	Sasanlimab+BCG (IND+MNT) (N=352)	Sasanlimab+BCG (IND) (N=352)	BCG (IND+MNT) (N=351)
Patients with event, n (%)	32 (9.1)	30 (8.5)	29 (8.3)
Patients censored, n (%)	320 (90.9)	322 (91.5)	322 (91.7)
Reason for censoring, n (%)			
Withdrawal of consent	32 (9.1)	38 (10.8)	30 (8.5)
Lost to follow-up[a]	8 (2.3)	7 (2.0)	3 (0.9)
Alive	280 (79.5)	277 (78.7)	289 (82.3)
Probability of being event-free (95% CI) [b]			
at 12 months	0.973 (0.949, 0.986)	0.968 (0.943, 0.982)	0.988 (0.969, 0.996)
at 24 months	0.955 (0.926, 0.972)	0.946 (0.916, 0.966)	0.955 (0.927, 0.973)
at 36 months	0.923 (0.888, 0.947)	0.920 (0.885, 0.945)	0.924 (0.890, 0.948)
at 48 months	0.754 (0.510, 0.888)	0.896 (0.850, 0.928)	0.799 (0.526, 0.925)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [c]			
Q1	NE (47.7, NE)	NE (NE, NE)	NE (47.7, NE)
Median	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q3	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Stratified analysis [d] Comparison vs BCG (IND+MNT)			
Hazard Ratio [e]	1.13	1.07	
95% CI [e]	0.681, 1.865	0.643, 1.787	
RCI [f]	0.433, 2.931	0.406, 2.827	
1-sided p-value [g]	0.6791	0.6043	
2-sided p-value [g]	0.6419	0.7914	

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group. NE = Not Estimable
a. Includes patients deemed to be lost to follow-up by the Investigator and patients with last follow-up > 365 days prior to data cutoff (02DEC2024).
b. CIs are derived using the log-log transformation with back transformation to untransformed scale.
c. CIs are calculated using the Brookmeyer and Crowley method.
d. Stratified by presence of carcinoma in situ (Yes vs No) at randomization and geography (US vs Western Europe and Canada vs Rest of World [ROW]). IRT stratification values used.
e. Hazard ratio based on stratified Cox proportional hazards model.
f. Repeated confidence interval method used to take into account the group-sequential nature of the design.
g. p-value based on stratified log-rank test.
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Figure 15: Kaplan-Meier Plot of OS (primary analysis) - FAS



Sensitivity analyses

For brevity, the (results of) the OS sensitivity analyses are not included in this report.

Key secondary objective –OS (Arm B vs Arm C)

The study did not meet this key secondary objective; no (statistically significant) improvement in OS was observed in the sasanlimab + BCG (IND) arm compared with the BCG (IND+MNT) arm. The observed stratified HR was 1.07 (95% CI: (0.643, 1.787); 2-sided p-value: 0.7914).

This subsection is shaded grey since the comparison of Arm B vs Arm C is not relevant for the proposed indication and posology. For the same reason, (further) results for this key secondary objective are not included in this report.

Secondary objective (non-key) – investigator-assessed CR rate and DoCR for patients with CIS at randomization

CR based on investigator assessment is summarized in Table 28. DoCR is presented in Table 29.

Table 28: Summary of investigator-assessed CR - patients with CIS at randomization in the FAS

	Sasanlimab+BCG (IND+MNT) (N=88)	Sasanlimab+BCG (IND) (N=93)	BCG (IND+MNT) (N=88)
Complete response (CR), n (%)	79 (89.8)	82 (88.2)	75 (85.2)
95% CI [a]	81.5, 95.2	79.8, 93.9	76.1, 91.9
Reason for non-CR, n (%)			
Disease assessment of non-CR	7 (8.0)	8 (8.6)	7 (8.0)
No adequate post-baseline assessment	2 (2.3)	3 (3.2)	6 (6.8)
Stratified analysis of CR rate Comparison vs BCG (INT and MNT)[b]			
Difference in CR Rates (%)	4.4	2.9	
95% CI [c]	-5.4, 14.2	-7.0, 12.8	
1-sided p-value [d]	0.1878	0.2815	
2-sided p-value [d]	0.3755	0.563	

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
The denominator to calculate percentages is N, the number of patients with CIS at Randomization in the full analysis set within each treatment group
a. Clopper-Pearson method used.
b. Stratified by geography (US vs Western Europe and Canada vs Rest of World [ROW]). IRT stratification values used
c. CIs are calculated using Mantel-Haenszel confidence limits
d. nominal p-value based on Mantel-Haenszel test
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Table 29: Summary of investigator-assessed DoCR - patients with CIS at randomization who achieved CR in the FAS

	Sasanlimab+BCG (IND+MNT) (N=79)	Sasanlimab+BCG (IND) (N=82)	BCG (IND+MNT) (N=75)
Patients with event, n (%)	8 (10.1)	21 (25.6)	20 (26.7)
Type of event, n (%)			
Progressive disease	3 (3.8)	4 (4.9)	6 (8.0)
Recurrence of high-grade disease	1 (1.3)	11 (13.4)	10 (13.3)
Death	4 (5.1)	6 (7.3)	4 (5.3)
Patients censored, n (%)	71 (89.9)	61 (74.4)	55 (73.3)
Reason for censoring, n (%)			
Event after 2 or more missing assessments	4 (5.1)	0	0
Withdrawal of consent	3 (3.8)	5 (6.1)	5 (6.7)
Lost to follow-up	0	1 (1.2)	0
Ongoing without an event	64 (81.0)	55 (67.1)	50 (66.7)
Probability of being event-free (95% CI) [a]			
at 6 months	1.000 (1.000, 1.000)	0.883 (0.787, 0.937)	0.931 (0.841, 0.970)
at 12 months	0.973 (0.897, 0.993)	0.842 (0.739, 0.907)	0.903 (0.807, 0.952)
at 18 months	0.946 (0.862, 0.979)	0.800 (0.690, 0.875)	0.861 (0.757, 0.923)
at 24 months	0.932 (0.843, 0.971)	0.800 (0.690, 0.875)	0.847 (0.741, 0.912)
at 36 months	0.917 (0.825, 0.962)	0.768 (0.652, 0.849)	0.677 (0.529, 0.787)
at 48 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]			
Q1	NE (43.1, NE)	36.0 (12.9, NE)	34.1 (24.5, NE)
Median	NE (NE, NE)	44.6 (44.6, NE)	NE (39.3, NE)

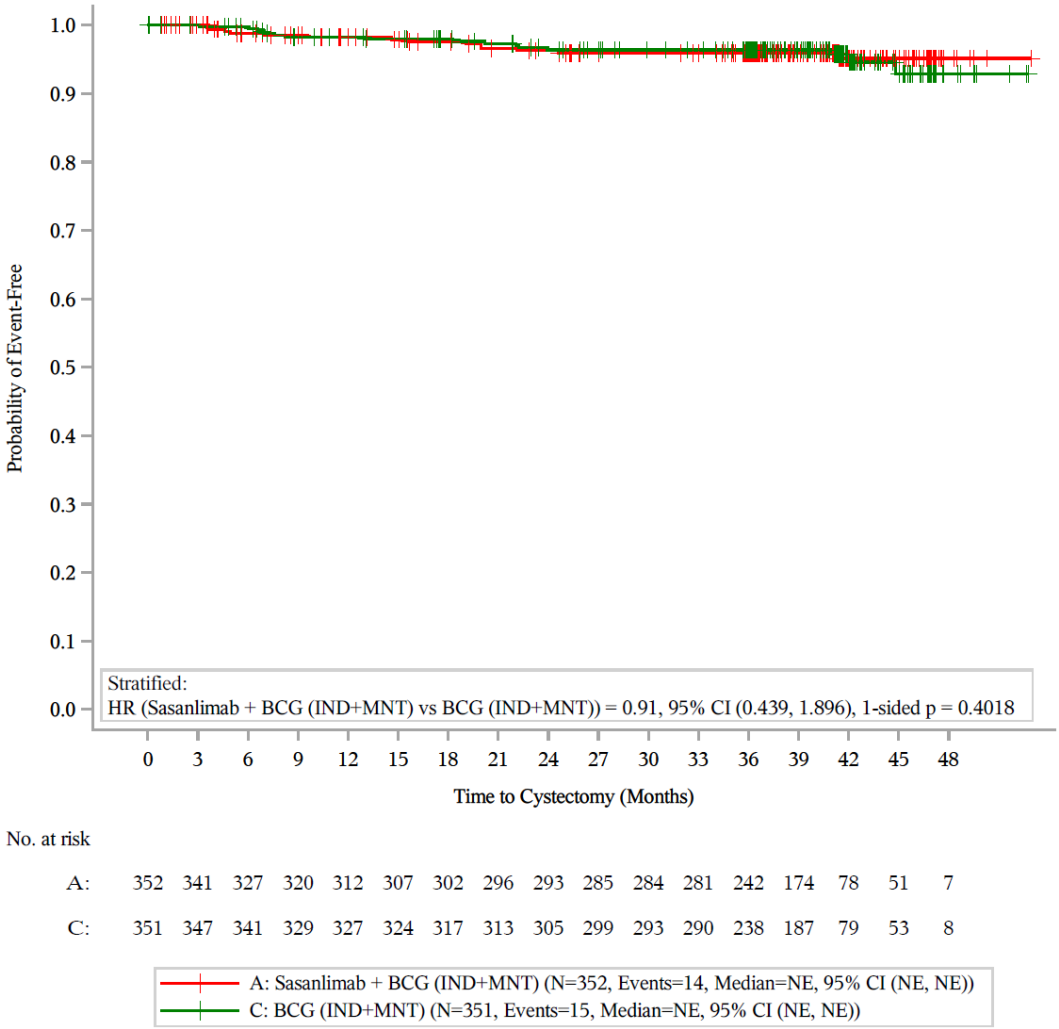
	Sasanlimab+BCG (IND+MNT) (N=79)	Sasanlimab+BCG (IND) (N=82)	BCG (IND+MNT) (N=75)
Q3	NE (NE, NE)	NE (44.6, NE)	NE (NE, NE)

Note: The column for Arm B which is not relevant for the proposed indication and posology is shaded grey.
a. CIs are derived using the log-log transformation with back transformation to untransformed scale.
b. CIs are calculated using the Brookmeyer and Crowley method.
NE = Not Estimable
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024)

Secondary objective (non-key) – time to cystectomy

Overall, 14 (4.0%) and 15 (4.3%) patients underwent RC in the sasanlimab + BCG (IND+MNT) and BCG (IND+MNT) arms, respectively. The stratified HR for the comparison of sasanlimab + BCG (IND+MNT) vs BCG (IND+MNT) was 0.91 [95% CI: 0.439, 1.896]), with medians of NE (95% CI: NE, NE) and NE (95% CI: NE, NE), respectively (Figure 16).

Figure 16: Kaplan-Meier plot of investigator-assessed time to cystectomy - FAS



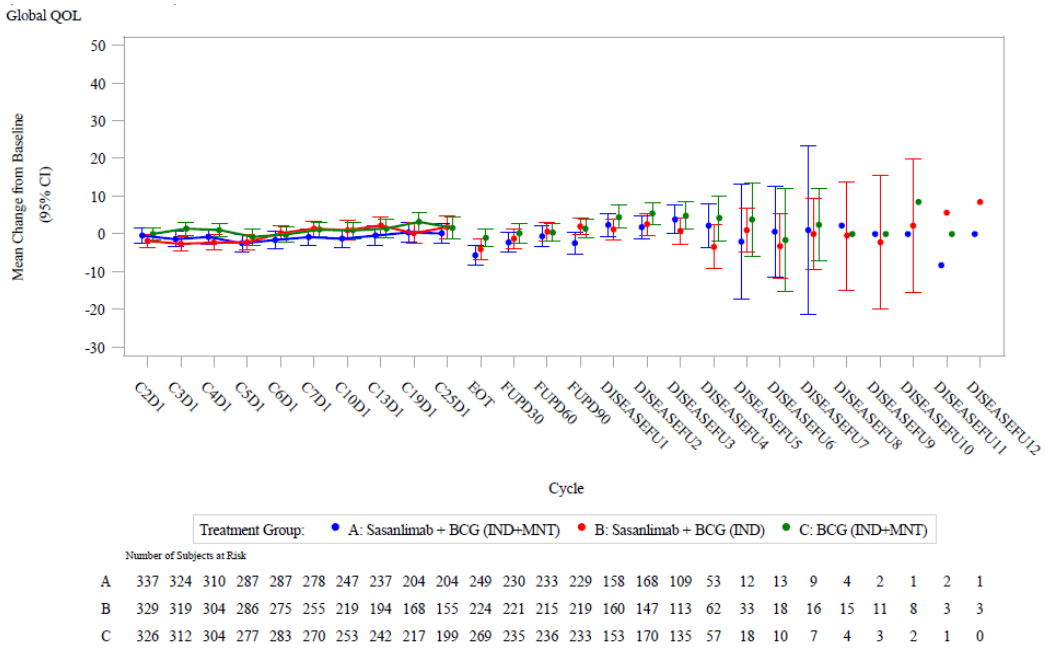
Secondary objective (non-key) – PRO endpoints

EORTC QLQ-C30

Mean change over baseline for Global Health Score is presented in Figure 17.

- Completion Rates: In all randomized patients, completion rates for the QLQ-C30 for the sasanlimab + BCG (IND+MNT) arm were >84% across all visits. Completion rates for the QLQ-C30 for the BCG (IND+MNT) arm were >85% across all visits through the end-of-treatment visit (Cycle 25).
- Descriptive Summaries: Change from baseline for QLQ-C30 Global Health Score/QoL and all subscales were numerically similar between the sasanlimab + BCG (IND+MNT) arm and the BCG (IND+MNT) arm in all randomized patients.
- Random Coefficient Models: Results for the QLQ-C30 mixed model analysis were similar between the sasanlimab + BCG (IND+MNT) arm and the BCG (IND+MNT) arm in all randomized patients.

Figure 17: Plot of mean change from baseline over time for EORTC QLQ-C30 by visit



Number of Subjects at Risk

A	337	324	310	287	287	278	247	237	204	204	249	230	233	229	158	168	109	53	12	13	9	4	2	1	2	1
B	329	319	304	286	275	255	219	194	168	155	224	221	215	219	160	147	113	62	33	18	16	15	11	8	3	3
C	326	312	304	277	283	270	253	242	217	199	269	235	236	233	153	170	135	57	18	10	7	4	3	2	1	0

The last assessment prior to randomization will serve as the baseline assessment, if such a value is missing, the last assessment prior to the date of first dose of study treatment will be used as the baseline assessment.
95% CI of mean change from baseline scores is truncated to be in (-100, 100).
95% CI not estimated for visits with n <5.

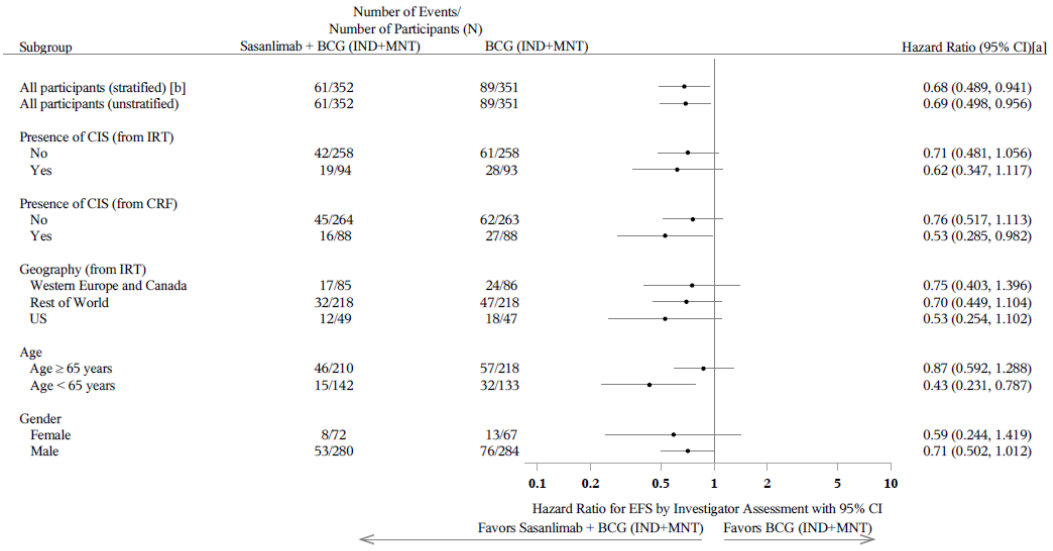
For brevity, not all (results for the) PRO endpoints are included in this report.

Pre-defined and ad-hoc important subgroup analyses

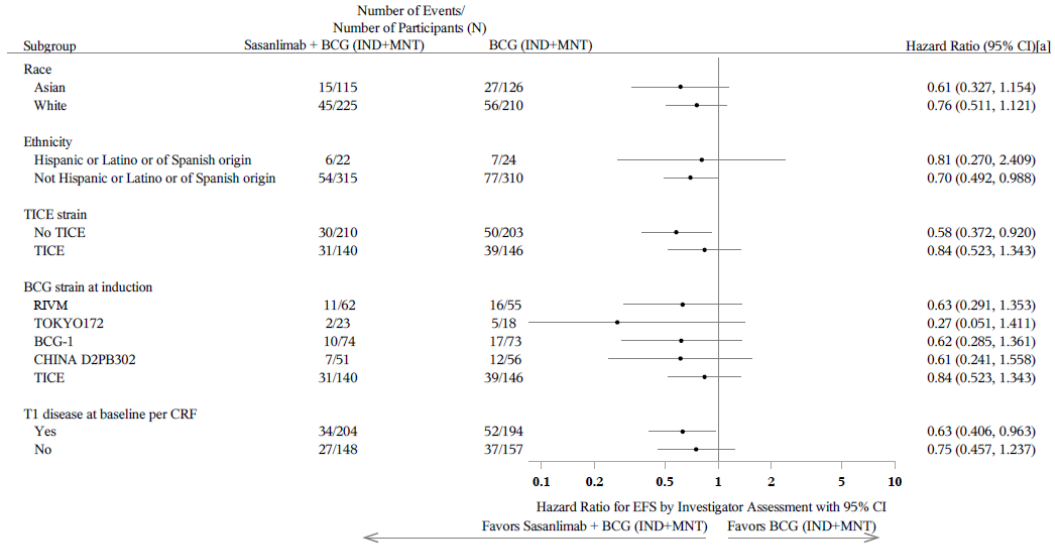
Primary objective – investigator-assessed EFS (Arm A vs Arm C) – subgroup analyses

See Figure 18 for the forest plot summary of subgroup analyses for EFS per investigator assessment.

Figure 18: Forest plot of investigator-assessed EFS - FAS



N is the number of participants in the full analysis set within each subgroup and treatment group.
[a]. Hazard ratios and associated CIs are calculated using stratified Cox proportional hazard model.
[b]. Stratified by presence of carcinoma in situ (Yes vs No) at randomization and geography (US vs Western Europe and Canada vs Rest of World [ROW]). IRT stratification values used.
All analyses by subgroups are unstratified.
Plot is presented on log scale (base=2).
Black or African American is not summarized due to number of participants is < 5% of the FAS.
PFIZER CONFIDENTIAL SDTM Creation: 19DEC2024 (17:50) Source Data: adtte Table Generation: 22JAN2025 (16:53)
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024) Output File: ./b8011006/B8011006_CSR1/adtte_efs_f003

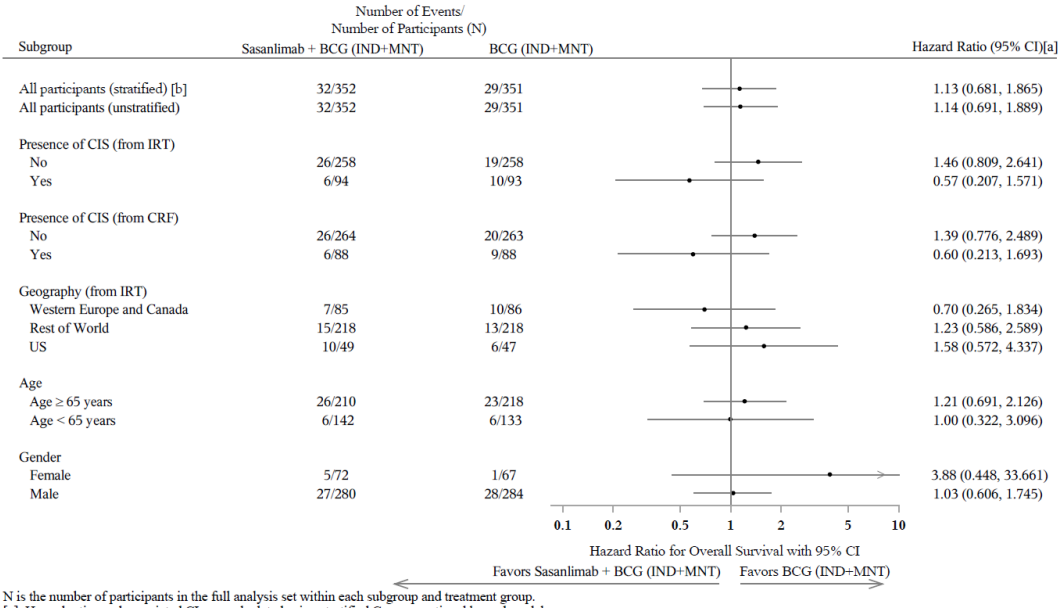


N is the number of participants in the full analysis set within each subgroup and treatment group.
[a]. Hazard ratios and associated CIs are calculated using stratified Cox proportional hazard model.
[b]. Stratified by presence of carcinoma in situ (Yes vs No) at randomization and geography (US vs Western Europe and Canada vs Rest of World [ROW]). IRT stratification values used.
All analyses by subgroups are unstratified.
Plot is presented on log scale (base=2).
Black or African American is not summarized due to number of participants is < 5% of the FAS.
PFIZER CONFIDENTIAL SDTM Creation: 19DEC2024 (17:50) Source Data: adtte Table Generation: 22JAN2025 (16:53)
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024) Output File: ./b8011006/B8011006_CSR1/adtte_efs_f003

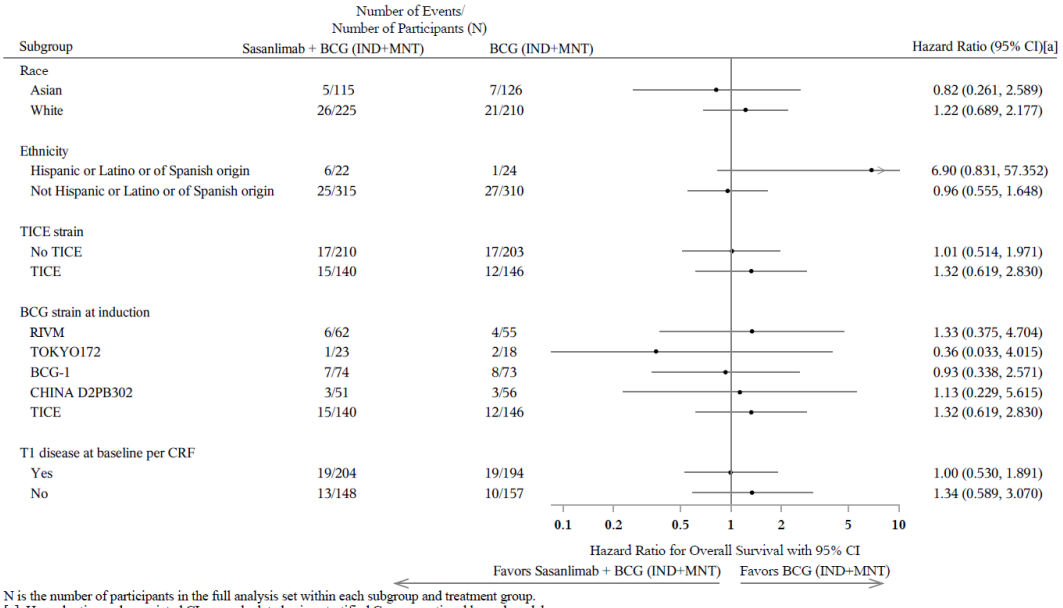
Key secondary objective – OS (Arm A vs Arm C) – subgroup analyses

See Figure 19 for the forest plot summary of subgroup analyses for OS.

Figure 19: Forest plot of OS - FAS



N is the number of participants in the full analysis set within each subgroup and treatment group.
[a]. Hazard ratios and associated CIs are calculated using stratified Cox proportional hazard model.
[b]. Stratified by presence of carcinoma in situ (Yes vs No) at randomization and geography (US vs Western Europe and Canada vs Rest of World [ROW]). IRT stratification values used.
All analyses by subgroups are unstratified.
Plot is presented on log scale (base=2).
Black or African American is not summarized due to number of participants is < 5% of the FAS.
PFIZER CONFIDENTIAL SDTM Creation: 19DEC2024 (17:50) Source Data: adtte Table Generation: 22JAN2025 (16:53)
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024) Output File: ./b8011006/B8011006_CSR1/adtte_os_f003



N is the number of participants in the full analysis set within each subgroup and treatment group.
[a]. Hazard ratios and associated CIs are calculated using stratified Cox proportional hazard model.
[b]. Stratified by presence of carcinoma in situ (Yes vs No) at randomization and geography (US vs Western Europe and Canada vs Rest of World [ROW]). IRT stratification values used.
All analyses by subgroups are unstratified.
Plot is presented on log scale (base=2).
Black or African American is not summarized due to number of participants is < 5% of the FAS.
PFIZER CONFIDENTIAL SDTM Creation: 19DEC2024 (17:50) Source Data: adtte Table Generation: 22JAN2025 (16:53)
(Data cutoff date : 02DEC2024 Database snapshot date : 19DEC2024) Output File: ./b8011006/B8011006_CSR1/adtte_os_f003

Ancillary analyses

Adjusted analyses were performed using a multivariable Cox regression model. The covariates that were used to define the subgroups were also used for adjusted analyses. Using a stepwise approach with level of significance for entering the model of 0.15 and level of significance for removing from the model of 0.40, presence of CIS, geography, age, gender and T1 at baseline remained in the final model (Table 30).

Table 30: Multivariate Cox regression analysis for investigator assessed EFS - FAS

Variables [a]	Levels	Parameter Estimate	Standard Error	Wald Chi-Square Statistic	p-value	Hazard Ratio	95% CI
Treatment Group	Sasanlimab + BCG (IND+MNT)	-0.382	0.1669	5.24	0.0220	0.68	0.492, 0.946
	BCG (IND+MNT) (Reference)						
Presence of CIS (from IRT)	No	-0.219	0.1824	1.44	0.2302	0.80	0.562, 1.149
	Yes (Reference)						
Geography (from IRT)	Western Europe and Canada	-0.368	0.2420	2.32	0.1281	0.69	0.431, 1.112
	Rest of World	-0.672	0.2237	9.03	0.0027	0.51	0.329, 0.792
	US (Reference)						
Age	Age ≥ 65 years	0.339	0.1791	3.59	0.0583	1.40	0.988, 1.994
	Age < 65 years (Reference)						
Gender	Female	-0.452	0.2363	3.66	0.0558	0.64	0.401, 1.011
	Male (Reference)						
T1 disease at baseline	Yes	0.276	0.1763	2.45	0.1177	1.32	0.933, 1.861
	No (Reference)						

a. Explanatory variables are selected using stepwise selection procedure. The level of significance for an explanatory variable to enter the model is set to 0.15 and the significance level for removing it is set to 0.40.
Black or African American is not summarized due to number of participants is < 5% of the FAS.

5.3.3. Subgroup analyses/clinical studies in special populations

No specific information on clinical efficacy studies in special populations, e.g., in the elderly, and in patients with renal or hepatic impairment, could be located in the application dossier.

Zumrad is not indicated for use in paediatric patients. A product-specific waiver was granted for studies in paediatric patients (EMEA-002777-PIP01-20; P/0290/2020).

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive studies

See Table 1. The Phase 1 Study B8011001 (Johnson et al. JAMA Oncol. 2019; Cho et al. ESMO Open. 2023) and the Phase 1b/2 Study B8011007 (Penkov et al. Ther Adv Med Oncol. 2024), however, only enrolled patients with locally advanced or metastatic solid tumours. These studies are, therefore, not considered supportive for the assessment of efficacy for the proposed indication in BCG-naïve, HR NMIBC.

Patient Preference Study B8011013

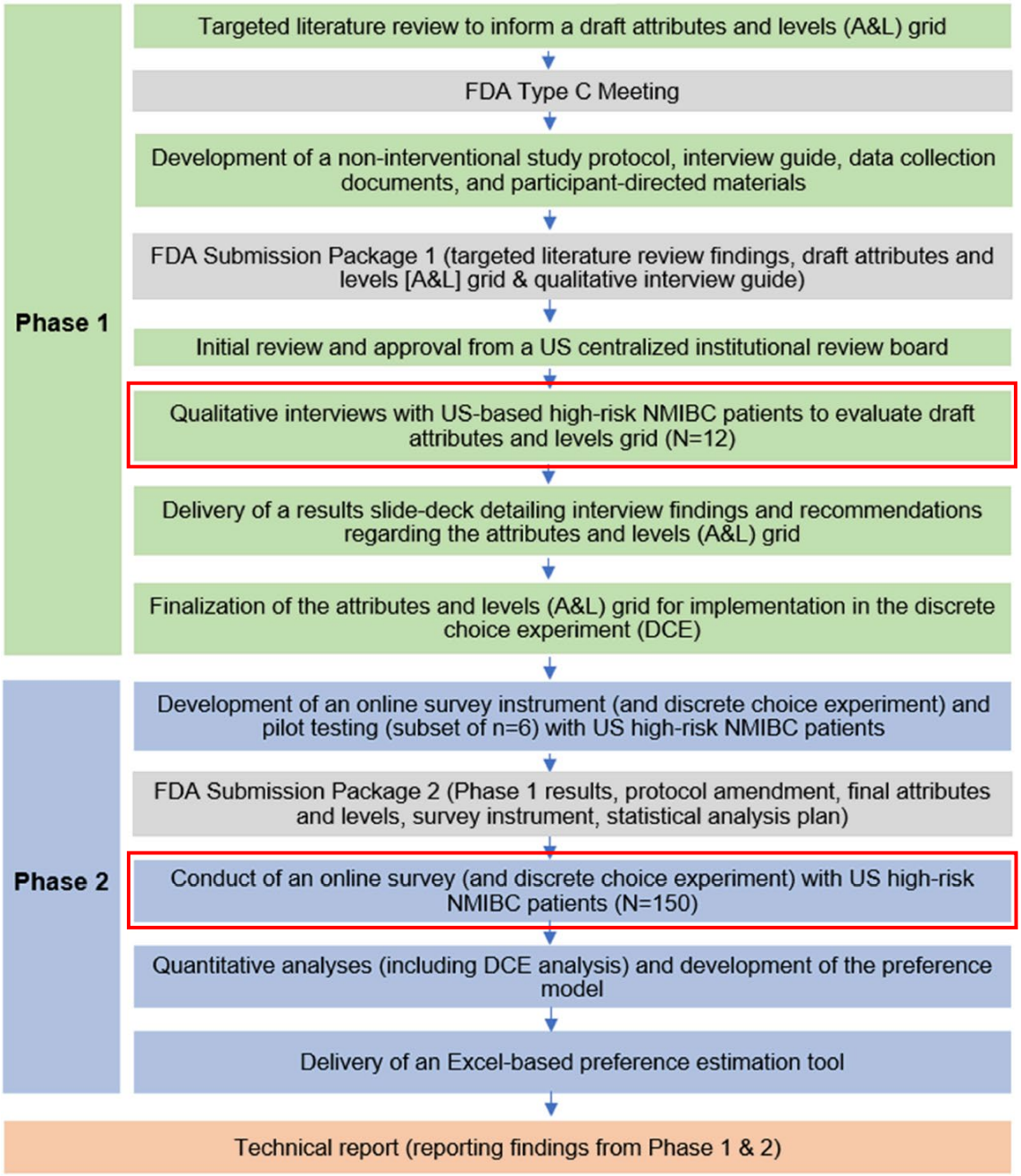
To gain an understanding on the perspectives and preferences held by patients with HR NMIBC regarding current and potential treatment options for their disease, a Discrete Choice Experiment (DCE) was conducted to elicit their treatment preferences. The official title of this supportive study is 'Patient Preferences in NMIBC: A Discrete Choice Experiment (see also Table 1).

The overall objective of this study was to quantify patient preferences for attribute levels relating to investigational PD-(L)1 regimens used in combination with BCG as alternatives to SOC (BCG alone) to treat patients with HR NMIBC. Attributes of interest in this study included efficacy/progression outcomes, safety outcomes, and process/administration related characteristics.

This was a cross-sectional, primary data collection, non-interventional study. Qualitative and quantitative evidence-generation activities with US-based HR-NMIBC patients were conducted in two

phases. Figure 20 summarizes the sequence of study activities conducted for each phase.
Phase 1 focused on the development and content validation of a draft set of attributes and levels (A&L grid) to be used in the DCE (Phase 2). Specific activities in Phase 1 included the conduct of a targeted literature review and qualitative interviews with US-based HR-NMIBC patients (n=12).
Phase 2 focused on the administration of an online DCE survey among this study population (N=150), from which individual-level preference estimates for attribute levels relating to PD-(L)1 inhibitors (ICIs, hereafter) and BCG were derived statistically.

Figure 20: Overview of the two-phase design of patient preference study B8011013



The DCE quantified preferences for attribute levels related to BCG and ICIs. Attributes and levels were informed by a literature review, patient interviews, regulatory scientific advice, clinical experts, and a patient advocate. Patients completed a set of experimentally-designed hypothetical choice tasks, including the following attributes:

- Administration mode and frequency for ICIs and BCG (IND+MNT)

- Median EFS
- AEs (i.e., bladder AEs, chronic endocrine conditions, serious immune AEs).

Hierarchical Bayesian modelling estimated preference weights for attribute levels. Relative attribute importance was calculated as the mean of the maximum utility difference for each attribute as a proportion of the maximum utility differences of all attributes for all patients in the sample.

Summary of Results and Interpretation

Overall, 150 US patients with HR NMIBC completed the survey. The sample was 51% male, had a median age of 63 years (range: 49-74), and was diverse by race (Caucasian 46%; African American/Black 27%; Other 27%) and ethnicity (Hispanic/Latino/Spanish 21%).
Regarding BCG status, 51% of patients were BCG-naïve and 49% BCG-experienced. On average, those patients with experience of BCG had received BCG therapy 8 times (range 3-14). No patients had received chemotherapy to treat their bladder cancer, nor were actively participating in a clinical trial.
A total of 38% of patients reported experiencing at least one bladder-related symptom. Symptoms relating to ICI AEs (namely, thyroid problems 1.3%; adrenal gland problems 0%) were reported by very few (if any) patients in the survey sample.

On average, relative attribute importance was highest for the EFS attribute (27%), indicating that this attribute was the most important driver of treatment choice given the attributes and levels included defining the hypothetical treatments in this study. The safety attributes were next most important: bladder problems (27%); serious immune AEs (14%), and chronic endocrine conditions (10%). Administration-related attributes had lower relative importance scores but still impacted treatment choice. The most important administration attributes were ICI frequency (6%) and ICI administration (6%). The BCG schedule attribute (6%) is the least important attribute overall. Relative importance was lowest (4%) for therapy type (ICI alone, BCG alone, or ICI & BCG) when considered independently of other administration attributes.
Contrary to the above model-derived relative importance scores (where bladder problems had the highest level of importance among the safety-related attributes), fewer patients (47%) rated bladder problems as extremely important (i.e., as a 9 or 10 on the 0-10 numerical rating scale) compared with chronic endocrine conditions and serious immune AEs (both 61%). EFS was (again) most frequently rated by patients as an extremely important attribute (71%).

According to the Applicant, this study demonstrated that patients with HR NMIBC have a strong preference towards treatments with improved EFS outcomes and those which prolong the time to potential cystectomy. The findings highlight the value of treatments which can prolong the time to disease recurrence or progression and demonstrates the importance of bladder preservation from the patient perspective, so highlighting the value of improved bladder-sparing strategies. These findings are consistent with another DCE that recently explored treatment preferences among NMIBC patients and align broadly with DCE findings in other oncology patient populations in which attributes relating to survival/progression outcomes are most frequently ranked as the most important attributes (Smith et al. J Clin Oncol. 2025 [abstract]; Collacott et al. Patient. 2021).

The bladder-problems attribute had the second-highest relative importance, meaning the risk of bladder-related AEs was the second most important attribute among attributes tested. Additionally, the bladder-problems attribute was the most important safety-related attribute, with attributes associated with ICIs (i.e., serious immune AEs and chronic endocrine conditions) being less important to patients with HR NMIBC over the ranges presented in the study.

The reported preference weights were used to calculate predicted choice probabilities for the treatment arms included in CREST, sasanlimab + BCG (IND+MNT) and BCG (IND+MNT). The predicted choice probability is the average probability that an individual in the sample would choose a specific

alternative when presented with two or more alternatives. To conduct this analysis, it was necessary to make two key assumptions. First, because median EFS was not yet reached in either arm in CREST, it was assumed that the difference in median EFS between the two arms corresponds to the difference of 10 months in first-quartile EFS: 46 months for sasanlimab + BCG (IND+MNT) vs 36 months for BCG (IND+MNT). Because the highest level of EFS in the DCE was 36 months, it was necessary to extrapolate the preference weights beyond the maximum level of EFS. To conduct this extrapolation, the utility of each additional month of EFS beyond 36 months was assumed to be 0.75 times the average utility of each additional month of EFS in the DCE. The 0.75 factor was added to ensure a conservative approach to the extrapolation because the actual utility of each additional month beyond 36 months is unknown. However, when a 50% discount factor was applied, the model predicted a greater probability that patients would select the BCG (IND+MNT) profile (53%) relative to the sasanlimab + BCG (IND+MNT) profile (47%). Specifically, a greater relative probability of selecting the sasanlimab + BCG (IND+MNT) profile over the BCG (IND+MNT) profile was observed until a dampening factor of 41% was applied.

The resulting analysis indicates that the sasanlimab + BCG (IND+MNT) profile is likely to have a greater predicted choice probability (56%) than the BCG (IND+MNT) profile (44%). Therefore, it is likely that patients will perceive the EFS benefits of sasanlimab + BCG (IND+MNT) treatment to outweigh the risks of the combination, compared with BCG (IND+MNT).

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

Not applicable.

5.3.7. Observational data or Data from registries

Not applicable.

5.3.8. Patient experience data (PED)

Not applicable.

5.3.9. Healthcare professional engagement

Upon invitation from the CHMP, the EORTC shared their healthcare professional experience of and/or relevant perspectives on the treatment of adult patients with BCG-naïve, HR NMIBC.

The EORTC among other things state:

- "*From a clinical perspective, the key outcomes of interest include recurrence-free survival, progression-free survival, overall survival and bladder preservation. At the same time, tolerability and treatment burden are central to treatment decisions in this population. … systemic or long-lasting side effects, particularly those that affect organ function or require hospitalisation, are less acceptable in a disease that is localised and for which curative treatment is possible.*"; and
- "*… BCG continues to be the standard of care for patients with BCG-naïve high-risk NMIBC. However, the long duration and intensity of the maintenance phase represent a burden for many patients and limit treatment adherence. … For any treatment that adds to this burden, clear and measurable benefits must be demonstrated.*".

The EORTC provided the following summary of their input:

"*BCG remains the standard of care for BCG-naïve, high-risk non-muscle invasive bladder cancer (NMIBC), offering effective oncological control and bladder preservation. However, the full maintenance schedule is lengthy, often poorly tolerated, and logistically burdensome, which may compromise adherence and limit effectiveness. There is a clinical need for therapeutic approaches that address these limitations.*

Key Objectives for New Treatments:

1. *Provide clinically meaningful alternatives that reduce, replace, or optimise the BCG maintenance phase, particularly for patients unable to complete the full course due to toxicity, access issues, or personal preference.*
2. *Demonstrate a favourable balance of efficacy and tolerability when used in combination with or in sequence after BCG, with measurable improvements in recurrence rates, progression, survival, or patient-reported outcomes.*
3. *Be feasible for broad implementation across diverse healthcare settings, with acceptable safety profiles, suitability for outpatient use, and reduced treatment burden without compromising oncological outcomes.*
4. *Integrate predictive biomarkers to personalize therapy and enhance treatment effectiveness.*"

The input of the EORTC is welcomed and fully agreed, especially the above two (bulleted) statements and Key Objective #2.

5.3.10. Overall discussion and conclusions on clinical efficacy

5.3.10.1. Discussion

Initially proposed indication – Zumrad, in combination with Bacillus Calmette-Guérin (BCG), is indicated for the treatment of adult patients with BCG-naïve, high-risk, non-muscle invasive bladder cancer (NMIBC).

The proposed indication wording could be acceptable, as it reflects the patient population of the pivotal study (see below). The term 'high-risk' can be explained in section 5.1 of the SmPC. Moreover, it is considered sufficient to include in section 5.1 the information that in the pivotal study prior to randomisation, all patients had undergone transurethral resection of bladder tumour (TURBT) to remove all resectable papillary disease (Ta and T1). Adding the term 'adjuvant' in the indication would be incorrect since patients with CIS (were included in the pivotal study and) are also included in the target population and CIS cannot be resected completely.

Importantly, the proposed target population consists of patients with early-stage disease with an established SOC (i.e., BCG) which is generally well tolerated, and the short-term risk for serious disease-related morbidity/mortality is low.

Initially proposed posology – The recommended dose of sasanlimab is 300 mg every 4 weeks (Q4W) administered as a single 2 mL subcutaneous injection. Treatment with sasanlimab should be given in combination with BCG induction and maintenance, and should be continued until recurrence of HG disease, disease progression, persistence of carcinoma in situ (CIS), unacceptable toxicity or up to 24 months. No dose reductions of sasanlimab are recommended. Sasanlimab should be withheld or discontinued to manage adverse reactions.

The proposed maximum treatment duration of 24 months is aligned with the maximum treatment duration in the pivotal study (see below).

Clinical studies – The clinical data from the single, pivotal Phase 3 Study B8011006 (CREST) is considered key for the (clinical) benefit-risk (B/R) assessment (Table 1). The three supportive studies are considered less relevant.

Dose response study(ies) – The Applicant had not conducted any dedicated dose response study(ies) before initiating the pivotal study with the sasanlimab dose regimen of 300 mg SC Q4W which is also the proposed posology. It is also noted that the Applicant used data from this pivotal study with a single dose regimen to explore the E-R efficacy relationship. This is considered far from ideal. Nevertheless, since the proposed posology was used in the pivotal study, this can be acceptable. The Applicant is, however, encouraged to further investigate and optimize the sasanlimab dosing (see section 8.6.2.1. 'Areas for further treatment optimisation').

CREST study design – The pivotal Study B8011006 (CREST; Shore et al. Nat Med. 2025) is an open-label, randomized, controlled Phase 3 trial vs an active SOC comparator (Cohort A).
A blinded approach would, however, be considered the best option as blinding can reduce early drop-outs in the control arm and investigator's bias in progression endpoints. If a study is conducted open label, this has implications with respect to the choice of study endpoints, independent review, conduct of sensitivity analyses and other measures to be undertaken to limit potential bias related to the open-label nature of the trial. (EMA/CHMP/205/95 Rev.6).
The randomized study design is in line with the specific recommendations of the International Bladder Cancer Group (IBCG; of clinical experts) for the (chosen) BCG-naïve, HR NMIBC setting (Kamat et al. J Clin Oncol. 2016; Kamat et al. J Clin Oncol. 2023).

CREST also included a Cohort B investigating sasanlimab as a single agent in patients with BCG-unresponsive NMIBC (NCT04165317). Due to a business strategy decision, however, enrolment to Cohorts B1 and B2 was closed/stopped early. Efficacy data from Cohorts B1 and B2 were not analysed, nor provided and are, therefore, not discussed.

The focus of the efficacy assessment will be the comparison of Arm A vs Arm C (of Cohort A), i.e., sasanlimab in combination with BCG induction and maintenance (the proposed posology) vs BCG induction and maintenance (the current SOC). See Figure 8.

Study population – The in- and exclusion criteria are in general considered acceptable, selecting a study population representative of the proposed target population, i.e., adult patients with BCG-naïve, HR NMIBC. Nevertheless, the study population is considered heterogeneous regarding the risk for progression (to MIBC), with the lowest risk in patients with HG pTa disease without CIS and the highest risk in patients with HG pT1 disease with CIS (who in fact have *very* HR NMIBC).

Prior BCG treatment was allowed if stopped >2 years from randomization.

The study enrolled both patients with HG Ta/T1 (papillary) tumours only (without CIS) and patients with CIS with or without HG Ta/T1 (papillary) tumours. Notably, complete resection of all Ta/T1 papillary disease (including in patients with concurrent CIS) was mandatory prior to randomisation. Residual CIS not amenable to complete resection was allowed, as CIS is not always visible and, therefore, cannot be resected completely. This has implications for the efficacy objectives/endpoints.

Randomisation and blinding – The stratification factors, i.e., presence of CIS (yes vs no) and geography (US vs Western Europe and Canada vs ROW), are acceptable, which was also stated at the 2019 EMA SA.

CREST is an open-label study. At the 2019 EMA SA, the choice for not blinding the study was criticized, see below at 'Primary objective (and estimand)'.

According to the protocol – as this is an open-label study – the Applicant was allowed to conduct

unblinded reviews of the data during the course of the study for the purpose of data cleaning at the patient level. According to the CSR, however, the study team remained fully blinded to aggregate/cumulative data summaries by treatment arm until the PCD. It is not considered acceptable that the Applicant was allowed to conduct unblinded reviews of the data during the course of the study. The Applicant is, therefore, requested to confirm that the *entire* study team remained fully blinded to aggregate/cumulative data summaries by treatment arm until the PCD (**part of joint Rapps MO on PA5**).

Description of trial intervention (Study treatment) – The sasanlimab dose regimen of 300 mg SC Q4W used in CREST is also the proposed posology. This is acceptable (see also the discussion on the lack of any dedicated dose-response study[ies]). No justification has, however, been provided for the used (and proposed) maximum duration of treatment up to 25 cycles (2 years) (**Rapp OC**).

The BCG dose regimen used in CREST, both for the induction and the maintenance period, is in line with the proposed posology and current clinical guidelines (e.g., EAU guidelines). It is, therefore, acceptable. More specifically, the 2-year duration of BCG maintenance is also acceptable, plus it was agreed at the 2019 EMA SA.

Several BCG strains could be used since several BCG strains were/are approved in the different countries where CREST was/is conducted. Also, the Applicant states that despite the genetic differences, BCG strains share a similar mechanism of action and have been found to have similar safety profiles. For this reason, different BCG strains approved in the respective countries were allowed to be used in CREST. This is in line with the information in current clinical guidelines (e.g., EAU guidelines).

Following (first) BCG induction (± sasanlimab), patients with CIS at randomisation who had persistent disease and patients who had recurrence of HG Ta disease were allowed to continue study treatment and receive BCG re-induction (± sasanlimab) (Figure 8). This is in line with current clinical guidelines stating that patients who experience recurrence with HG NMIBC after BCG without meeting BCG-unresponsive criteria may benefit from additional BCG therapy, i.e. a category that includes persistent or recurrent Ta HG and/or CIS disease at three months (EAU guidelines).

Study assessments – The efficacy assessments every 12 weeks for 2 years from randomisation and then every 24 weeks thereafter for two years with cytology and cystoscopy, and biopsy(ies) and imaging when clinically indicated are clinically validated, as they are in line with recommendations in current clinical guidelines (EAU guidelines). These are, therefore, considered sufficient for detecting recurrences of HG NMIBC. The provided decision algorithm (Figure 9) is agreed.

The independent central review of tumour tissue samples, even though done retrospectively, is acknowledged.

The Applicant should, however, explain the decision strategy in case of discordance between BICR and local assessment of pathology (bladder biopsies) (**part of Co-Rapp OC**).

The choice for mandatory biopsies for patients with CIS at the 24 week disease assessment (unless collection at the 12 week disease assessment had been performed and showed a CR) is considered a strength of the study, as it limits investigator bias/assessment error. The Applicant should, however, clarify if biopsy confirmation of CR (at Week 12 and/or Week 24) included random biopsies at predefined locations in the bladder in patients with CIS at baseline. If not, the Applicant should explain the biopsy strategy at Week 12 and/or Week 24 in patients with CIS at baseline (**part of Co-Rapp OC**). In addition, the Applicant should summarize the proportion of patients with CIS at baseline who had CR confirmation biopsy at each time point, i.e., at 12 and/or at 24 weeks. The number of patients that had random and/or targeted biopsies should be included in the response

(**part of Co-Rapp OC**).

The protocol definitions for no evidence of disease, CR, persistence of CIS, recurrence of HG/LG disease, and progression of disease are in general acceptable.

Primary objective (and estimand) – In principle, EFS can be acceptable as primary endpoint for a pivotal randomized, controlled Phase 3 study (EMA/CHMP/205/95 Rev.6). Clinical experts, however, for the BCG-naïve, HR NMIBC setting recommend alternative primary endpoints for two specific subgroups of patients (Kamat et al. J Clin Oncol. 2016; Kamat et al. J Clin Oncol. 2023). For patients with HG pTa/T1 papillary disease (without CIS), they recommend recurrence-free survival (RFS), as prior to randomisation patients had undergone TURBT to remove all papillary disease leaving the patients without active disease at baseline. For patients with CIS (with or without papillary disease), they recommend CR rate, as CIS cannot be resected completely and these patients, therefore, have active disease at baseline.. See Table 6 which specifies EFS events for the two specific subgroups of patients, i.e., patients with and without CIS at randomization. All in all, this can be acceptable, also since CR rate in patients with CIS at randomization is included as a secondary endpoint (albeit non-key) (Table 5).

Recurrence of LG disease is not an EFS event (Table 6). This is agreed, as the development of LG lesions does not affect the decisions regarding cystectomy because these patients can be treated with TURBT alone (FDA guidance). It is also in line with the IBCG recommendations (Kamat et al. J Clin Oncol. 2016).

At EMA SA (EMEA/H/SA/4238/1/2019/III), EFS was considered overall acceptable (apart from the below critical issue), although it was preferred that local progression criteria would be consistent with criteria for cystectomy or that, alternatively, support for clinical benefit of an EFS improvement could be provided by the secondary time-to-cystectomy endpoint.

CREST is an open-label study. Also in the submitted dossier, no justification was found for not blinding the study. Independent reviewers did provide a central assessment of clinical efficacy assessments, but this was done retrospectively (**part of merged Rapps MO on the B/R**).

Tt was also stated that when using EFS as a primary endpoint, the treatment effect on EFS will need to be sufficiently large to allow confidence that the clinical benefit outweighs the added toxicity (**part of merged Rapps MO on the B/R**).

The censoring rule described in the second row of Table 7 is not in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). A sensitivity analysis that *is* in line with EMA guidance was, however, performed.

Supportive estimand 2 is not properly defined. The summary measure is defined to be HR for EFS excluding randomized patients who did not receive at least 1 dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2. The exclusion of patients cannot be part of the summary measure. Besides, the ICEs are not defined properly. Therefore, supportive estimand 2 is not considered appropriate.

The intercurrent events (ICEs) are not explicitly defined and the estimands used for specific ICEs is not explicitly defined corresponding to the clinical question of interest. The estimand table is not filled by the Applicant (**Rapp OC**).

Key secondary objectives (and estimands) – The key secondary objectives/endpoints pertaining to the comparison of Arm B vs Arm C are not considered relevant for the proposed indication and posology, and are, therefore, not discussed.

The choice for OS as key secondary endpoint, when EFS is the primary endpoint, is in line with EMA

guidance (EMA/CHMP/205/95 Rev.6) and, therefore, fully agreed. It is also agreed that OS is included in the testing hierarchy (Figure 10).

The ICEs and estimand for OS are not explicitly defined. The Applicant is requested to define the ICEs explicitly and provide the estimand table together with exact definition of the estimand of interest.

Statistical methods

Planned analyses –The Cox proportional hazards model is used for the analyses. Kaplan Meier plots are created to visualize the data. In case of deviations from the assumptions of Cox PH model, RMST method is used. Several sensitivity analysis are planned to assess the robustness of the results. The analyses approach are considered in general adequate.

As stated above, the censoring rule for the primary analysis of investigator-assessed EFS described in the second row of Table 7 is not in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). This flaw is also applicable for the sensitivity analysis of EFS based on BICR assessment, and the (primary analysis) of investigator-assessed DoCR and time to recurrence of LG disease. For investigator-assessed EFS a sensitivity analysis has been performed not censoring events after ≥2 missing or inadequate post-baseline disease assessments (i.e., counting all events), which *is* in line with EMA guidance. Such a sensitivity analysis has, however, not been done for BICR-assessed EFS and investigator-assessed DoCR. The Applicant is, therefore requested to provide these sensitivity analyses (**Rapp OC**).

Planned subgroup analyses – All subgroup analyses were exploratory, as no adjustment for multiplicity was performed. The planned subgroup analyses are acceptable. It is, however, noted that no subgroup analysis of efficacy by PD-L1 expression was planned (see below).

Sample size determination – Sample size calculation was based on detecting a HR of 0.69 using a log-rank test with one-sided alpha level of 0.025. This is considered to be acceptable.

Error probabilities, adjustment for multiplicity and interim analyses – Due to slow accrual of events, IA2 was removed to and multiplicity correction methods are adjusted accordingly. The multiplicity adjustment methods are considered acceptable.

Changes from protocol-specified analyses –

Protocol amendments – There were five amendments to the CREST study protocol, with PA5 being the most relevant (for the current submission).

PA5 was dated 17-Jun-2024, i.e., <6 months before the PCD/DCO date of 02-Dec-2024.

According to the Applicant, the rationale for PA5 was based on the observation that EFS events were accumulating at a much slower rate than originally projected, together with an increasing rate of patients dropping out from EFS observation.

With PA5, the Applicant for the primary endpoint of investigator-assessed EFS (for Arm A vs Arm C) removed the initially planned, event-driven IA2 (based on 272 EFS events) and instead planned to perform the EFS FA based on a calendar-based data cut-off date (while the EFS FA was initially event driven, to be based on 389 EFS events).
Additionally, the Applicant removed the dual primary endpoint of EFS for Arm B vs Arm C (downgraded it to a key secondary endpoint) with equal alpha allocation (1-sided 0.0125 for each test) and instead considered only one primary endpoint (EFS for Arm A vs Arm C) with an alpha of 0.025 (1-sided).

On 30-May-2024, the Applicant requested EMA SA on the proposal for PA5 and on 25-Jul-2024 received this SA (EMA/SA/0000180440). The Applicant thus proceeded with implementing PA5 *before*

receipt of the requested SA. This is considered very disappointing, especially as the Applicant's proposal for PA5 was heavily criticized at EMA SA.

In summary, the Applicant with PA5 –– implemented major changes to the protocol (and SAP) of a fully enrolled, ongoing, open-label study where a considerable amount of information was already available. Moreover, following PA5 the main hypothesis was to be tested with a higher alpha (0.025 instead of 0.0125 [both 1-sided]), therefore, having a higher chance for CREST to be declared positive. As a result, the study integrity is seriously questioned (as are the reported results). The Applicant is, therefore, requested to thoroughly justify that these decisions were taken without any knowledge of the results by treatment arm and that only the global rate of progression triggered the decision, thereby maintaining the integrity of the study.
This justification should at minimum include data providing convincing support for the Applicant's rationale for PA5, i.e., data showing that EFS events were accumulating at a much slower rate than originally projected, together with an increasing rate of patients dropping out from EFS observation. Additionally, the Applicant is requested to confirm that the *entire* study team remained fully blinded to aggregate/cumulative data summaries by treatment arm until the PCD (**joint Rapps MO on PA5**).

With PA5, the Applicant caused a second critical issue, i.e., (severe) immaturity of the primary endpoint EFS results at the EFS FA.
Before PA5, EFS IA2 was planned to be based on 272 EFS events and the EFS FA was planned to be based on 389 EFS events. With PA5, however, EFS IA2 was removed and the EFS FA was to be based on a calendar-based data cut-off date (i.e., change from being event driven to time driven). In fact, it was estimated that the EFS FA was to be performed at around 174 events. This is far less than (174 / 272 x 100% = 64.0% of) the number of EFS events initially planned for EFS IA2 and even less than half (174 / 389 x 100% = 44.7%) of the number of EFS events initially planned for the EFS FA. It is, therefore, highly uncertain whether the observed immature effect is representative of the real treatment effect, with patients with a poorer prognosis being over-represented. In addition, the interpretation of subgroup analyses will likely be hampered by the limited number of events in each one of the comparisons of interest. Lastly, the OS results at the time of the EFS FA could be too low to exclude a detrimental effect on OS (EMA/CHMP/205/95 Rev.6).
Because of this immaturity of EFS events, an analysis according to the initial plan (according to the protocol/SAP before PA5) cannot be conducted.
See the Rapporteur's comments to the EFS FA results below.

Protocol deviations – Overall, 46.4% of patients had at least one IPD (Table 15). The incidence of IPDs was numerically higher in Arm A (51.4%) compared to Arm C (44.2%). Reassuringly, most IPDs were in the categories of 'Procedures/Tests' (with most in the subcategory of 'Abnormal procedure/test result not followed up per protocol') and 'Informed Consent' (with most in the subcategory of 'Subsequent (revised, updated) ICD not signed or not signed at the first patient visit after the revised/approved ICD was available at site'). The numerical difference between Arm A and Arm C seems to be caused primarily by numerical differences in the IPD categories of 'Inclusion/Exclusion' and 'Investigational Product'. Although the patients with 'Abnormal procedure/test result not followed up per protocol' are evenly distributed across arms, the overall proportion of 18.1% is relatively high and should be further specified to be able to consider potential implications for the B/R (**Co-Rapp OC**).

Overall, the reported IPDs are not considered to have any relevant impact on the results of CREST and/or the interpretability. Plus, for the primary endpoint of investigator-assessed EFS a sensitivity analysis was performed for patients in the per-protocol analysis set. For the per-protocol analysis set, not all patients with IPDs were excluded from the FAS (see footnote to Table 16), but this is acceptable.

Participant flow and numbers analysed – Of the 1394 screened patients, there were 290 screen failures (20.8%) (Figure 11). The reasons for the screen failures could, however, not be located in the dossier (**Rapp OC**).

See Figure 11, in Arm A there were more withdrawals from overall treatment (n=229) than in Arm C (n=146). The most common reason for withdrawal in Arm A was an AE (n=131 [vs n=37 in Arm C]). This large difference is noted. In addition, the number of patients who withdrew from overall treatment due to a(n) AE(s) does not seem to be in line with the information in Table 33 (**Rapp OC**). The most common reason for withdrawal in Arm C was lack of efficacy (n=54 [vs n=32 in Arm C]). In both study arms, there were quite a few withdrawals by subject, i.e., n=41 in Arm A vs n=29 in Arm C.

Because of the high amount of withdrawals, the Applicant is requested to provide a time-to-treatment-failure analysis (**Rapp OC**).

The full analysis set (FAS) on which the primary and secondary efficacy analyses are based (Table 9 and Table 16) includes all patients randomized to study treatment and, therefore, adheres to the "intention to treat" principle. This is endorsed.

Baseline data – The majority of patients in CREST was ≥65 years of age (median 67.0 years) and predominantly male (81.8%) (Table 17), which is in line with the indication target population. Patients with ECOG PS 2 were, however, hardly represented which impacts the external validity of the study. The majority was White (61.2%) and approximately half of patients was from Europe. The large majority of patients had newly diagnosed disease (74.0%) and did not have CIS (73.4% per IRT; 74.5% per CRF), and over half of patients had pT1 disease (54.2%) (Table 18).

All patients had undergone prior anticancer surgery (TURBT) and a minority had received ≥1 prior anticancer drug therapy (31.7%) (Table 19). This were primarily the 'antineoplastic agents' gemcitabine, doxorubicin, mitomycin, pirarubicin, and epirubicin (data not shown), most likely given in the form of intravesical instillations. This was allowed per CREST eligibility criteria. Sixteen (16; 4.5%) patients in Arm A and 14 patients (4.0%) in Arm C had received prior BCG. This was also allowed per CREST eligibility criteria, if stopped >2 years from randomization. As stated above, the reason for allowing this is not fully understood and it would have been preferred to only enrol (truly) BCG-naïve patients in the study. This will, however, not be pursued seeing the small number/percentage of patients which is, moreover, similar in Arm A and Arm C.

Overall, there were no discrepancies in demographic characteristics, baseline (disease) characteristics, and prior therapy. The CREST study population can be considered to reflect the proposed indication target population. Given the heterogeneity in the risk for progression, however, the treatment effect for EFS (and OS) across relevant subgroups will be scrutinized, i.e., for patients with pTa vs pT1 disease, and with vs without CIS (see below).

Concomitant therapy – Concomitant medication use was reported (by ATC2 code) at a higher frequency in Arm A compared to Arm C, with prominent (numerical) discrepancies for corticosteroids for systemic use (47.4% vs 16.0%, respectively; including high dose corticosteroids, i.e., ≥40 mg daily prednisolone or equivalent), immunosuppressants (4.3% vs 0.6%, respectively), pituitary and hypothalamic hormones and analogues (3.4% vs 0.9%, respectively), and thyroid therapy (22.6% vs 4.3%, respectively). The frequent use of systemic corticosteroids in Arm A is of concern considering the potential negative impact on the efficacy of BCG due to immunosuppression.

Post-intervention (subsequent) anticancer therapy - More patients in Arm C than in Arm A received ≥1 type of follow-up anticancer therapy (32.2% vs 25.9%, respectively), including subsequent anticancer drug therapy (13.4% vs 7.4%, respectively; Table 20). These percentages

are, however, considered rather low, which is likely caused by the rather low percentage of patients in CREST with an EFS event at the EFS FA (Table 23), reflecting the immaturity of efficacy data.

The subsequent anticancer drug therapies included, e.g., BCG and gemcitabine (intravesical), and PD-(L)1 inhibitors.

Secondary objective (non-key) – biomarkers – PD-L1 expression in pre-treatment tumour tissue – The results for this secondary (non-key) objective are to be considered as baseline disease characteristics. There was no discrepancy for PD-L1 expression in pre-treatment tumour tissue between study arms.

Primary objective – investigator assessed EFS – CREST met its primary objective showing a statistically significant improvement in investigator-assessed EFS for Arm A compared with arm C, i.e., adding sasanlimab to BCG (IND+MNT) (Table 23 and Figure 12). The following critical remarks are, however, made.

1. as blinding was considered of importance since assessment by the investigator via cystoscopy played a fundamental role in the study. **For an open-label study, investigator assessment is not considered appropriate as primary endpoint** (**Error! Reference source not found.**). It is acknowledged that independent reviewers did provide a central assessment of clinical efficacy assessments, but this was done retrospectively. Although a sensitivity analysis based on BIRC was pre-planned and performed, the BIRC results cannot be meaningfully interpreted. Therefore, a critical issue for the evaluation of benefit is whether the investigator-assessed EFS results are reliable in the context of an open-label trial. In order to enable a conclusion regarding the validity of the EFS results based on investigator-assessed progression, the Applicant is requested:

- to provide an overview of the reasons for discordance between the investigator and the BIRC assessments (including a quantitative comparison of investigator vs BIRC assessments, e.g., kappa, percent agreement) and a breakdown of discordant cases by event type (recurrence, progression, CIS, death) to identify whether specific events drive the discrepancies); and
- to provide information on any training that was provided to investigators, standardization procedures, and quality control measures in order to minimise bias (**Rapp OC**).

2. With 17.3% vs 25.4% events in Arm A vs Arm C, respectively, **the EFS FA results are considered too immature**. (**Error! Reference source not found.**). Median EFS has not been reached in Arm A or Arm C and only a relative risk in terms of a HR is currently available for assessment. Moreover, the EFS FA was performed with even fewer events than projected at the time of this SA. The EFS FA was performed with 150 events (Table 23). This is little more than half (150 / 272 x 100% = 55.1%) of the number of EFS events initially planned for EFS IA2 and little more than one third (150 / 389 x 100% = 38.6%) of the number of EFS events initially planned for the EFS FA. It is, therefore, highly uncertain whether the observed immature effect is representative of the real treatment effect, with patients with a poorer prognosis being over-represented. In addition, the interpretation of subgroup analyses will be hampered by the limited number of events in each one of the comparisons of interest (see below).

3. Although the observed difference between Arm A and Arm C in investigator-assessed EFS was statistically significant, **the clinical relevance of the observed treatment effect magnitude is highly uncertain**.
The difference in EFS events (17.3% vs 25.1%) is considered rather small. As communicated by the Rapporteurs at the pre-submission meeting (**Error! Reference source not found.**), the IBCG of clinical experts considers a difference of 10% at 2 years as a clinically meaningful magnitude of effect (Kamat et al. J Clin Oncol. 2016; Kamat et al. J Clin Oncol. 2023). The observed difference of <5% at 24 months (Table 23 and Figure 12) thus does not meet this bar.

In addition, EFS is a composite endpoint comprised of events of varying clinical meaningfulness. When looking at Table 23 (and Table 24), the type of EFS events driving the difference between Arm A and Arm C is recurrence of HG disease (7.4% vs 15.1%), while the rates of other types of EFS events (i.e., progressive disease, persistence of CIS, and death) are (more) similar. Events of disease progression which would require cystectomy (instead of further intravesical therapy) and/or deaths are considered more clinically relevant than recurrence of HG disease *per se* which could be treated by, e.g., (repeated) TURBT and further BCG treatment.

4. The investigator-assessed EFS result is not considered robust, as statistical significance is lost for two (very) important sensitivity analyses.
Firstly, as stated above the censoring rule for the primary analysis of investigator-assessed EFS described in the second row of Table 7 is not in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). A sensitivity analysis was performed though, not censoring events after ≥2 missing or inadequate post-baseline disease assessments (i.e., counting all events), which *is* in line with EMA guidance. For this sensitivity analysis, i.e., when following EMA-preferred censoring rules, the EFS result was no longer statistically significant (Table 26 and Figure 14). When comparing Table 23 and Figure 12 vs Table 26 and Figure 14, one of the most important difference is the higher number of deaths in Arm A. The additional/extra events for Arm A pull down its Kaplan Meier curve, while there is virtually no effect on Arm C (and its curve). For clarity, the Applicant is requested to provide a swim lane/swimmer plot for the patients who have discordant results between the primary analysis and this sensitivity analysis, stratified by EFS event type and censoring (**Rapp OC**).
Secondly, the BICR-assessed EFS result was not statistically significant (Shore et al. Nat Med. 2025 and Figure 13). This is important since in the open-label study CREST, the BICR-assessed EFS result is assumed to be less biased than the investigator-assessed EFS. When comparing Table 23 with Table 25, it is noted that the difference in the number/rate of EFS events between Arm A and Arm C is smaller in the latter. This is caused by a much smaller reduction in events in Arm A from Table 23 to Table 25 (61 – 54 = 7) compared with Arm C (89 – 71 = 18), due to a much smaller reduction in events of recurrence of HG disease in Arm A (26 – 25 = 1) compared with Arm C (53 – 40 = 13). It thus seems that in Arm C EFS events (of recurrence of HG disease) were more frequently scored/called by investigators than by BICR, compared to Arm A. This could be a reflection of investigator bias.
Thirdly, the result of the investigator-assessed primary analysis (with 0.941 as upper limit of 95% CI and p=0.0191) is not considered particularly compelling with respect to statistical significance in the light of an application with a single pivotal study (CPMP/EWP/2330/99).

As a sidenote, in both study arms there was a rather large rate of censoring due to withdrawal of consent (Table 23), i.e., 8.2% vs 7.4%. Since this rate was similar in both arms though, this will not be pursued.

To further examine the robustness of the EFS result, the Applicant is asked to provide sensitivity analyses of EFS both by Investigator and BICR assessment, where start of new anti-cancer therapy is considered an event, and events after 2 or more missing assessments are not censored (**Co-Rapp OC**).

5. There is no (clear, nor statistically significant) **support from the secondary endpoints.** In particular, the estimated treatment effect on OS (Table 27 and Figure 15) cannot ensure that there are no relevant negative effects on this endpoint (EMA/CHMP/205/95 Rev.6).

In conclusion, even though CREST met its primary objective showing a statistically significant improvement in investigator-assessed EFS for Arm A compared with arm C, i.e., adding sasanlimab to BCG (IND+MNT), efficacy has not sufficiently/convincingly been demonstrated, as:

- for an open-label study, investigator-assessed EFS is not considered appropriate as primary

endpoint;
- the EFS FA results are considered too immature;
- the clinical relevance of the observed treatment effect magnitude is uncertain;
- the result is not considered robust; and
- there is no support from secondary endpoints (e.g., OS, time to cystectomy) (**part of merged Rapps MO on the B/R**).

The type of HG recurrence is not specified in the CSR. This is of clinical relevance as recurrence of CIS has a poorer prognosis than recurrence of most papillary tumours. Furthermore, recurrence of CIS may trigger a different therapeutic approach than for papillary tumours, which may not require immediate cystectomy. The Applicant should summarize the tumour pathology (T1, Ta, CIS) in all patients with recurrence of HG disease in study arms A and C (**Co-Rapp OC**).

Key secondary objective – OS – This key secondary objective of CREST was not met; the OS IA performed at the time of the EFS FA did not show a(n) (statistically significant) improvement in OS for Arm A compared with arm C (Table 27 and Figure 15).

With only 9.1% vs 8.3% deaths, the OS data are considered very immature. The immaturity of the OS data complicates the interpretation. If/when available, the Applicant should, therefore, provide updated OS data.
The OS FA will occur approximately 5 years after the last patient was randomized (Table 13). As randomization was completed on 16-Nov-2021, the OS FA will not occur until Nov-2026. This is, however, beyond the timelines for the current application.

Similar to the primary endpoint of investigator-assessed EFS (see above), in both study arms there was a rather large rate of censoring for OS due to withdrawal of consent (Table 27), i.e., 9.1% vs 8.5%. Again, this will not be pursued since the rate was similar in both arms.

The currently provided OS data are not considered reassuring. With an OS HR of 1.13 and an upper limit of the 95% CI of 1.865, the estimated treatment effect on OS cannot ensure that there are no relevant negative effects on this endpoint (EMA/CHMP/205/95 Rev.6).
The results for the OS sensitivity analyses, i.e., with OS HRs of 1.06 and 1.14, are in line with the results of the primary analysis and thus also not considered reassuring.
The key secondary endpoint OS, therefore, does not provide any support for the primary endpoint (**part of merged Rapps MO on the B/R**).

Secondary objective (non-key) – investigator-assessed CR rate and DoCR for patients with CIS at randomization – Only 25% of patients in Arm A and Arm C had CIS at baseline (per CRF; Table 18); the results for this objective/these endpoints are limited to this subgroup of patients.
The large majority of patients with CIS at randomization both in Arm A and Arm C had a CR (Table 28), i.e., 89.8% vs 85.2%, respectively and the (numerical) difference in CR rate of 4.6% is considered quite small and of uncertain clinical relevance. Moreover, CR with biopsy confirmation by BICR was 86.6% in arm A vs 85.7% in Arm C (data not shown). Thus, the difference in CR between Arm A and Arm C was not confirmed by BICR.
It is, therefore, considered that this (non-key) secondary endpoint also does not provide any support for the primary endpoint (**part of merged Rapps MO on the B/R**).

The results for DoCR are, naturally, limited to an even smaller subgroup of patients, i.e., the patients with CIS at randomization who achieved a CR (Table 29). Moreover, the number of events in both arms is (very) limited, i.e. 8 vs 20, which hampers the interpretation. This is another reflection of the immaturity of the efficacy data which is a direct consequence of PA5 (**Error! Reference source not found.**).
In addition, four events in Arm A (vs none in Arm C) were censored being after ≥2 missing

assessments, which is not in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). The Applicant is, therefore, requested to provide a sensitivity analysis for DoCR according to EMA-preferred censoring rules, i.e., counting all events (**Rapp OC**).

Secondary objective (non-key) – time to cystectomy – It is agreed with the Applicant that due to the very low number/rate of events (4.0% vs 4.3%), interpretation of the data is limited (Figure 16). This is unfortunate, as this objective/endpoint reflects an important treatment goal in the HR NMIBC setting, i.e., to avoid or delay a RC.

Acknowledging that the decision to perform/undergo a RC is a multifactorial one, it is noted that of the 61 vs 89 patients with an investigator-assessed EFS event (and the 18 vs 22 patients with progressive disease) only 14 vs 15 patients underwent a RC. The Applicant did provide a summary of the follow-up anticancer therapies received (Table 20), but this is not considered to provide further insights. The Applicant is, therefore, requested to provide updated data on time to cystectomy and further description of the pathological evaluation at cystectomy. The response should include response status during study, information regarding treatment exposure (re-induction, maintenance etc.), time since last study treatment, reason for cystectomy per individual patient etc. (**merged Rapps OC**).

Secondary objective (non-key) – PRO endpoints – The interpretation of PRO endpoints is hampered by the open-label design of CREST. Moreover, the results of this non-key secondary objective are merely descriptive. The results of the PRO endpoints are, therefore, considered of limited value for the B/R assessment and will not be discussed.

Primary objective – investigator-assessed EFS (Arm A vs Arm C) – subgroup analyses – All prespecified subgroup analyses consistently showed an investigator-assessed EFS HR <1 for the comparison of the sasanlimab + BCG (IND+MNT) arm vs the BCG (IND+MNT) arm (Figure 18). As stated above, however, the immaturity of the EFS data hampers the interpretation of the subgroup analyses by the limited number of events in each one of the comparisons of interest. This is also illustrated by the rather wide 95% CIs in the forest plot with the majority of 95% CIs also including '1' (unity).

No subgroup analysis of efficacy by PD-L1 expression (in pre-treatment tumour tissue) was performed. This is considered a shortcoming of the study design and a cause for uncertainty, given the regulatory precedents for restricting bladder cancer/UC indications to patients with (tumours with) high(er) PD-L1 expression (Keytruda and Tecentriq; Opdivo II/100 EPAR).

If performed now, such an analysis would be post hoc. Plus, the immaturity of the EFS data for the above-mentioned reasons would likely hamper the interpretation. Also, the large majority of patients had 'Low' PD-L1 expression (in their pre-treatment tumour tissue) and only a minority of patients had 'High' PD-L1 expression (Table 22), which would likely further limit the value. For completeness, the Applicant is nevertheless requested to provide a subgroup analysis of investigator-assessed EFS (Arm A vs Arm C) by baseline PD-L1 expression (**Rapps OC**). In addition, the Applicant is requested to clarify whether PD-L1 expression data are available from patients while on treatment (**Rapps OC**).

Key secondary objective – OS (Arm A vs Arm C) – subgroup analyses – The (large) majority of prespecified subgroup analyses showed an OS HR >1 for the comparison of the sasanlimab + BCG (IND+MNT) arm vs the BCG (IND+MNT) arm (Figure 19). Also for OS, the immaturity of the data hampers the interpretation of the subgroup analyses by the (very) limited number of events in each one of the comparisons of interest. This is again illustrated by the wide 95% CIs in the forest plot.

Ancillary analyses – The multivariable Cox regression showed no changes compared to the primary analysis.

Subgroup analyses/clinical studies in special populations – No specific information on clinical efficacy studies in special populations, e.g., in the elderly, and in patients with renal or hepatic impairment, could be located in the application dossier. The Applicant is, therefore, requested to clarify and/or justify the absence of such information, and thereby also justify the proposed recommendations/information in the subsection 'Special populations' in section 4.2 of the SmPC. Plus, the Applicant is requested to complete **Error! Reference source not found.**, for completeness (**Rapp OC**).

Supportive study – Patient Preference Study B8011013 –

Regarding the (results of) PPS itself, the following remarks are made.

On the study population, the sample size is considered very small for Phase 1 (n=12) and limited for Phase 2 (n=150) (Figure 20). All patients were from the US and, the results may not be relevant for the European setting.

On the results, efficacy (EFS) was the most important driver of treatment choice, which can be understood. The most important safety-related attribute, was the bladder-problems attribute, with attributes associated with ICIs (i.e., serious immune AEs and chronic endocrine conditions) being less important. Then again, it was the other way round when ranked as 'extremely important'. Moreover, 38% of study patients had experienced at least one bladder-related symptom, while virtually none had experienced symptoms related to ICIs. it thus seems that the study mostly reflects perceived preferences and not preferences based on true experiences.
The two key assumptions made (see above) add uncertainty to the interpretation of the results of the PPS. The first assumption, i.e., that the difference in median EFS between the two arms corresponds to the difference of 10.1 months in first-quartile EFS, seems rather bold, given the immaturity of the CREST primary endpoint results (see Table). Regarding the second assumption, it is noted that the outcome was dependent of the applied dampening factor applied to the extrapolated EFS preference weights.

The Applicant concludes that it is likely that patients will perceive the EFS benefits of sasanlimab + BCG (IND+MNT) treatment to outweigh the risks of the combination, compared with BCG (IND+MNT). This conclusion, however, seems not sufficiently substantiated. Plus, efficacy has not sufficiently/convincingly been demonstrated in CREST (**part of merged Rapps MO on the B/R**). All in all, in line with the caution expressed at the time of the EMA SA, the PPS is not considered substantial to the B/R assessment, nor are its results.

GCP aspects – See section 5.1.1. . The Applicant indicated that a GCP inspection has been conducted in 2019, in Ukraine. Given the information in Table 1 this inspection in Ukraine was for the Phase 1 Study B8011001. The report for this GCP inspection in Ukraine could, however, not be located in the dossier (**Rapp OC**).

A request for routine GCP inspection has been adopted for the pivotal Phase 3 Study B8011006. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181 (see section 2.4.3.).

Based on the review of clinical data, no need for a further (triggered) GCP inspection of the clinical trials included in this dossier was identified at this time.

5.3.10.2. Conclusions on the clinical efficacy

In the pivotal open-label, Phase 3 Study B8011006 (CREST), a statistically significant improvement in investigator-assessed EFS was shown for adding sasanlimab to BCG induction and maintenance

(compared to BCG induction and maintenance alone), in patients with BCG-naïve, HR NMIBC.

It is, however, considered that efficacy has not sufficiently been demonstrated, as:

- for an open-label study, investigator-assessed EFS is not considered appropriate as primary endpoint;
- the EFS FA results are considered too immature;
- the clinical relevance of the observed treatment effect magnitude is uncertain;
- the result is not considered robust; and
- there is no support from secondary endpoints (e.g., OS, time to cystectomy) (**part of merged Rapps MO on the B/R**).

Furthermore, with Protocol Amendment 5 (PA5) the Applicant implemented major changes to the protocol (and SAP) of a fully enrolled, ongoing, open-label study where a considerable amount of information was already available. Moreover, following PA5 the main hypothesis was to be tested with a higher alpha (0.025 instead of 0.0125 [both 1-sided]), therefore, having a higher chance for CREST to be declared positive. As a result, the study integrity is seriously questioned (as are the reported results) (**joint Rapps MO on PA5**).
PA5 also caused the (severe) immaturity of the primary endpoint EFS results at the EFS FA which is reflected in the MO on the B/R.

Updated data on OS and time to cystectomy are requested, however these data will not mitigate the above uncertainties that include the questionable clinical relevance and lack of robustness of the EFS primary endpoint. The main treatment goal in this setting is postponing cystectomy and preventing progression to muscle invasive disease (≥T2). Neither postponement of cystectomy nor reduction in risk for progression has currently been demonstrated by the pivotal trial data submitted to support the sought indication.

Importantly, the proposed target population consists of patients with early-stage disease with an established SOC (i.e., BCG) which is generally well tolerated, and the short-term risk for serious disease-related morbidity/mortality is low. Adding a systemic therapy with clinically relevant toxicity to this SOC for an extended period of time could only be justified by a clearly positive benefit-risk ratio (**part of merged Rapps MO on the B/R**).

5.4. Clinical safety

Please refer to the table of studies in section 6.3.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies

and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety analysis in this SCS applied MedDRA version 27.1 across all studies, except for the irAEs analyses which applied the MedDRA version of each respective study CSRs, i.e., MedDRA version 27.1 (B8011006), 23.1 (B8011001), and 25.0 (B8011007); NCI CTCAE version 5.0 was applied to studies B8011006 and B8011007 and version 4.03 was applied to study B8011001.

Any AE reported with an onset date occurring during the on-treatment period is considered treatment-emergent (TEAE) and of any relationship to study drug unless otherwise specified. Safety endpoints are summarized based on the on-treatment period unless otherwise specified, as follows for all studies:

The on-treatment period was defined as the time from the first dose of study treatment through a minimum of 30 days + last dose of study treatment or start day of new anticancer drug therapy minus 1 day, except for irAEs.

The on-treatment period for Study B8011001 (28 days from last dose of study treatment in CSR) was redefined to 30 days in the integrated analysis plan (iAP) for consistency with the other studies.

Summaries of irAEs include AEs classified as irAEs with an onset date on or after the first dose of study drug and on or before 90 days (B8011006 and B8011007) or 120 days (B8011001) after the last dose of study drug.

Relatedness to Study Intervention

Treatment-related TEAEs were those judged by the investigator to be at least possibly related to any of the study drugs (i.e., at least one of the study drugs), or for which drug relatedness was recorded as unknown by the investigator.

Safety Analysis Population

The primary population for evaluating safety is the Safety Analysis Set (SAS) which includes data from patients in Study B8011006 Cohort A who received at least one dose of study treatment (sasanlimab and/or BCG) and patients who received at least one dose of sasanlimab 300 mg SC Q4W as monotherapy in Study B8011001, Study B8011007 and Study B8011006 Cohort B1.

5.4.2. Patient exposure

Treatment Exposure

Treatment exposure was defined as the period from the first dose of study drug to permanent treatment discontinuation of study drug, or the data cutoff date, whichever was earlier. Exposure is summarized by study drug for each study (eg, sasanlimab or BCG).

Study drug exposure data are summarized in terms of treatment duration, cumulative dose, relative dose intensity, and percentages of patients with dose reductions, dose interruption (ie, temporary treatment discontinuation), and permanent treatment discontinuations.

Extent of Exposure

The duration and extent of treatment exposure is summarized in Table 31 (overall) and Table 32 (by month).

Table 31: Duration and extent of exposure to sasanlimab and BCG (overall) - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)	Pooled Sasanlimab Monotherapy (N=183)
	Sasanlimab	BCG	Sasanlimab	BCG	Sasanlimab	BCG	BCG	Sasanlimab
Duration of treatment (weeks)[a]								
n	350	350	348	348	698	698	349	183
Mean (SD)	65.4 (37.25)	68.6 (38.24)	65.5 (37.07)	6.4 (2.40)	65.5 (37.13)	37.6 (41.27)	75.6 (34.96)	36.4 (34.10)
Median	80.3	98.1	84.8	6.0	84.5	7.0	98.9	20.0
(Q1, Q3)	(24.0, 100.0)	(27.0, 99.7)	(27.6, 100.0)	(6.0, 6.2)	(25.1, 100.0)	(6.0, 98.1)	(51.0, 99.7)	(11.9, 59.9)
Range (min, max)	(4.0, 103.9)	(2.0, 125.1)	(4.0, 104.4)	(1.0, 34.9)	(4.0, 104.4)	(1.0, 125.1)	(2.0, 110.0)	(4.0, 125.4)
Person exposure-100 years[b]	4.39	4.60	4.37	0.43	8.76	5.03	5.05	1.27

a. Duration of treatment to Sasanlimab in weeks is defined as (last dose date of Sasanlimab – first dose date of Sasanlimab + 28)/7. Duration of treatment to BCG in weeks is defined as (last dose date of BCG – first dose date of BCG + 7)/7.

b. Person exposure-100 years = Sum of duration of exposure (in days) to Sasanlimab or BCG for all patients/ (100*365.25).

The descriptive summary statistics are calculated based on n, the number of patients who have received at least one non-zero dose of the study drug.

PFIZER CONFIDENTIAL Source Data: adex ADaM Creation: 28JAN2025 (12:00) Date of Table Generation: 28JAN2025 (15:25)

PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output File: ./b801_scs/B801_SCS_CSR1/adex_s001b

Table 14.4.1.1 is for Pfizer internal use.

Table 32: Extent of exposure to sasanlimab in months - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)	B8011006 Sasanlimab + BCG (IND) (N=348)	B8011006 Pooled Sasanlimab + BCG (N=698)	Pooled Sasanlimab Monotherapy (N=183)
Person exposure-100 years	4.39	4.37	8.76	1.27
Duration of treatment, n (%)				
>0 month	350 (100.0)	348 (100.0)	698 (100.0)	183 (100.0)
>1 month	343 (98.0)	338 (97.1)	681 (97.6)	169 (92.3)
>2 months	330 (94.3)	326 (93.7)	656 (94.0)	140 (76.5)
>3 months	311 (88.9)	308 (88.5)	619 (88.7)	119 (65.0)
>6 months	258 (73.7)	264 (75.9)	522 (74.8)	77 (42.1)
>9 months	228 (65.1)	230 (66.1)	458 (65.6)	60 (32.8)
>12 months	207 (59.1)	199 (57.2)	406 (58.2)	49 (26.8)
>15 months	189 (54.0)	190 (54.6)	379 (54.3)	39 (21.3)
>18 months	177 (50.6)	184 (52.9)	361 (51.7)	30 (16.4)
>21 months	171 (48.9)	167 (48.0)	338 (48.4)	19 (10.4)
>24 months	0	1 (0.3)	1 (0.1)	13 (7.1)

Person exposure-100 years = Sum of duration of exposure (in days) to sasanlimab for all patients/ (100*365.25)
The denominator to calculate percentages is N, the number of patients treated with sasanlimab within each treatment group.
PFIZER CONFIDENTIAL Source Data: adex ADaM Creation: 28JAN2025 (12:00) Date of Table Generation: 19FEB2025 (15:34)
PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output
File: ./b801_scs/B801_SCS_CSR1/adex_s001b_mth_BDR
Table 14.4.1.1.11 is for Pfizer internal use.

5.4.3. Adverse events

A summary of TEAEs is presented in Table 33.

Table 33: Summary of adverse events - SAS

Number (%) of Patients	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Patients with TEAEs	341 (97.4)	326 (93.7)	667 (95.6)	310 (88.8)	177 (96.7)
Patients with grade ≥ 3 TEAEs	171 (48.9)	141 (40.5)	312 (44.7)	90 (25.8)	84 (45.9)
Patients with treatment-related TEAEs	305 (87.1)	275 (79.0)	580 (83.1)	245 (70.2)	107 (58.5)

Table 33: Summary of adverse events - SAS

Number (%) of Patients	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Patients with grade ≥ 3 treatment-related TEAEs	102 (29.1)	76 (21.8)	178 (25.5)	22 (6.3)	24 (13.1)
Patients with TEAEs leading to interruption of Sasanlimab	167 (47.7)	143 (41.1)	310 (44.4)	NA	53 (29.0)
Patients with TEAEs leading to interruption of BCG	142 (40.6)	45 (12.9)	187 (26.8)	102 (29.2)	NA
Patients with TEAEs leading to discontinuation of Sasanlimab	108 (30.9)	67 (19.3)	175 (25.1)	NA	25 (13.7)
Patients with TEAEs leading to discontinuation of BCG	77 (22.0)	9 (2.6)	86 (12.3)	35 (10.0)	NA
Patients with TEAEs leading to discontinuation of all study drugs	28 (8.0)	4 (1.1)	32 (4.6)	NA	NA
Patients with treatment-related TEAEs leading to discontinuation of Sasanlimab	92 (26.3)	58 (16.7)	150 (21.5)	NA	10 (5.5)
Patients with treatment-related TEAEs leading to discontinuation of BCG	59 (16.9)	8 (2.3)	67 (9.6)	30 (8.6)	NA
Patients with treatment-related TEAEs leading to discontinuation of all study drugs	(4.0)	3 (0.9)	17 (2.4)	NA	NA
Patients with serious TEAEs	120 (34.3)	99 (28.4)	219 (31.4)	49 (14.0)	57 (31.1)
Patients with treatment-related serious TEAEs	62 (17.7)	43 (12.4)	105 (15.0)	5 (1.4)	12 (6.6)
Patients with TEAEs leading to death	6 (1.7)	4 (1.1)	10 (1.4)	2 (0.6)	21 (11.5)
Patients with treatment-related TEAEs leading to death	0	2 (0.6)	2 (0.3)	0	0
Patients with Injection site reactions (ISRs) Related to Sasanlimab	8 (2.3)	13 (3.7)	21 (3.0)	0	4 (2.2)

Table 33: Summary of adverse events - SAS

Number (%) of Patients	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Patients with immune-related adverse events (irAEs)	149 (42.6)	163 (46.8)	312 (44.7)	5 (1.4)	52 (28.4)

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Treatment-related TEAEs include TEAEs related to at least one study drug in the combination.
All study drugs = all study drugs in the combination; NA = not applicable.
MedDRA v27.1 coding dictionary applied.
TEAEs leading to interruption/discontinuation of BCG, treatment-related TEAEs leading to discontinuation of BCG are not applicable for pooled Sasanlimab monotherapy.
TEAEs leading to interruption/discontinuation of Sasanlimab, treatment-related TEAEs leading to discontinuation of Sasanlimab are not applicable for B8011006 BCG (IND+MNT) arm.

All-causality Adverse Events

The most common all-causality TEAEs of Any Grade and Grade ≥3 are summarized in Table 34.

Table 34: Summary of most common TEAEs (any grade in ≥ 10% or grade ≥ 3 in ≥ 2% patients in any treatment group), by PT and maximum CTCAE grade during the on-treatment period - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with Any Adverse Event	341 (97.4)	171 (48.9)	326 (93.7)	141 (40.5)	667 (95.6)	312 (44.7)	310 (88.8)	90 (25.8)	177 (96.7)	84 (45.9)
Dysuria	115 (32.9)	0	72 (20.7)	0	187 (26.8)	0	126 (36.1)	0	3 (1.6)	0
Haematuria	98 (28.0)	20 (5.7)	51 (14.7)	7 (2.0)	149 (21.3)	27 (3.9)	90 (25.8)	12 (3.4)	4 (2.2)	0
Urinary tract infection	92 (26.3)	10 (2.9)	55 (15.8)	3 (0.9)	147 (21.1)	13 (1.9)	82 (23.5)	2 (0.6)	11 (6.0)	2 (1.1)
Pollakiuria	83 (23.7)	0	39 (11.2)	0	122 (17.5)	0	74 (21.2)	0	3 (1.6)	0
Lipase increased	76 (21.7)	27 (7.7)	56 (16.1)	11 (3.2)	132 (18.9)	38 (5.4)	28 (8.0)	3 (0.9)	12 (6.6)	5 (2.7)
Pyrexia	75 (21.4)	1 (0.3)	51 (14.7)	0	126 (18.1)	1 (0.1)	52 (14.9)	0	16 (8.7)	0
Alanine aminotransferase increased	57 (16.3)	10 (2.9)	38 (10.9)	5 (1.4)	95 (13.6)	15 (2.1)	30 (8.6)	4 (1.1)	23 (12.6)	1 (0.5)

Table 34: Summary of most common TEAEs (any grade in ≥ 10% or grade ≥ 3 in ≥ 2% patients in any treatment group), by PT and maximum CTCAE grade during the on-treatment period - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Amylase increased	56 (16.0)	10 (2.9)	42 (12.1)	5 (1.4)	98 (14.0)	15 (2.1)	15 (4.3)	0	13 (7.1)	5 (2.7)
SARS-CoV-2 test positive	56 (16.0)	2 (0.6)	37 (10.6)	0	93 (13.3)	2 (0.3)	49 (14.0)	1 (0.3)	1 (0.5)	0
Hypothyroidism	55 (15.7)	2 (0.6)	49 (14.1)	0	104 (14.9)	2 (0.3)	3 (0.9)	0	13 (7.1)	0
Aspartate aminotransferase increased	53 (15.1)	9 (2.6)	37 (10.6)	7 (2.0)	90 (12.9)	16 (2.3)	25 (7.2)	1 (0.3)	16 (8.7)	1 (0.5)
Arthralgia	52 (14.9)	1 (0.3)	44 (12.6)	4 (1.1)	96 (13.8)	5 (0.7)	14 (4.0)	2 (0.6)	14 (7.7)	1 (0.5)
Fatigue	52 (14.9)	1 (0.3)	42 (12.1)	1 (0.3)	94 (13.5)	2 (0.3)	21 (6.0)	0	22 (12.0)	4 (2.2)
Pruritus	48 (13.7)	0	43 (12.4)	1 (0.3)	91 (13.0)	1 (0.1)	8 (2.3)	0	18 (9.8)	0
Cystitis	43 (12.3)	1 (0.3)	19 (5.5)	0	62 (8.9)	1 (0.1)	37 (10.6)	0	1 (0.5)	0
Constipation	41 (11.7)	0	25 (7.2)	0	66 (9.5)	0	21 (6.0)	0	11 (6.0)	0
Diarrhoea	41 (11.7)	0	39 (11.2)	2 (0.6)	80 (11.5)	2 (0.3)	19 (5.4)	0	18 (9.8)	1 (0.5)
Asthenia	40 (11.4)	3 (0.9)	34 (9.8)	2 (0.6)	74 (10.6)	5 (0.7)	20 (5.7)	0	23 (12.6)	5 (2.7)
Micturition urgency	40 (11.4)	0	16 (4.6)	0	56 (8.0)	0	41 (11.7)	0	1 (0.5)	0
Decreased appetite	31 (8.9)	2 (0.6)	35 (10.1)	3 (0.9)	66 (9.5)	5 (0.7)	3 (0.9)	1 (0.3)	28 (15.3)	2 (1.1)
Anaemia	27 (7.7)	3 (0.9)	29 (8.3)	3 (0.9)	56 (8.0)	6 (0.9)	14 (4.0)	2 (0.6)	43 (23.5)	13 (7.1)
Hypertension	22 (6.3)	8 (2.3)	24 (6.9)	7 (2.0)	46 (6.6)	15 (2.1)	33 (9.5)	14 (4.0)	5 (2.7)	2 (1.1)
Dyspnoea	20 (5.7)	0	14 (4.0)	2 (0.6)	34 (4.9)	2 (0.3)	7 (2.0)	0	28 (15.3)	4 (2.2)
Gamma-glutamyltransferase increased	16 (4.6)	7 (2.0)	8 (2.3)	2 (0.6)	24 (3.4)	9 (1.3)	10 (2.9)	2 (0.6)	4 (2.2)	0
Pneumonia	16 (4.6)	7 (2.0)	6 (1.7)	2 (0.6)	22 (3.2)	9 (1.3)	5 (1.4)	4 (1.1)	8 (4.4)	5 (2.7)
Hyponatraemia	11 (3.1)	1 (0.3)	8 (2.3)	1 (0.3)	19 (2.7)	2 (0.3)	7 (2.0)	2 (0.6)	7 (3.8)	4 (2.2)
Sepsis	4 (1.1)	4 (1.1)	1 (0.3)	1 (0.3)	5 (0.7)	5 (0.7)	0	0	4 (2.2)	4 (2.2)
Disease progression	0	0	0	0	0	0	0	0	10 (5.5)	10 (5.5)

Table 34: Summary of most common TEAEs (any grade in ≥ 10% or grade ≥ 3 in ≥ 2% patients in any treatment group), by PT and maximum CTCAE grade during the on-treatment period - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Patients reporting more than one adverse event within a preferred term are counted only once in that preferred term.
For patients reporting more than one AE within a preferred term, the AE with maximum grade are included in the table.
With any adverse events row includes all patients without cutoff.
MedDRA v27.1 coding dictionary applied.

The most common treatment-related TEAEs are summarized in Table 35.

Table 35: Summary of most common treatment-related TEAEs (any grade in ≥ 5% or grade ≥ 3 in ≥ 2% patients in any treatment group), by PT and maximum CTCAE grade during the on-treatment period - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
Preferred Term	**Any Grade n (%)**	**Grade ≥ 3 n (%)**	**Any Grade n (%)**	**Grade ≥ 3 n (%)**	**Any Grade n (%)**	**Grade ≥ 3 n (%)**	**Any Grade n (%)**	**Grade ≥ 3 n (%)**	**Any Grade n (%)**	**Grade ≥ 3 n (%)**
Patients with Any Adverse Event	305 (87.1)	102 (29.1)	275 (79.0)	76 (21.8)	580 (83.1)	178 (25.5)	245 (70.2)	22 (6.3)	107 (58.5)	24 (13.1)
Dysuria	103 (29.4)	0	46 (13.2)	0	149 (21.3)	0	112 (32.1)	0	0	0
Pollakiuria	80 (22.9)	0	27 (7.8)	0	107 (15.3)	0	66 (18.9)	0	1 (0.5)	0
Haematuria	73 (20.9)	14 (4.0)	31 (8.9)	5 (1.4)	104 (14.9)	19 (2.7)	70 (20.1)	11 (3.2)	0	0
Urinary tract infection	67 (19.1)	7 (2.0)	28 (8.0)	2 (0.6)	95 (13.6)	9 (1.3)	70 (20.1)	2 (0.6)	0	0
Lipase increased	61 (17.4)	21 (6.0)	42 (12.1)	5 (1.4)	103 (14.8)	26 (3.7)	0	0	10 (5.5)	4 (2.2)
Pyrexia	54 (15.4)	1 (0.3)	35 (10.1)	0	89 (12.8)	1 (0.1)	41 (11.7)	0	6 (3.3)	0
Hypothyroidism	50 (14.3)	2 (0.6)	44 (12.6)	0	94 (13.5)	2 (0.3)	0	0	10 (5.5)	0
Amylase increased	41 (11.7)	8 (2.3)	33 (9.5)	3 (0.9)	74 (10.6)	11 (1.6)	0	0	7 (3.8)	3 (1.6)
Alanine aminotransferase increased	38 (10.9)	8 (2.3)	24 (6.9)	2 (0.6)	62 (8.9)	10 (1.4)	6 (1.7)	1 (0.3)	13 (7.1)	0
Cystitis	38 (10.9)	1 (0.3)	10 (2.9)	0	48 (6.9)	1 (0.1)	30 (8.6)	0	0	0
Aspartate aminotransferase increased	37 (10.6)	7 (2.0)	21 (6.0)	4 (1.1)	58 (8.3)	11 (1.6)	5 (1.4)	0	11 (6.0)	0
Micturition urgency	36 (10.3)	0	11 (3.2)	0	47 (6.7)	0	37 (10.6)	0	0	0
Fatigue	35 (10.0)	1 (0.3)	26 (7.5)	1 (0.3)	61 (8.7)	2 (0.3)	11 (3.2)	0	8 (4.4)	2 (1.1)
Pruritus	34 (9.7)	0	37 (10.6)	1 (0.3)	71 (10.2)	1 (0.1)	1 (0.3)	0	12 (6.6)	0
Asthenia	27 (7.7)	1 (0.3)	19 (5.5)	0	46 (6.6)	1 (0.1)	9 (2.6)	0	7 (3.8)	1 (0.5)
Hyperthyroidism	27 (7.7)	0	26 (7.5)	0	53 (7.6)	0	0	0	14 (7.7)	0
Arthralgia	21 (6.0)	0	25 (7.2)	4 (1.1)	46 (6.6)	4 (0.6)	2 (0.6)	1 (0.3)	6 (3.3)	0
Rash maculo-papular	18 (5.1)	3 (0.9)	11 (3.2)	2 (0.6)	29 (4.2)	5 (0.7)	1 (0.3)	0	1 (0.5)	0
Decreased appetite	15 (4.3)	2 (0.6)	22 (6.3)	2 (0.6)	37 (5.3)	4 (0.6)	1 (0.3)	0	10 (5.5)	1 (0.5)
Rash	9 (2.6)	0	12 (3.4)	0	21 (3.0)	0	1 (0.3)	0	10 (5.5)	0

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Patients reporting more than one adverse event within a preferred term are counted only once in that preferred term.

Table 35: Summary of most common treatment-related TEAEs (any grade in ≥ 5% or grade ≥ 3 in ≥ 2% patients in any treatment group), by PT and maximum CTCAE grade during the on-treatment period - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

For patients reporting more than one AE within a preferred term, the AE with maximum grade are included in the table.
With any adverse events row includes all patients without cutoff.
Treatment-related AEs include AEs related to at least one study drug in the combination.
MedDRA v27.1 coding dictionary applied.

5.4.3.1. Adverse drug reactions

ADRs included TEAEs for which, after thorough assessment, a causal relationship between sasanlimab in combination with BCG and the TEAE was at least a reasonable possibility.

The ADRs included TEAEs that were classified as irAEs or TEAEs reported in ≥10% of patients by PT or cluster of PTs in either the sasanlimab + BCG (IND+MNT) or sasanlimab + BCG (IND) arms and at higher rate (≥5% for Any Grade or ≥2% for Grade ≥3) than the BCG (IND+MNT) arm (Table 36). In addition, ADRs reported at ≥10% and known to be adverse drug reactions to intravesical BCG were also included (i.e., Urinary signs and symptoms) to more properly reflect the safety profile of the sasanlimab + BCG combination treatment.

The ADRs proposed for inclusion in the SmPC are depicted in Table 36.

Table 36: ADRs proposed for sasanlimab in Combination with BCG for inclusion in the SmPC

Infections and infestations		Link to data*
Very Common	Urinary tract infection[a]	Table 45: Summary of adverse drug reactions by SOC and PT or cluster term - SAS day-80-assessment-report-clinical-template-guidance-rev-0325-revamp_en
Blood and lymphatic system disorders		
Uncommon	Immune thrombocytopenia	
Immune system disorders		
Uncommon	Sarcoidosis[b]	
Endocrine disorders		
Very Common	Hypothyroidism[c], Hyperthyroidism[d]	
Common	Adrenal insufficiency[e], Hypopituitarism[f], Thyroiditis[g]	
Uncommon	Hypophysitis[h]	
Metabolism and nutrition disorders		
Common	Diabetes mellitus[i], Hyperglycaemia, Decreased appetite	
Nervous system disorders		
Uncommon	Myasthenia gravis[j]	
Eye disorders		
Uncommon	Uveitis	
Cardiac disorders		
Uncommon	Myocarditis[k]	
Respiratory, thoracic and mediastinal disorders		
Common	Pneumonitis[l]	
Gastrointestinal disorders		
Very Common	Diarrhoea	
Common	Colitis[m] Pancreatitis[n] Constipation	
Hepatobiliary disorders		
Very Common	Hepatotoxicity[o]	
Skin and subcutaneous tissue disorders		
Very Common	Rash[p] Pruritus	
Common	Psoriasis[q]	
Uncommon	Vitiligo	
Musculoskeletal and connective tissue disorders		
Very Common	Arthralgia	

Uncommon	Myositis[r] Polymyalgia rheumatica Rheumatoid arthritis Sjogren's syndrome	
Renal and urinary disorders		
Very Common	Haematuria Dysuria Pollakiuria	
Common	Acute kidney injury[s] Micturition urgency	
Uncommon	Nephritis[t]	
Investigations		
Very Common	Lipase increased[x] Amylase increased[y]	

a. Urinary tract infection includes cystitis, escherichia urinary tract infection, klebsiella urinary tract infection, pyelonephritis, pyelonephritis acute, pyelonephritis chronic, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, urosepsis.
b. Sarcoidosis includes pulmonary sarcoidosis, sarcoidosis.
c. Hypothyroidism includes blood thyroid stimulating hormone increased, hypothyroidism, immune-mediated hypothyroidism, thyroid function test abnormal, thyroxine decreased, thyroxine free decreased, tri-iodothyronine decreased, tri-iodothyronine free decreased.
d. Hyperthyroidism includes blood thyroid stimulating hormone decreased, hyperthyroidism, tri-iodothyronine increased.
e. Adrenal insufficiency includes adrenal disorder, adrenal insufficiency, immune-mediated adrenal insufficiency, secondary adrenocortical insufficiency.
f. Hypopituitarism includes hypopituitarism, hypothalamo-pituitary disorder.
g. Thyroiditis includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis, thyroiditis subacute.
h. Hypophysitis includes hypophysitis, immune-mediated hypophysitis, lymphocytic hypophysitis.
i. Diabetes mellitus includes diabetes mellitus, diabetic ketoacidosis, type 1 diabetes mellitus.
j. Myasthenia gravis includes myasthenic syndrome, ocular myasthenia.
k. Myocarditis includes immune-mediated myocarditis, myocarditis.
l. Pneumonitis includes immune-mediated lung disease, interstitial lung disease, pneumonitis.
m. Colitis includes colitis, colitis microscopic, colitis ulcerative, immune-mediated enterocolitis.
n. Pancreatitis includes autoimmune pancreatitis, immune-mediated pancreatitis, pancreatitis, pancreatitis acute.
o. Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis acute, hepatobiliary disease, hepatotoxicity, hypertransaminasaemia, immune-mediated hepatic disorder, immune-mediated hepatitis, liver injury.
p. Rash includes dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, erythema, erythema multiforme, haemorrhagic vasculitis, immune-mediated dermatitis, lichen planus, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, toxic epidermal necrolysis, urticaria.
q. Psoriasis includes psoriasis, dermatitis psoriasiform.
r. Myositis includes autoimmune myositis, immune-mediated myositis, myositis.
s. Acute kidney injury includes acute kidney injury, renal failure, renal impairment.
t. Nephritis includes glomerulonephritis, glomerulonephritis membranous, nephritis.
u. Fatigue includes asthenia, fatigue, malaise.
v. Pyrexia includes pyrexia, body temperature increased, hyperthermia.
w. Injection site reaction includes injection site discolouration, injection site erythema, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site reaction, injection site swelling.
x. Lipase increased includes lipase increased, hyperlipasaemia.
y. Amylase increased includes amylase increased, hyperamylasaemia.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

AESIs are irAEs. irAEs were identified based on a combination of programmatic checks and medical review. AEs were classified as irAEs by the Sponsor using a combination of programmatic checks and medical review as defined in the iAP. irAEs are presented by irAEs clusters and PTs. ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

AEs classified as irAEs were categorized according to the irAEs clusters below.

List of irAE Clusters

- IR PNEUMONITIS
- IR COLITIS
- IR HEPATITIS

- IR ENDOCRINOPATHIES – THYROID DISORDERS
- IR ENDOCRINOPATHIES – ADRENAL INSUFFICIENCY
- IR ENDOCRINOPATHIES – HYPOPHYSITIS/HYPOPITUITARISM
- IR ENDOCRINOPATHIES – TYPE 1 DIABETES MELLITUS
- IR NEPHRITIS AND RENAL DYSFUNCTION
- IR RASH
- IR PANCREATITIS
- MYOCARDITIS
- IR MYOSITIS
- MYASTHENIC SYNDROME/MYASTHENIA GRAVIS
- IR UVEITIS
- OTHER IR EVENTS

Table 37: Summary of irAEs (any Grade and Grade ⩾ 3) by cluster and PT - SAS

Cluster and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
Patients With Any Adverse Event	149 (42.6)	55 (15.7)	163 (46.8)	49 (14.1)	312 (44.7)	104 (14.9)	5 (1.4)	0	52 (28.4)	11 (6.0)
IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS	62 (17.7)	2 (0.6)	71 (20.4)	1 (0.3)	133 (19.1)	3 (0.4)	5 (1.4)	0	29 (15.8)	0
Hypothyroidism	50 (14.3)	2 (0.6)	42 (12.1)	0	92 (13.2)	2 (0.3)	1 (0.3)	0	12 (6.6)	0
Hyperthyroidism	23 (6.6)	0	25 (7.2)	0	48 (6.9)	0	1 (0.3)	0	11 (6.0)	0
Blood thyroid stimulating hormone decreased	5 (1.4)	0	3 (0.9)	0	8 (1.1)	0	0	0	2 (1.1)	0
Blood thyroid stimulating hormone increased	5 (1.4)	0	16 (4.6)	0	21 (3.0)	0	2 (0.6)	0	4 (2.2)	0
Thyroiditis	4 (1.1)	0	6 (1.7)	0	10 (1.4)	0	1 (0.3)	0	1 (0.5)	0
Autoimmune thyroiditis	2 (0.6)	0	2 (0.6)	0	4 (0.6)	0	1 (0.3)	0	1 (0.5)	0
Immune-mediated thyroiditis	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)	0	0	0	0
Thyroxine decreased	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
Tri-iodothyronine decreased	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
Tri-iodothyronine free decreased	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0	0	0	0
Basedow's disease	0	0	0	0	0	0	0	0	1 (0.5)	0
Immune-mediated hypothyroidism	0	0	2 (0.6)	0	2 (0.3)	0	0	0	0	0
Thyroid function test abnormal	0	0	1 (0.3)	0	1 (0.1)	0	0	0	0	0
Thyroiditis subacute	0	0	0	0	0	0	1 (0.3)	0	0	0
Thyroxine free decreased	0	0	1 (0.3)	0	1 (0.1)	0	0	0	0	0
Tri-iodothyronine increased	0	0	1 (0.3)	0	1 (0.1)	0	0	0	0	0
IMMUNE-RELATED RASH	46 (13.1)	10 (2.9)	48 (13.8)	8 (2.3)	94 (13.5)	18 (2.6)	0	0	13 (7.1)	0
Pruritus	22 (6.3)	0	18 (5.2)	1 (0.3)	40 (5.7)	1 (0.1)	0	0	10 (5.5)	0
Rash maculo-papular	14 (4.0)	4 (1.1)	6 (1.7)	2 (0.6)	20 (2.9)	6 (0.9)	0	0	1 (0.5)	0
Immune-mediated dermatitis	4 (1.1)	0	0	0	4 (0.6)	0	0	0	0	0
Rash	4 (1.1)	0	7 (2.0)	0	11 (1.6)	0	0	0	5 (2.7)	0
Dermatitis	3 (0.9)	0	6 (1.7)	1 (0.3)	9 (1.3)	1 (0.1)	0	0	1 (0.5)	0

Table 37: Summary of irAEs (any Grade and Grade ⩾ 3) by cluster and PT - SAS

Cluster and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
Erythema	3 (0.9)	0	3 (0.9)	0	6 (0.9)	0	0	0	0	0
Drug eruption	2 (0.6)	0	4 (1.1)	2 (0.6)	6 (0.9)	2 (0.3)	0	0	1 (0.5)	0
Pemphigoid	2 (0.6)	2 (0.6)	2 (0.6)	0	4 (0.6)	2 (0.3)	0	0	0	0
Dermatitis acneiform	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
Dermatitis bullous	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	1 (0.5)	0
Erythema multiforme	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
Haemorrhagic vasculitis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Lichen planus	1 (0.3)	1 (0.3)	4 (1.1)	1 (0.3)	5 (0.7)	2 (0.3)	0	0	0	0
Rash erythematous	1 (0.3)	0	4 (1.1)	0	5 (0.7)	0	0	0	0	0
Rash macular	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)	0	0	0	0
Rash pruritic	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Toxic epidermal necrolysis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Rash papular	0	0	4 (1.1)	0	4 (0.6)	0	0	0	0	0
IMMUNE-RELATED HEPATITIS	15 (4.3)	12 (3.4)	14 (4.0)	11 (3.2)	29 (4.2)	23 (3.3)	0	0	12 (6.6)	5 (2.7)
Alanine aminotransferase increased	11 (3.1)	8 (2.3)	5 (1.4)	4 (1.1)	16 (2.3)	12 (1.7)	0	0	9 (4.9)	1 (0.5)
Aspartate aminotransferase increased	10 (2.9)	7 (2.0)	6 (1.7)	4 (1.1)	16 (2.3)	11 (1.6)	0	0	7 (3.8)	1 (0.5)
Autoimmune hepatitis	2 (0.6)	1 (0.3)	0	0	2 (0.3)	1 (0.1)	0	0	0	0
Hepatitis	2 (0.6)	2 (0.6)	4 (1.1)	2 (0.6)	6 (0.9)	4 (0.6)	0	0	1 (0.5)	0
Hypertransaminasaemia	2 (0.6)	1 (0.3)	0	0	2 (0.3)	1 (0.1)	0	0	0	0
Immune-mediated hepatitis	2 (0.6)	1 (0.3)	2 (0.6)	2 (0.6)	4 (0.6)	3 (0.4)	0	0	1 (0.5)	1 (0.5)
Drug-induced liver injury	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)	0	0	0	0
Hepatic enzyme increased	0	0	0	0	0	0	0	0	1 (0.5)	1 (0.5)
Hepatitis acute	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)	0	0	0	0
Immune-mediated hepatic disorder	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)	0	0	0	0
Liver injury	0	0	2 (0.6)	2 (0.6)	2 (0.3)	2 (0.3)	0	0	0	0
Transaminases increased	0	0	0	0	0	0	0	0	2 (1.1)	2 (1.1)

Table 37: Summary of irAEs (any Grade and Grade ⩾ 3) by cluster and PT - SAS

Cluster and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
IMMUNE-RELATED PANCREATITIS	14 (4.0)	7 (2.0)	10 (2.9)	6 (1.7)	24 (3.4)	13 (1.9)	0	0	1 (0.5)	1 (0.5)
Pancreatitis	8 (2.3)	6 (1.7)	7 (2.0)	3 (0.9)	15 (2.1)	9 (1.3)	0	0	0	0
Pancreatitis acute	3 (0.9)	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.7)	3 (0.4)	0	0	1 (0.5)	1 (0.5)
Immune-mediated pancreatitis	2 (0.6)	0	1 (0.3)	1 (0.3)	3 (0.4)	1 (0.1)	0	0	0	0
Autoimmune pancreatitis	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0	0	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY	12 (3.4)	6 (1.7)	12 (3.4)	5 (1.4)	24 (3.4)	11 (1.6)	0	0	1 (0.5)	0
Adrenal insufficiency	11 (3.1)	4 (1.1)	9 (2.6)	4 (1.1)	20 (2.9)	8 (1.1)	0	0	0	0
Adrenal disorder	2 (0.6)	0	1 (0.3)	0	3 (0.4)	0	0	0	0	0
Secondary adrenocortical insufficiency	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	3 (0.4)	3 (0.4)	0	0	0	0
Immune-mediated adrenal insufficiency	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0	0	0	0
Glucocorticoid deficiency	0	0	0	0	0	0	0	0	1 (0.5)	0
IMMUNE-RELATED PNEUMONITIS	10 (2.9)	4 (1.1)	4 (1.1)	1 (0.3)	14 (2.0)	5 (0.7)	0	0	6 (3.3)	1 (0.5)
Pneumonitis	5 (1.4)	3 (0.9)	4 (1.1)	1 (0.3)	9 (1.3)	4 (0.6)	0	0	6 (3.3)	1 (0.5)
Immune-mediated lung disease	4 (1.1)	1 (0.3)	0	0	4 (0.6)	1 (0.1)	0	0	0	0
Interstitial lung disease	2 (0.6)	0	0	0	2 (0.3)	0	0	0	0	0
IMMUNE-RELATED COLITIS	9 (2.6)	5 (1.4)	9 (2.6)	3 (0.9)	18 (2.6)	8 (1.1)	0	0	3 (1.6)	0
Colitis ulcerative	4 (1.1)	2 (0.6)	3 (0.9)	1 (0.3)	7 (1.0)	3 (0.4)	0	0	0	0
Diarrhoea	3 (0.9)	0	4 (1.1)	2 (0.6)	7 (1.0)	2 (0.3)	0	0	3 (1.6)	0
Colitis	2 (0.6)	1 (0.3)	3 (0.9)	1 (0.3)	5 (0.7)	2 (0.3)	0	0	0	0
Colitis microscopic	2 (0.6)	2 (0.6)	1 (0.3)	0	3 (0.4)	2 (0.3)	0	0	0	0
Immune-mediated enterocolitis	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: HYPOPHYSITIS/HYPOPITUITARISM	8 (2.3)	4 (1.1)	9 (2.6)	3 (0.9)	17 (2.4)	7 (1.0)	0	0	1 (0.5)	1 (0.5)
Hypopituitarism	4 (1.1)	2 (0.6)	8 (2.3)	2 (0.6)	12 (1.7)	4 (0.6)	0	0	0	0
Blood corticotrophin decreased	2 (0.6)	1 (0.3)	0	0	2 (0.3)	1 (0.1)	0	0	0	0

Table 37: Summary of irAEs (any Grade and Grade ⩾ 3) by cluster and PT - SAS

Cluster and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
Hypophysitis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.4)	2 (0.3)	0	0	1 (0.5)	1 (0.5)
Hypothalamo-pituitary disorder	2 (0.6)	1 (0.3)	0	0	2 (0.3)	1 (0.1)	0	0	0	0
Adrenocorticotropic hormone deficiency	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Immune-mediated hypophysitis	0	0	1 (0.3)	0	1 (0.1)	0	0	0	0	0
Lymphocytic hypophysitis	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)	0	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS	8 (2.3)	1 (0.3)	16 (4.6)	4 (1.1)	24 (3.4)	5 (0.7)	0	0	1 (0.5)	0
Psoriasis	5 (1.4)	0	3 (0.9)	1 (0.3)	8 (1.1)	1 (0.1)	0	0	1 (0.5)	0
Vitiligo	2 (0.6)	0	3 (0.9)	0	5 (0.7)	0	0	0	0	0
Dermatitis psoriasiform	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0	0	0	0
Polymyalgia rheumatica	1 (0.3)	0	5 (1.4)	2 (0.6)	6 (0.9)	2 (0.3)	0	0	0	0
Rheumatoid arthritis	1 (0.3)	1 (0.3)	1 (0.3)	0	2 (0.3)	1 (0.1)	0	0	0	0
Sjogren's syndrome	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0	0	0	0
Immune thrombocytopenia	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)	0	0	0	0
Pulmonary sarcoidosis	0	0	1 (0.3)	0	1 (0.1)	0	0	0	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS	7 (2.0)	6 (1.7)	4 (1.1)	4 (1.1)	11 (1.6)	10 (1.4)	0	0	3 (1.6)	2 (1.1)
Diabetes mellitus	4 (1.1)	3 (0.9)	0	0	4 (0.6)	3 (0.4)	0	0	1 (0.5)	0
Diabetic ketoacidosis	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	3 (0.4)	3 (0.4)	0	0	0	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	3 (0.9)	3 (0.9)	4 (0.6)	4 (0.6)	0	0	0	0
Hyperglycaemia	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)	0	0	2 (1.1)	2 (1.1)
IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION	6 (1.7)	4 (1.1)	9 (2.6)	7 (2.0)	15 (2.1)	11 (1.6)	0	0	2 (1.1)	1 (0.5)
Acute kidney injury	2 (0.6)	1 (0.3)	5 (1.4)	4 (1.1)	7 (1.0)	5 (0.7)	0	0	1 (0.5)	0
Renal impairment	2 (0.6)	1 (0.3)	1 (0.3)	0	3 (0.4)	1 (0.1)	0	0	0	0
Glomerulonephritis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Nephritis	1 (0.3)	1 (0.3)	3 (0.9)	3 (0.9)	4 (0.6)	4 (0.6)	0	0	0	0

Table 37: Summary of irAEs (any Grade and Grade ⩾ 3) by cluster and PT - SAS

Cluster and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
Renal failure	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Glomerulonephritis membranous	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)	0	0	0	0
Tubulointerstitial nephritis	0	0	0	0	0	0	0	0	1 (0.5)	1 (0.5)
MYASTHENIC SYNDROME/MYASTHENIA GRAVIS	2 (0.6)	1 (0.3)	0	0	2 (0.3)	1 (0.1)	0	0	0	0
Myasthenic syndrome	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Ocular myasthenia	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
MYOCARDITIS	1 (0.3)	1 (0.3)	3 (0.9)	2 (0.6)	4 (0.6)	3 (0.4)	0	0	0	0
Immune-mediated myocarditis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Myocarditis	0	0	3 (0.9)	2 (0.6)	3 (0.4)	2 (0.3)	0	0	0	0
MYOSITIS	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	3 (0.4)	2 (0.3)	0	0	0	0
Autoimmune myositis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Immune-mediated myositis	0	0	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.1)	0	0	0	0
UVEITIS	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	1 (0.5)	0
Uveitis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Iritis	0	0	0	0	0	0	0	0	1 (0.5)	0

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Patients reporting more than one adverse event within a preferred term are counted only once in that preferred term.
Patients reporting multiple preferred terms within the same cluster are counted only once within each cluster.
For patients reporting more than one AE within a cluster or preferred term, the AE with maximum grade is included in the table.
MedDRA v23.1 applied for B8011001, MedDRA v25.0 applied for B8011007 and MedDRA v27.1 applied for B8011006.
PFIZER CONFIDENTIAL Source Data: adaei ADaM Creation: 28JAN2025 (12:37) Date of Table Generation: 31JAN2025 (13:44)
PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output File: ./b801_scs/B801_SCS_CSR1/adaei_s0311
Table 14.3.1.6.1 is for Pfizer internal use.

Serious Adverse Events

All-causality SAEs

The most common (≥2 patients) all-causality SAEs are summarized by PT in Table 38.

Table 38: Summary of most common serious TEAEs (≥ 2 patients in any treatment group) by PT during the on-treatment period - SAS

Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Patients with Any Adverse Event	120 (34.3)	99 (28.4)	219 (31.4)	49 (14.0)	57 (31.1)
Pneumonia	9 (2.6)	3 (0.9)	12 (1.7)	4 (1.1)	5 (2.7)
COVID-19	6 (1.7)	5 (1.4)	11 (1.6)	4 (1.1)	0
Urinary tract infection	5 (1.4)	1 (0.3)	6 (0.9)	1 (0.3)	1 (0.5)
Arthritis	4 (1.1)	0	4 (0.6)	0	0
Pancreatitis	4 (1.1)	1 (0.3)	5 (0.7)	0	0
Sepsis	4 (1.1)	1 (0.3)	5 (0.7)	0	3 (1.6)
Acute kidney injury	3 (0.9)	4 (1.1)	7 (1.0)	0	1 (0.5)
Adrenal insufficiency	3 (0.9)	3 (0.9)	6 (0.9)	0	0
Breast cancer	3 (0.9)	0	3 (0.4)	0	0
Colitis ulcerative	3 (0.9)	1 (0.3)	4 (0.6)	0	0
Coronary artery disease	3 (0.9)	0	3 (0.4)	1 (0.3)	0
Diabetes mellitus	3 (0.9)	1 (0.3)	4 (0.6)	0	0
Immune-mediated lung disease	3 (0.9)	0	3 (0.4)	0	0
Pneumonitis	3 (0.9)	2 (0.6)	5 (0.7)	0	2 (1.1)
Type 2 diabetes mellitus	3 (0.9)	0	3 (0.4)	0	0
Acute myocardial infarction	2 (0.6)	0	2 (0.3)	0	0
Autoimmune hepatitis	2 (0.6)	0	2 (0.3)	0	0
Cardiac failure	2 (0.6)	0	2 (0.3)	1 (0.3)	1 (0.5)
Chronic obstructive pulmonary disease	2 (0.6)	1 (0.3)	3 (0.4)	0	1 (0.5)
Diabetic ketoacidosis	2 (0.6)	1 (0.3)	3 (0.4)	0	0
Haematuria	2 (0.6)	1 (0.3)	3 (0.4)	0	0
Hepatitis	2 (0.6)	0	2 (0.3)	0	0
Hypopituitarism	2 (0.6)	2 (0.6)	4 (0.6)	0	0
Hypotension	2 (0.6)	0	2 (0.3)	0	1 (0.5)

Table 38: Summary of most common serious TEAEs (≥ 2 patients in any treatment group) by PT during the on-treatment period - SAS

Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Myocardial infarction	2 (0.6)	3 (0.9)	5 (0.7)	1 (0.3)	0
Pancreatitis acute	2 (0.6)	2 (0.6)	4 (0.6)	1 (0.3)	1 (0.5)
Peripheral arterial occlusive disease	2 (0.6)	0	2 (0.3)	0	0
Pyrexia	2 (0.6)	0	2 (0.3)	0	0
Respiratory failure	2 (0.6)	0	2 (0.3)	0	0
Angina pectoris	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)	0
Arthralgia	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Arthritis reactive	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Asthenia	1 (0.3)	2 (0.6)	3 (0.4)	0	0
COVID-19 pneumonia	1 (0.3)	3 (0.9)	4 (0.6)	0	0
Cataract	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Cerebrovascular accident	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.6)	0
Cholecystitis	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Cholecystitis acute	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Dermatitis allergic	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Hypophysitis	1 (0.3)	1 (0.3)	2 (0.3)	0	1 (0.5)
Inguinal hernia	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Intervertebral disc protrusion	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Lacunar infarction	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Peripheral ischaemia	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Prostate cancer	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)	0
Renal colic	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Respiratory tract infection	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)	0
Secondary adrenocortical insufficiency	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Suspected COVID-19	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Type 1 diabetes mellitus	1 (0.3)	2 (0.6)	3 (0.4)	0	0
Urethral stenosis	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Urinary retention	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)	0

Table 38: Summary of most common serious TEAEs (≥ 2 patients in any treatment group) by PT during the on-treatment period - SAS

Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Anaemia	0	3 (0.9)	3 (0.4)	1 (0.3)	5 (2.7)
Atrial fibrillation	0	0	0	2 (0.6)	0
Benign prostatic hyperplasia	0	0	0	2 (0.6)	0
Bronchitis	0	2 (0.6)	2 (0.3)	0	1 (0.5)
Disease progression	0	0	0	0	10 (5.5)
Dysphagia	0	0	0	0	2 (1.1)
Haemoptysis	0	0	0	0	2 (1.1)
Hydronephrosis	0	0	0	0	2 (1.1)
Hyponatraemia	0	2 (0.6)	2 (0.3)	1 (0.3)	0
Large intestine polyp	0	0	0	2 (0.6)	0
Lung neoplasm malignant	0	0	0	1 (0.3)	3 (1.6)
Myocarditis	0	2 (0.6)	2 (0.3)	0	0
Pneumonia bacterial	0	2 (0.6)	2 (0.3)	0	0
Polymyalgia rheumatica	0	2 (0.6)	2 (0.3)	0	0
Pyelonephritis	0	2 (0.6)	2 (0.3)	0	1 (0.5)

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Patients reporting more than one adverse event within a preferred term are counted only once in that preferred term.
Sorted in descending order of the frequency of PTs by all grades in B801006 Sasanlimab + BCG (IND+MNT) arm.
MedDRA v27.1 coding dictionary applied.
With any adverse events row includes all patients without cutoff.
PFIZER CONFIDENTIAL Source Data: adae ADaM Creation: 28JAN2025 (12:33) Date of Table Generation: 20FEB2025 (14:02)
PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output File: ./b801_scs/B801_SCS_CSR1/adae_s183ms Table 14.3.2.2.4 is for Pfizer internal use.

Deaths

Deaths are summarized in Table 39.

Table 39: Summary of deaths - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)	B8011006 Sasanlimab + BCG (IND) (N=348)	B8011006 Pooled Sasanlimab + BCG (N=698)	B8011006 BCG (IND+MNT) (N=349)	Pooled Sasanlimab Monotherapy (N=183)

Table 39: Summary of deaths - SAS

	B8011006 Sasanlimab + BCG (IND+MNT) (N=350)	B8011006 Sasanlimab + BCG (IND) (N=348)	B8011006 Pooled Sasanlimab + BCG (N=698)	B8011006 BCG (IND+MNT) (N=349)	Pooled Sasanlimab Monotherapy (N=183)
Deaths	32 (9.1)	29 (8.3)	61 (8.7)	29 (8.3)	80 (43.7)
Cause of death					
Disease under study	5 (1.4)	3 (0.9)	8 (1.1)	10 (2.9)	65 (35.5)
Study treatment toxicity	0	3 (0.9)	3 (0.4)	1 (0.3)	0
Other	18 (5.1)	19 (5.5)	37 (5.3)	12 (3.4)	11 (6.0)
Unknown	9 (2.6)	4 (1.1)	13 (1.9)	6 (1.7)	4 (2.2)
Deaths within 30 days after last dose of study treatment	6 (1.7)	4 (1.1)	10 (1.4)	2 (0.6)	21 (11.5)
Cause of death					
Disease under study	0	0	0	0	14 (7.7)
Study treatment toxicity	0	2 (0.6)	2 (0.3)	0	0
Other	6 (1.7)	2 (0.6)	8 (1.1)	2 (0.6)	6 (3.3)
Unknown	0	0	0	0	1 (0.5)
Deaths due to COVID-19	3 (0.9)	0	3 (0.4)	2 (0.6)	1 (0.5)

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
"Other" includes adverse events not related to study treatment.
PFIZER CONFIDENTIAL Source Data: adsl ADaM Creation: 27JAN2025 (16:52) Date of Table Generation: 31JAN2025 (15:01)
PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output File: ./b801_scs/B801_SCS_CSR1/adae_s500a

TEAEs leading to death are summarized in Table 40. In the pooled sasanlimab + BCG group, the MedDRA SOC with the highest frequency of TEAEs leading to death was Infections and Infestations (5 out of 10), followed by Cardiac Disorders (4 out of 10). Treatment-related TEAEs leading to death occurred in 2 (0.6%) patients in the sasanlimab + BCG (IND) arm and included Myocarditis and Pneumonia bacterial (Table not shown). The fatal TEAE of Pneumonia bacterial occurred in a patient with ongoing myocarditis.

Table 40: Summary of TEAEs during the on-treatment period leading to death by SOC and PT - SAS

System Organ Class and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)

Table 40: Summary of TEAEs during the on-treatment period leading to death by SOC and PT - SAS

System Organ Class and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Patients With Any Adverse Event	6 (1.7)	4 (1.1)	10 (1.4)	2 (0.6)	21 (11.5)
INFECTIONS AND INFESTATIONS	3 (0.9)	2 (0.6)	5 (0.7)	1 (0.3)	1 (0.5)
COVID-19	1 (0.3)	0	1 (0.1)	0	0
Pneumonia	1 (0.3)	0	1 (0.1)	1 (0.3)	0
Sepsis	1 (0.3)	0	1 (0.1)	0	0
Suspected COVID-19	1 (0.3)	0	1 (0.1)	0	0
Pneumonia bacterial	0	1 (0.3)	1 (0.1)	0	0
Septic shock	0	1 (0.3)	1 (0.1)	0	0
Urinary tract infection	0	0	0	0	1 (0.5)
CARDIAC DISORDERS	2 (0.6)	2 (0.6)	4 (0.6)	0	2 (1.1)
Cardiac arrest	1 (0.3)	0	1 (0.1)	0	0
Cardiac failure	1 (0.3)	0	1 (0.1)	0	1 (0.5)
Cardiogenic shock	0	0	0	0	1 (0.5)
Myocardial infarction	0	1 (0.3)	1 (0.1)	0	0
Myocarditis	0	1 (0.3)	1 (0.1)	0	0
NERVOUS SYSTEM DISORDERS	1 (0.3)	0	1 (0.1)	0	1 (0.5)
Cerebrovascular accident	1 (0.3)	0	1 (0.1)	0	0
Cerebral infarction	0	0	0	0	1 (0.5)
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (0.5)
Gastric ulcer haemorrhage	0	0	0	0	1 (0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	0	11 (6.0)
Disease progression	0	0	0	0	10 (5.5)
Multiple organ dysfunction syndrome	0	0	0	0	1 (0.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	1 (0.3)	4 (2.2)
Lung neoplasm malignant	0	0	0	0	3 (1.6)
Neoplasm progression	0	0	0	0	1 (0.5)
Non-Hodgkin's lymphoma	0	0	0	1 (0.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	1 (0.5)

Table 40: Summary of TEAEs during the on-treatment period leading to death by SOC and PT - SAS

System Organ Class and Preferred Term	B8011006 Sasanlimab + BCG (IND+MNT) (N=350) n (%)	B8011006 Sasanlimab + BCG (IND) (N=348) n (%)	B8011006 Pooled Sasanlimab + BCG (N=698) n (%)	B8011006 BCG (IND+MNT) (N=349) n (%)	Pooled Sasanlimab Monotherapy (N=183) n (%)
Acute respiratory distress syndrome	0	0	0	0	1 (0.5)

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Patients reporting more than one adverse event within a preferred term are counted only once in that preferred term.
Patients reporting multiple preferred terms within the same system organ class (SOC) are counted only once within each SOC.
MedDRA v27.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae ADaM Creation: 28JAN2025 (12:33) Date of Table Generation: 31JAN2025 (13:44)
PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output File: ./b801_scs/B801_SCS_CSR1/adae_s050 Table 14.3.1.2.7 is for Pfizer internal use.

5.4.5. Discontinuation due to adverse events

Treatment-related TEAEs leading to discontinuation of sasanlimab occurred in 26.3% of patients in the sasanlimab + BCG (IND+MNT) and in 16.7% of patients in the sasanlimab + BCG (IND) arm. The most frequent treatment-related TEAEs leading to discontinuation of sasanlimab were: Sasanlimab + BCG (IND+MNT) (⩾1% of patients): lipase increased (3.4%), amylase increased and adrenal insufficiency (1.4%), each, pancreatitis, arthralgia, pyrexia, and diabetes mellitus (1.1% each). Sasanlimab + BCG (IND) (⩾0.9% of patients): lipase increased and adrenal insufficiency (0.9% each).

Treatment-related TEAEs leading to discontinuation of BCG occurred in 16.9% of patients in the sasanlimab + BCG (IND+MNT) arm, 2.3% of patients in the sasanlimab + BCG (IND), and 8.6% of patients in the BCG (IND+MNT).

The most frequent treatment-related TEAEs leading to discontinuation of BCG were:

Sasanlimab + BCG (IND+MNT) (⩾1.0% of patients): dysuria and pollakiuria (1.7% each), and urinary tract infection and cystitis (1.1% each).

Sasanlimab + BCG (IND) (⩾0.6% of patients): Arthritis reactive and BCG-related cystitis (0.6% each).

BCG (IND+MNT) (⩾1.0% of patients): Dysuria and pollakiuria (2.0% each), cystitis (1.4%), and pyrexia (1.1%).

5.4.6. Safety in special populations

Table 41: Summary of adverse events by age group – SAS

		B8011006 Sasanlimab + BCG (IND+MNT) (N=350)		B8011006 Sasanlimab + BCG (IND) (N=348)		B8011006 Pooled Sasanlimab + BCG (N=698)		B8011006 BCG (IND+MNT) (N=349)		Pooled Sasanlimab Monotherapy (N=183)	
Number (%) of Patients		**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**	
Number of patients by age group [1]											
Age	<65 years	140	(40.0)	140	(40.2)	280	(40.1)	133	(38.1)	82	(44.8)
Age	≥65 years	210	(60.0)	208	(59.8)	418	(59.9)	216	(61.9)	101	(55.2)
Patients with TEAEs											
Age	<65 years	133	(95.0)	125	(89.3)	258	(92.1)	119	(89.5)	79	(96.3)
Age	≥65 years	208	(99.0)	201	(96.6)	409	(97.8)	191	(88.4)	98	(97.0)
Patients with grade ≥ 3 TEAEs											
Age	<65 years	65	(46.4)	54	(38.6)	119	(42.5)	34	(25.6)	39	(47.6)
Age	≥65 years	106	(50.5)	87	(41.8)	193	(46.2)	56	(25.9)	45	(44.6)
Patients with treatment-related TEAEs											
Age	<65 years	117	(83.6)	107	(76.4)	224	(80.0)	92	(69.2)	49	(59.8)
Age	≥65 years	188	(89.5)	168	(80.8)	356	(85.2)	153	(70.8)	58	(57.4)
Patients with grade ≥ 3 treatment-related TEAEs											
Age	<65 years	38	(27.1)	31	(22.1)	69	(24.6)	10	(7.5)	14	(17.1)
Age	≥65 years	64	(30.5)	45	(21.6)	109	(26.1)	12	(5.6)	10	(9.9)
Patients with serious TEAEs											
Age	<65 years	34	(24.3)	34	(24.3)	68	(24.3)	13	(9.8)	22	(26.8)
Age	≥65 years	86	(41.0)	65	(31.3)	151	(36.1)	36	(16.7)	35	(34.7)
Patients with treatment-related serious TEAEs											
Age	<65 years	21	(15.0)	16	(11.4)	37	(13.2)	1	(0.8)	5	(6.1)
Age	≥65 years	41	(19.5)	27	(13.0)	68	(16.3)	4	(1.9)	7	(6.9)
Patients with TEAEs leading to death											
Age	<65 years	4	(2.9)	0		4	(1.4)	1	(0.8)	6	(7.3)
Age	≥65 years	2	(1.0)	4	(1.9)	6	(1.4)	1	(0.5)	15	(14.9)
Patients with treatment-related TEAEs leading to death											
Age	<65 years			0		0		0		0	

Age	≥65 years	0		2	(1.0)	2	(0.5)	0		0	
Patients with Injection site reactions (ISRs) Related to Sasanlimab											
Age	<65 years	2	(1.4)	4	(2.9)	6	(2.1)	0		1	(1.2)
Age	≥65 years	6	(2.9)	9	(4.3)	15	(3.6)	0		3	(3.0)

Abbreviations: BCG: Bacillus Calmette-Guérin; IND+MNT I+M: induction + maintenance; ISRs: injection site reactions; TEAEs: treatment-emergent adverse events.

5.4.7. Immunological events

Immunogenicity

Evaluation of the impact of immunogenicity on PK, efficacy, and safety results were limited due to the low immunogenicity incidence. At the proposed dose of 300 mg SC Q4W, administered as monotherapy or in combination with BCG, the ADA and neutralizing antibody (Nab) incidence was 6.0% (51/855) and 0.6% (5/855), respectively. The median onset of treatment emergent ADA was 140 days (ranging from 25 days – 434 days). For more details see section 5.2.3.5.

5.4.8. Safety related to drug-drug interactions and other interactions

The risk of DDIs with sasanlimab is low. Sasanlimab is not renally excreted and is expected to be metabolized primarily by catabolic degradation following endocytosis by the mononuclear phagocytic system. Based on nonclinical studies, sasanlimab has low potential for DDI via cytokine modulation. It is not expected to interact with other mAbs at therapeutic levels.

In Study B8011006 Cohort A, there were no differences in sasanlimab PK between the sasanlimab + BCG (IND+MNT) arm and the sasanlimab + BCG (IND) arm. Additionally, the absence of apparent differences in sasanlimab exposure between the two arms even after patients were no longer receiving BCG in Arm B (sasanlimab + BCG [IND]) indicates that concomitant intravesical administration of BCG does not impact sasanlimab PK.

There were no adverse drug interactions reported based on the search using the MedDRA HLT Interactions.

5.4.9. Vital signs and laboratory findings

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital sign abnormalities were reported as TEAEs. No clinically meaningful findings in ECGs were observed in any treatment arm/group.

Gender

- In the pooled sasanlimab + BCG combination group, the median duration of exposure to sasanlimab and BCG tended to be higher in females than males.
- There were no relevant differences in TEAEs between gender subgroups, however, serious treatment-related TEAEs appear to be more frequent in males than females.

Race – White/Asian/Black or African American/Other

- Treatment exposure was similar between race subgroups of White and Asian. There was a small number of Black or African American patients, limiting comparisons with this subgroup.
- There were no relevant differences in TEAEs between the White and Asian subgroups, however frequencies of treatment-related Grade 3 and serious TEAEs appear to be higher in Asian than White patients.
- TEAEs leading to death appear to be more frequent in White patients than in Asian patients, however, the overall number of TEAEs leading to death is small.
- There was a low number of patients of Hispanic or Latino or of Spanish origin, which limits comparisons between subgroups. However, there were no apparent differences in the exposure or frequency of TEAEs across the ethnicity subgroups.

Geographic Region (US/Western Europe and Canada/ROW)

Median duration of treatment exposure was generally higher in the geographic subgroup for Rest of World, compared with the US and Western Europe/Canada.

No relevant differences were observed across geographic regions on the frequencies of TEAEs, except discontinuations due to TEAEs (all causalities and treatment-related) appear to be higher in Western Europe than other regions.

Haematology and Chemistry Laboratory Evaluations

Shifts from Grade ≤2 to Grade 3 and Grade 4 for all haematology tests occurred in <1% of patients except lymphocyte count decreased, in which shifts to Grade 3 occurred in 6 (1.72%) patients in the sasanlimab + BCG (IND+MNT) arm. A summary of maximum on-treatment CTCAE Grade 3-4 chemistry laboratory results is provided in Table 42.

Liver Function Tests

B8011006 Cohort A

ALT, AST, and bilirubin elevations occurred most frequently in the sasanlimab + BCG (IND+MNT) arm, followed by the sasanlimab + BCG (IND) arm (Table 42). There were no patients in any of the treatment arms with liver function tests consistent with Hy's Law criteria.

Pooled Sasanlimab Monotherapy

There were no patients with liver function tests consistent with Hy's law criteria.

Thyroid Function Tests

The number of patients with at least 1 on-treatment abnormality was:

- Sasanlimab + BCG (IND+MNT): 48/308 (46.2%);
- Sasanlimab + BCG (IND): 48/302 (46.6%)
- BCG (IND+MNT): 29/311 (25.7%)
- Pooled sasanlimab monotherapy: 10/116 (62.5%)

Table 42: Shift summary of chemistry laboratory test results during the on-treatment period by maximum CTCAE grade (grade ⩽ 2 to grade 3/4) - SAS

	Maximum On-treatment CTCAE Grade																			
	B8011006 Sasanlimab + BCG (IND+MNT)				B8011006 Sasanlimab + BCG (IND)				B8011006 Pooled Sasanlimab + BCG				B8011006 BCG (IND+MNT)				Pooled Sasanlimab Monotherapy			
		Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4
Parameter	**N**	**n**	**(%)**	**n (%)**	**N**	**n**	**(%)**	**n (%)**	**N**	**n**	**(%)**	**n (%)**	**N**	**n**	**(%)**	**n (%)**	**N**	**n**	**(%)**	**n (%)**
Alanine aminotransferase increased	348	11	(3.16)	4 (1.15)	346	8	(2.31)	2 (0.58)	694	19	(2.74)	6 (0.86)	346	4	(1.16)	0	178	5	(2.81)	1 (0.56)
Alkaline phosphatase increased	348	5	(1.44)	0	346	4	(1.16)	0	694	9	(1.30)	0	346	0		0	177	3	(1.69)	0
Aspartate aminotransferase increased	348	12	(3.45)	4 (1.15)	346	9	(2.60)	2 (0.58)	694	21	(3.03)	6 (0.86)	346	2	(0.58)	0	177	2	(1.13)	2 (1.13)
Blood bilirubin increased	348	1	(0.29)	0	346	2	(0.58)	0	694	3	(0.43)	0	346	0		0	177	1	(0.56)	0
Creatinine increased	347	4	(1.15)	2 (0.58)	346	6	(1.73)	0	693	10	(1.44)	2 (0.29)	346	1	(0.29)	0	177	3	(1.69)	0
Hypercalcemia	348	0		4 (1.15)	344	0		1 (0.29)	692	0		5 (0.72)	346	1	(0.29)	2 (0.58)	177	1	(0.56)	3 (1.69)
Hyperkalemia	349	3	(0.86)	1 (0.29)	346	9	(2.60)	1 (0.29)	695	12	(1.73)	2 (0.29)	346	5	(1.45)	1 (0.29)	177	4	(2.26)	0
Hypermagnesemia	347	5	(1.44)	0	346	6	(1.73)	0	693	11	(1.59)	0	346	10	(2.89)	0	177	11	(6.21)	0
Hypernatremia	348	0		1 (0.29)	346	0		2 (0.58)	694	0		3 (0.43)	346	2	(0.58)	1 (0.29)	177	2	(1.13)	0
Hypoalbuminemia	348	0		0	345	0		0	693	0		0	346	3	(0.87)	0	177	1	(0.56)	0
Hypocalcemia	348	5	(1.44)	7 (2.01)	344	0		5 (1.45)	692	5	(0.72)	12 (1.73)	346	7	(2.02)	4 (1.16)	177	0		2 (1.13)
Hypoglycemia	350	2	(0.57)	2 (0.57)	345	1	(0.29)	1 (0.29)	695	3	(0.43)	3 (0.43)	346	0		0	125	0		0
Hypokalemia	349	5	(1.43)	1 (0.29)	346	2	(0.58)	0	695	7	(1.01)	1 (0.14)	346	2	(0.58)	0	177	3	(1.69)	0
Hypomagnesemia	347	0		0	346	1	(0.29)	0	693	1	(0.14)	0	346	1	(0.29)	1 (0.29)	177	3	(1.69)	0
Hyponatremia	348	13	(3.74)	1 (0.29)	346	9	(2.60)	2 (0.58)	694	22	(3.17)	3 (0.43)	346	9	(2.60)	2 (0.58)	177	11	(6.21)	2 (1.13)
Lipase increased	346	57	(16.47)	29 (8.38)	344	30	(8.72)	20 (5.81)	690	87	(12.61)	49 (7.10)	344	27	(7.85)	3 (0.87)	175	7	(4.00)	6 (3.43)
Serum amylase increased	342	27	(7.89)	6 (1.75)	338	23	(6.80)	5 (1.48)	680	50	(7.35)	11 (1.62)	336	4	(1.19)	0	177	8	(4.52)	1 (0.56)

The denominator to calculate percentages is N, the number of patients in the safety analysis set who have at least one on-treatment assessment for the parameter of interest in each treatment group.
NCI-CTCAE criteria version 5.0 is used. NA: CTCAE grade not defined.
PFIZER CONFIDENTIAL Source Data: adlb ADaM Creation: 28JAN2025 (12:42) Date of Table Generation: 03FEB2025 (16:02)
PF-06801591 Study B8011006 - (Cutoff Date: 02Dec2024 Snapshot Date: 19Dec2024) Pooled Sasanlimab Monotherapy: Study B8011001 - (Cutoff Date: 19Nov2020, Snapshot Date: 23Dec2020) and Study B8011007 - (Cutoff Date: 07Sep2022, Snapshot Date: 04Oct2022) Output File: ./b801_scs/B801_SCS_CSR1/adlb_s516_a1
Table 14.3.4.1.2.2 is for Pfizer internal use.

5.4.10. Post-marketing experience

Sasanlimab has not been marketed in any country.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

Safety data collection

The safety data collection was based on MedDRA version 27.1 across all studies, except for the irAEs analyses which applied the MedDRA version of each respective study CSRs, ie, MedDRA version 27.1 (B8011006), 23.1 (B8011001), and 25.0 (B8011007); NCI CTCAE version 5.0 was applied to studies B8011006 and B8011007 and version 4.03 was applied to study B8011001. The used methods are considered standard and are therefore adequate to characterize the safety profile of sasanlimab. The open-label design of the pivotal study B8011006 combined with the prior knowledge of PD-1 receptor blockers and local BCG therapy could induce bias during the safety data collection of the combination therapy.

Based on the applied indication the safety assessment is focused on arm A sasanlimab + BCG (IND+MNT) versus arm C BCG (IND+MNT) for the B/R assessment. However, the Applicant presents the safety data of the pooled dataset of sasanlimab in combination with BCG in BCG-naïve, high-risk NMIBC (n=698) in the SmPC. The pooling of the data of sasanlimab in combination with BCG as IND or MNT in the sasanlimab SmPC is agreed even though the duration of BCG treatment was shorter in Arm B as patients continued treatment with sasanlimab in both arms up to 24 months.

Demographics and baseline disease characteristics

Overall, demographic and baseline disease characteristics were similar between treatment arms in study B8011006 Arm A. The median age was 67 years and approximately 80% of patients were males. Approximately 25% had CIS at randomization.

The demographic characteristics were overall similar between the pooled sasanlimab + BCG combination group and the sasanlimab monotherapy group except for ECOG PS which was mostly zero in the combination group and mostly 1 in the sasanlimab monotherapy group, reflecting the more advanced stage of the underlying disease in this group.

Patient exposure

The pivotal study B8011006 included several arms. The sasanlimab + BCG (IND+MNT) arm consisted of 350 patients included in the safety analysis set. The BCG (IND+MNT) control arm consisted of 349 patients. The sample size for the safety data base is considered sufficient.

The exposure to sasanlimab (median number of doses received and median treatment duration) was similar between the sasanlimab + BCG combination arms in study B8011006 arm A. Exposure to BCG was also similar between the sasanlimab + BCG (IND+MNT) arm and the BCG (IND+MNT) arm.

The median duration of exposure to sasanlimab was 80.3 weeks in the sasanlimab + BCG (IND+MNT) arm and 84.8 weeks in the sasanlimab + BCG (IND) arm. The median duration of exposure to BCG was 98.1 weeks in the sasanlimab + BCG (IND+MNT) arm, and 98.9 weeks in the BCG (IND+MNT) arm. The duration of exposure is considered sufficient. The extent of population exposure to assess the clinical safety is in line with the ICH E1 requirements population exposure.

The sasanlimab exposure was lower in the pooled sasanlimab monotherapy group (median 20.0 weeks, range 4.0-125.4 weeks) than in the pooled sasanlimab + BCG combination group (median 84.5 weeks, range 4.0-104.4 weeks). This could be due to the inclusion of patients with a lower performance status reflecting a worse prognosis as discussed in the demographics and baseline disease characteristics section.

Adverse events

The safety of sasanlimab in combination with BCG was evaluated in the pivotal study B8011006. Patients were treated with sasanlimab + BCG (IND+MNT, arm A) (N=350), sasanlimab + BCG (IND) (N=348), and BCG (IND+MNT, arm C) (N=349).

More patients **discontinued with BCG treatment due to treatment-emergent adverse events** (TEAEs) in the sasanlimab + BCG (IND+MNT) arm compared to the BCG arm, 22% versus 10% respectively. TEAEs leading to discontinuation of all study drugs occurred in 8% of the patients in the sasanlimab + BCG (IND+MNT) arm. Treatment-related TEAEs leading to discontinuation of sasanlimab occurred in 26.3% of the patients. The addition of sasanlimab to BCG (IND+MNT) induced additional toxicity which is illustrated by the increased rate of TEAEs including serious TEAEs. The added toxicity of sasanlimab to BCG (IND+MNT) could result in a loss of chance for patients to benefit from the current standard of care in this treatment setting.

TEAEs of any grade were reported in 97.4% of patients in the sasanlimab + BCG (IND+MNT) arm and 88.8% in the BCG (IND+MNT) arm. **Treatment related TEAEs** were reported in 87.1% of patients in the sasanlimab + BCG (IND+MNT) arm and 70.2% in the BCG (IND+MNT) arm.

Grade 3 or higher TEAEs were reported more frequently in patients in the sasanlimab + BCG (IND+MNT) arm 48.9% versus 25.8% in the BCG (IND+MNT) arm.

Serious TEAEs or higher TEAEs were reported more frequently in patients in the sasanlimab + BCG (IND+MNT) arm 34.3% versus 14.0% in the BCG (IND+MNT) arm C.

The most common (≥20%) all-causality TEAEs of any grade were dysuria (33%), haematuria (28%), urinary tract infection (26%), pollakiuria (24%), lipase increased (22%), and pyrexia (21%) in the sasanlimab + BCG (IND+MNT) arm.

The most common (≥3%) all-causality TEAEs of Grade ≥3 were lipase increased (7.7%) and haematuria (5.7%) in the sasanlimab + BCG (IND+MNT) arm and haematuria (3.4%) in the BCG (IND+MNT) arm.

The frequencies of treatment-related TEAEs Any Grade and Grade ≥3 were generally higher in the sasanlimab + BCG (IND+MNT) arm (87.1% and 29.1%, respectively) than in the BCG (IND+MNT) arm (70.2% and 6.3%, respectively).

The most common (≥10%) **treatment-related TEAEs of any grade** for **sasanlimab + BCG** (IND+MNT) were: dysuria (29.4%), pollakiuria (22.9%), haematuria (20.9%), urinary tract infection

(19.1%), lipase increased (17.4%), pyrexia (15.4), hypothyroidism (14.3), amylase increased (11.7%), alanine aminotransferase increased (10.9%), cystitis (10.9%), aspartate aminotransferase increased (10.6%), micturition urgency (10.3%), and fatigue (10.0%).

The most common (≥1%) **treatment-related TEAEs of Grade ≥3** for sasanlimab + BCG (IND+MNT) were: lipase increased (6.0%), haematuria (4.0%), amylase increased (2.3%), alanine aminotransferase increased (2.3%), aspartate aminotransferase increased (2.0%), urinary tract infection (2.0%), pancreatitis (1.7%), gamma-glutamyltransferase increased (1.4%), diabetes mellitus (1.1%), adrenal insufficiency (1.1%).

Adverse drug reactions

ADRs included TEAEs for which, after thorough assessment, a causal relationship between sasanlimab in combination with BCG and the TEAE was at least a reasonable possibility. The ADRs included TEAEs that were classified as irAEs or TEAEs reported in ≥10% of patients by PT or cluster of PTs in either the sasanlimab + BCG (IND+MNT) or sasanlimab + BCG (IND) arms and at higher rate (≥5% for Any Grade or ≥2% for Grade ≥3) than the BCG (IND+MNT) arm. In addition, ADRs reported at ≥10% and known to be adverse drug reactions to intravesical BCG were also included (i.e., urinary signs and symptoms) to more properly reflect the safety profile of the sasanlimab + BCG combination treatment. In the pooled sasanlimab + BCG combination group (N=698), the most frequent adverse reactions (≥20%) were urinary tract infection (28.9%), dysuria (26.8%), fatigue (24.2%), haematuria (21.3%), rash (20.9%), pyrexia (19.9%), lipase increased (19.5%) and hepatotoxicity (18.6%). The methodology to identify the ADRs is not fully agreed. The tabulated list of adverse reactions includes the frequencies which are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from the available data) in the SmPC description. The Applicant is requested to provide updated tables and also to include the ADRs which occurred at the lower frequencies (**Rapp OC**). In addition, the Applicant is requested to provide a separate table with the numerical frequencies. The identified ADRs resemble the expected ADR profile for the combination of systemic anti PD-1 therapies with local BCG therapy which is considered non-negligible.

Adverse Events of Special Interest (AESI): Immune-related AEs(irAEs)

In the pooled sasanlimab + BCG combination group, irAEs of Any Grade occurred in 312 (44.7%) of patients, including Grade 2 in 144 (20.6%), Grade 3 in 86 (12.3%), Grade 4 in 17 (2.4%) and Grade 5 in 1 (0.1%) (PT: Myocarditis). The most common irAEs Any Grade by Clusters were IR thyroid disorders in 133 (19.1%) and IR rash in 94 patients (13.5%). The most common irAEs Grade ≥3 by Clusters were IR hepatitis in 23 (3.3%) and IR rash in 18 (2.6%). The median time to onset of irAEs was 3.7 months (range: 0.0, 24.2 months). The median duration was 4.21 months (range: 0.0, 25.9+ months). irAEs leading to discontinuation of sasanlimab were reported in 112 (16.0%) of patients. irAEs leading to discontinuation of BCG were reported in 11 (1.6%) of patients. The most common irAEs leading to discontinuation of sasanlimab by Clusters were IR rash in 20 (2.9%), and IR hepatitis in 19 (2.7%).

Systemic corticosteroids were administered in 139/312 (44.6%) of patients who experienced irAEs, including 77/312 (24.7%) who were administered high dose corticosteroids (≥40 mg daily prednisolone or equivalent). The median duration of corticosteroid treatment was 3.65 months (range 0.0 – 46.4 months). Furthermore, 10 subjects required treatment with immunosuppressants to manage irAEs. This is concerning, as treatment with corticosteroids and immunosuppressants are contraindicated for BCG therapy. It remains unclear whether these treatments may increase vulnerability to systemic BCG infection. The Applicant is requested to discuss whether sasanlimab plus

BCG treated patients receiving systemic corticosteroids and/or immunosuppressants are at increased risk for serious infections and in particular systemic BCG infections. This should include a discussion whether recommendations for discontinuing BCG treatment and information on increased risk of infections, including systemic BCG infection, in these patients should be included in section 4.4 of the SmPC (see also 7.1.2. Discussion on proposed safety specification). Irrespectively, the Applicant should commit to monitoring serious systemic infections and in particular systemic BCG infections as safety issue in PSURs. (**Co-Rapp OC**).

irAEs were reported as resolved in 125/312 (40.1%) of patients at the time of database lock. In the pooled sasanlimab + BCG combination group, irAEs of Any Grade occurred in 312 (44.7%) of patients, including Grade 2 in 144 (20.6%), Grade 3 in 86 (12.3%), Grade 4 in 17 (2.4%) and Grade 5 in 1 (0.1%) (PT: Myocarditis). The irAEs **did not resolve** for the majority of the patients at the time of database lock. This confirms the persistence of long lasting irAEs.

The most common **irAEs Any Grade** by Clusters were IR thyroid disorders in 133 (19.1%) and immune-related rash in 94 patients (13.5%). The most common irAEs Grade ≥3 by Clusters were IR hepatitis in 23 (3.3%) and IR rash in 18 (2.6%). The median time to onset of irAEs was 3.7 months (range: 0.0, 24.2 months). The median duration was 4.21 months (range: 0.0, 25.9+ months). irAEs leading to discontinuation of sasanlimab were reported in 112 (16.0%) of patients. irAEs leading to discontinuation of BCG were reported in 11 (1.6%) of patients.

The most common **irAEs leading to discontinuation of sasanlimab** by clusters were IR rash in 20 (2.9%), and IR hepatitis in 19 (2.7%).

Systemic corticosteroids were administered in 139/312 (44.6%) of patients who experienced irAEs, including 77/312 (24.7%) who were administered high dose corticosteroids (≥40 mg daily prednisolone or equivalent).

The frequency of irAEs including irAEs Grade ≥3 was higher in the pooled sasanlimab + BCG combination group than in the pooled sasanlimab monotherapy group. This may be due to the longer exposure to sasanlimab in the pooled combination group compared to the monotherapy group according to the Applicant. In addition, the more advanced disease settings in Studies B8011001 and B8011007 could have contributed to a decreased immune response and a decreased frequency of irAEs occurrence. The explanation of the Applicant is acknowledged.

Serious Adverse Events

The frequencies of all-causality SAEs were higher in both the sasanlimab + BCG (IND+MNT) arm (34.3%) than in the BCG (IND+MNT) arm (14.0%).

The most common (>1%) all-causality SAEs for the sasanlimab + BCG (IND+MNT) arm were: pneumonia (2.6%), COVID-19 (1.7%), urinary tract infection (1.4%), arthritis (1.1%), and sepsis (1.1%), and pancreatitis (1.1%). For the BCG (IND+MNT) arm those were: pneumonia and COVID-19 (1.1% each).

The frequencies of treatment-related SAEs were higher in both the sasanlimab + BCG (IND+MNT) arm (17.7%) than in the BCG (IND+MNT) arm (1.4%).

The most common treatment-related SAEs (>2 patients) were: Pancreatitis, adrenal insufficiency, colitis ulcerative, diabetes mellitus, immune-mediated lung disease, pneumonitis, type 2 diabetes mellitus, and urinary tract infection in the sasanlimab + BCG (IND+MNT) arm. There were 2 patients with treatment-related SAEs including urinary tract infection and pancreatitis acute in the BCG (IND+MNT) arm.

The dossier lacks an analysis of the duration of all-causality and treatment-related SAEs. Based on the line listing, the duration of SAEs attributed to sasanlimab ranged from 3 days to over 800 days. Notably, for at least 24 of these events, changes in grade (worsening/improving) were recorded as recovered/resolved, with a new event onset recorded at the time of the grade change. This approach does not appropriately reflect the ongoing nature of the event. Additionally, for 10 of these cases, the final entry indicated that the event remained unresolved at the data lock point. The Applicant is requested to provide a summary of the duration of SAEs, irrespective of changes in grade, across the different treatment arms including the percentage of events that were resolved at the data lock point (**Co-Rapp OC**).

Deaths

Deaths were reported in 32 (9.1%) patients in the sasanlimab + BCG (IND+MNT) arm, 29 (8.3%) in the sasanlimab + BCG (IND) arm, and 29 (8.3%) in the BCG (IND+MNT) arm (Table 39). Frequencies of death were similar across all study arms, and most deaths occurred in the period greater than 30 days from the last dose of study treatment. The high rate of fatalities can partly be explained by the older patient population with the majority of patients having a former or currently smoker status. The majority of deaths were not associated with the disease under study. The Applicant is requested to provide Word tables with the cause of death for each grade 5 event in study B8011006 per study arm (**Rapp OC**).

All causality TEAEs leading to death were reported in 6 (1.7%) patients in the sasanlimab + BCG (IND+MNT) arm, 4 (1.1%) patients in the sasanlimab + BCG (IND) arm, and 2 (0.6%) patients in the BCG (IND+MNT) arm. Treatment-related TEAEs leading to death occurred in 2 (0.6%) participants in the sasanlimab + BCG (IND) arm and included Myocarditis and Pneumonia bacterial. In addition, one fatal case of immune-mediated hepatic disorder occurred beyond 30 days after the last sasanlimab dose in the sasanlimab + BCG (IND) arm. The event, deemed related to sasanlimab, originated as a Grade 3 event during the on-treatment period but worsened to Grade 5 outside of this period.

Discontinuation due to adverse events

Based on Figure 11: Participant flow, 131 out of 350 (37%) patients have withdrawn from overall treatment with reason adverse event in arm A versus 37 out of 349 (11%) patients in arm C. The number of patients who discontinued due to TEAEs is lower based on the summary of adverse events (Table 33). The Applicant is requested to clarify (**Rapp OC** in efficacy section). More patients discontinued due to treatment-related TEAEs in arm A sasanlimab + BCG (IND+MNT) versus arm C the BCG, 26.3% versus 8.6% respectively. In Arm A and B, the withdrawal from treatment was high (65% and 54%, respectively) compared to in Arm C (42%). The main reason was AEs, and discontinuation of sasanlimab dominated over discontinuation of BCG. Overall, there were a higher incidence of AEs leading to discontinuation of BCG in arm A than in arm C (22% vs. 10%). The high discontinuation rate is synonymous with a relatively low completion rate; only 34% and 45% completed study treatment as planned in the combinational arms (A and B, respectively), compared to 58% in the BCG only arm (Arm C). By the DCO of 02 Dec 2024, totally 846 participants are still ongoing in survival follow-up (approximately 280 individuals in each arm). Withdrawal from follow-up due to death was equally distributed across treatment arms (23, 20 and 23 subjects, respectively).

Discontinuations from sasanlimab during the treatment phase were reported for 53.7% (189/352) and 54.3% (191/352) participants in Arm A (sasanlimab + BCG [IND + MNT]) and Arm B (sasanlimab + BCG [IND]), respectively. Discontinuation from BCG during treatment was reported to be low in induction phase (1.7%-4.0%) and, as expected, higher during maintenance phase (46.6% in Arm A and 40.5% in Arm C). Based on the higher discontinuation and dose interruption rate of BCG in Arm A compared to Arm C (BCG monotherapy) both during induction and maintenance phase, it seems that

add on treatment may lead to earlier discontinuation and lower exposure to standard of care (BCG). This is of concern due to implications for efficacy of BCG in combinational treatment arms (Arm A and B).

The primary efficacy outcome measure was investigator-assessed event-free survival (EFS) in an open label study design. Based on the clinical trial protocol for patients in Cohort A, it may be necessary for a patient to permanently discontinue one of the two study interventions. In that case, the patient would still continue with the other study intervention. If it is necessary for the patient to permanently discontinue both sasanlimab and BCG, the patient would remain in the study and move into the post-treatment follow-up period to allow for an adequate evaluation of the study objectives based on the prespecified estimands. Note that permanent discontinuation of study treatment does not represent withdrawal from the study. Information bias is introduced as the investigator is aware of discontinuation due to AE while the patient continues to evaluation of the other study objectives. Patients in arm B who all discontinued BCG after the induction period had the worst treatment outcome in the study. The median EFS (95% CI) was 50.1 months (47.1, NE). The median EFS had not been reached in the other treatment arms. Discontinuation of BCG treatment induces an unfavourable prognosis for patients.

Safety in special populations

Treatment exposure was generally higher in the subgroup for age <65 years, except the pooled monotherapy group, in which exposure was similar between age subgroups.

No relevant differences were noted in TEAEs between patients who were ≥65 years compared with patients under 65 years, however, serious TEAEs were more frequent in patients age ≥65 years which is possibly associated with comorbidities in the elderly population rather than adverse drug reactions since the rates of treatment-related serious TEAEs were similar in both age groups.

The Applicant provided separate safety data based on Age <65 years and Age ≥65 years in Table 41. More detailed safety data across different age strata is warranted for further analysis (**Rapp OC**). Based on the provided analysis of the Applicant it is agreed that no relevant differences were noted in TEAEs between patients who were ≥65 years compared with patients under 65 years, however, serious TEAEs were more frequent in patients age ≥65 years which is possibly associated with comorbidities in the elderly population rather than adverse drug reactions since the rates of treatment-related serious TEAEs were similar in both age groups.

No data on ADRs in special populations have been submitted (**Rapp OC**).

Safety related to drug-drug interactions and other interactions

It is agreed with the Applicant that the risk of DDIs with sasanlimab is low based on the expected absence of renal excretion. Sasanlimab is not renally excreted and is expected to be metabolized primarily by catabolic degradation following endocytosis by the mononuclear phagocytic system. Based on nonclinical studies, sasanlimab has low potential for DDI via cytokine modulation. It is not expected to interact with other mAbs at therapeutic levels.

In Study B8011006 Arm A, there were no differences in sasanlimab PK between the sasanlimab + BCG (IND+MNT) arm and the sasanlimab + BCG (IND) arm. Additionally, the absence of apparent differences in sasanlimab exposure between the two arms even after patients were no longer receiving BCG in Arm B (sasanlimab + BCG [IND]) indicates that concomitant intravesical administration of BCG does not impact sasanlimab PK.

There were no adverse drug interactions reported based on the search using the MedDRA HLT Interactions. However, the Applicant is requested to include guidance in the SmPC section 4.5 aligned

with other approved PD-1 inhibitors (**SmPC comment**). Systemic corticosteroids were administered in 139/312 (44.6%) of patients who experienced irAEs, including 77/312 (24.7%) who were administered high dose corticosteroids (≥40 mg daily prednisolone or equivalent).

The overall **immunogenicity risk** for sasanlimab is low and no clear association was observed between the emergence of ADA to sasanlimab and its PK, safety, or efficacy.

Haematology and Chemistry Laboratory Evaluations

Shifts from Grade ≤2 to Grade 3 and Grade 4 for all haematology tests occurred in <1% of patients except lymphocyte count decreased, in which shifts to Grade 3 occurred in 6 (1.72%) patients in the sasanlimab + BCG (IND+MNT) arm. Shifts from Grade ≤2 to Grade 3 and Grade 4 for all chemistry tests occurred more frequently in the sasanlimab combination arms compared with the BCG arm; the most frequent were: lipase increased, aspartate aminotransferase increased, and alanine aminotransferase increased.

ALT, AST, and bilirubin elevations occurred most frequently in the sasanlimab + BCG (IND+MNT) arm, followed by the sasanlimab + BCG (IND) arm. There were no patients in any of the treatment arms with liver function tests consistent with Hy's Law criteria.

Elevations in liver function parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, were more frequently observed in the sasanlimab combination arms, compared with the BCG control arm. Increased ALT and AST have been addressed in the proposed SmPC. The Applicant is requested to discuss whether elevated bilirubin should be included in the SmPC (see **Co-Rapp SmPC OC**).

Thyroid abnormalities (46.2%) were more common in the sasanlimab arms compared to the BCG control arm (25.7%) consistent with the adverse events reported for other PD-1 inhibitors.

No clinically meaningful findings in ECGs were observed in any treatment arm/group.

There were no relevant differences in TEAEs between gender subgroups, however, serious treatment-related TEAEs appear to be more frequent in males than females.

There were no relevant differences in TEAEs between the White and Asian subgroups, however frequencies of treatment-related Grade 3 and serious TEAEs appear to be higher in Asian than White patients. However, the interpretation of these differences is complicated due to the limited number of the specific events in the unbalanced subpopulation.

No relevant differences were observed across geographic regions on the frequencies of TEAEs, except discontinuations due to TEAEs (all causalities and treatment-related) appear to be higher in Western Europe than other regions.

5.4.12.1.2. Adverse drug reactions (ADRs) in the SmPC

Table 43 ADRs proposed for sasanlimab in Combination with BCG for inclusion in the SmPC

Infections and infestations		Link to data*
Very Common	Urinary tract infection[a]	*Table 36*
Blood and lymphatic system disorders		
Uncommon	Immune thrombocytopenia	
Immune system disorders		
Uncommon	Sarcoidosis[b]	
Endocrine disorders		
Very Common	Hypothyroidism[c], Hyperthyroidism[d]	

Common	Adrenal insufficiency[e], Hypopituitarism[f], Thyroiditis[g]	
Uncommon	Hypophysitis[h]	
Metabolism and nutrition disorders		
Common	Diabetes mellitus[i], Hyperglycaemia, Decreased appetite	
Nervous system disorders		
Uncommon	Myasthenia gravis[j]	
Eye disorders		
Uncommon	Uveitis	
Cardiac disorders		
Uncommon	Myocarditis[k]	
Respiratory, thoracic and mediastinal disorders		
Common	Pneumonitis[l]	
Gastrointestinal disorders		
Very Common	Diarrhoea	
Common	Colitis[m] Pancreatitis[n] Constipation	
Hepatobiliary disorders		
Very Common	Hepatotoxicity[o]	
Skin and subcutaneous tissue disorders		
Very Common	Rash[p] Pruritus	
Common	Psoriasis[q]	
Uncommon	Vitiligo	
Musculoskeletal and connective tissue disorders		
Very Common	Arthralgia	
Uncommon	Myositis[r] Polymyalgia rheumatica Rheumatoid arthritis Sjogren's syndrome	
Renal and urinary disorders		
Very Common	Haematuria Dysuria Pollakiuria	
Common	Acute kidney injury[s] Micturition urgency	
Uncommon	Nephritis[t]	
Investigations		
Very Common	Lipase increased[x] Amylase increased[y]	

The safety profile of sasanlimab is generally consistent with other PD1-inhibitors. However, several ADRs known for PD1-inhibitors were not included for sasanlimab, despite being reported with clear imbalances in the incidence of both all-causality AEs and AEs related to sasanlimab when comparing the combination treatment arms to the BCG control arm.

The following terms, including related terms, should be included as ADRs in 4.8 with appropriately estimated frequency, or justified otherwise (**Co-Rapp OC**):

System organ class	Adverse reaction
Infections and infestations	pneumonia
Blood and lymphatic system disorders	anaemia, eosinophilia
Investigations	weigth decreased
Psychiatric disorders	insomnia
Nervous system disorders	headache, dizziness, dysgeusia and neuropathy peripheral
Eye disorders	Eyelid ptosis
Respiratory, thoracic, mediastinal disorders	Dyspnoea, cough
General disorders	Oedema/Oedema peripheral
Investigations	Increased alkaline phosphatase (ALP), Increased creatinine

Sepsis was reported as a SAE in 5 subjects in arm A. Among these, 1 case was deemed related to sasanlimab. Additionally, 4 subjects in arm B reported SAEs of sepsis, including a fatal event, however, these were not considered related to sasanlimab. Given the occurrence of related cases and the severity of sepsis events, including a fatal case, the Applicant is requested to discuss whether sepsis should be included as an ADR in the SmPC (**Co-Rapp OC**).

The Applicant should discuss whether terms, which are listed as ADRs for other PD1-inhibitors and show imbalances in the incidence of all-causality and related AEs between the sasanlimab treatment arms and the BCG control arm should be included as ADRs for sasanlimab in 4.8 (**Co-Rapp OC**).

This includes, but is not limited to:

- thrombocytopenia
- polyneuropathy
- grouped term Sensory abnormalities (HLT) including paraesthesia, dysesthesia, hypo- and hyperesthesia.
- dry eye
- grouped term cardiac arrythmia (including artrial fibrillation)
- gastritis
- stomatitis
- hyponatraemia
- increased bilirubin

In line with the SmPC guideline, AEs typically associated with BCG instillation such as dysuria, pollakiuira, haematuria and micturition urgency, were included as ADRs for the combination of sasanlimab with BCG, despite being considered almost exclusively related to BCG in both arm A and B. These AEs were reported with comparable frequency in arm A and arm C and were approximately 10-fold less frequent in the sasanlimab monotherapy group, with only one case of pollakiuria considered related to sasanlimab.

Several ADRs in the SOC 'Skin and Subcutaneous Tissue Disorders' have been included as a footnote under the PT 'Rash', irrespective of their severity. Consequently, serious skin reactions such as maculopapular rash (5 cases, grade > 3), drug eruption (2 cases, grade > 3), and severe, potential

life-threatening toxic epidermal necrolysis (1 case, grade 4) have been grouped under the general PT 'Rash'. Furthermore, the inclusion and classification of ADRs within this SOC appear to lack a clear and consistent rationale. The Applicant should discuss the rationale for the inclusion and classification of ADRs within this SOC. In the response, the Applicant should address whether it is warranted to include an additional ADR category of "Severe cutaneous adverse reaction" to specifically capture serious skin disorders like toxic epidermal necrolysis. (**Co-Rapp OC**)

Hepatitis is listed as a common ADR for multiple other PD-1 inhibitors and was pre-defined as AESI in the pivotal study. Hepatitis terms have been reported more frequently in subjects treated with sasanlimab + BCG (1.4%) compared to those treated with BCG alone (0%). In the proposed product information, the PT 'Hepatitis' is currently included in a footnote under 'Hepatotoxicity.' However, the term hepatitis is considered not accurately represented by the group term hepatotoxicity obscuring the immune-mediated nature of the reported AEs of hepatitis. In addition, information on treatment modification to manage the adverse reaction of hepatitis are given in 4.2 and 4.4. In conclusion, 'hepatitis' should be included as a separate PT under the SOC 'Hepatobiliary Disorders,' with a footnote specifying the reported terms (including autoimmune hepatitis, drug-induced liver injury, acute hepatitis, immune-mediated hepatic disorder, and immune-mediated hepatitis). (**Co-Rapp OC**)

5.4.12.2. Conclusions on clinical safety

The safety profile of sasanlimab *in combination with BCG for the treatment of adult patients with BCG-naïve, high-risk NMIBC* resembles the expected safety profile of a systemically administrated PD-1 inhibitor in combination with locally administered BCG. The combination therapy results in a worse safety profile due to partly non-overlapping toxicities. The immune-related AEs did not resolve for the majority of the patients at the time of database lock. This confirms the persistence of long lasting immune-related AEs. The incidence of Grade ≥3 TEAEs and SAEs doubled in patients treated with sasanlimab in combination with BCG induction and maintenance therapy. More patients discontinued BCG treatment due to TEAEs and can no longer have benefit from BCG treatment. The added toxicity of sasanlimab to BCG (IND+MNT) could result in a loss of chance for patients to benefit from the current standard of care in this treatment setting. In conclusion, it is unclear if the substantial added toxicity due to sasanlimab, including fatal cases, leading to an increased need for systemic corticosteroid and other immunosuppressant treatment and reduced exposure to BCG maintenance treatment, is outweighed by a treatment benefit of uncertain clinical relevance in a first-line therapy setting (refer to **merged Rapps MO on the B/R**).

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 44: Summary of safety concerns in proposed RMP

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies (thyroid disorders, adrenal insufficiency, hypophysitis/hypopituitarism, type 1 diabetes mellitus), severe rash, pancreatitis, and other immune-

Summary of safety concerns	
	mediated adverse reactions (myocarditis, myositis, myasthenic syndrome/ myasthenia gravis, and uveitis)
Important potential risks	None
Missing information	None

The proposed important identified risks are immune-mediated adverse reactions including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies (thyroid disorders, adrenal insufficiency, hypophysitis/hypopituitarism, type 1 diabetes mellitus), severe rash, pancreatitis, and other immune-mediated adverse reactions (myocarditis, myositis, myasthenic syndrome/ myasthenia gravis, and uveitis). These immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving sasanlimab. Most immune-mediated adverse reactions occurring during treatment with sasanlimab were reversible and managed with interruptions of sasanlimab, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of sasanlimab. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Some adverse reactions may be irreversible.

6.1.2. Discussion on proposed safety specification

CHMP Rapporteurs' position:

Risks not considered important for inclusion in the list of safety concerns in the RMP

The following adverse drug reactions were identified in patients treated with sasanlimab in combination with BCG and are not considered important as they have a low potential for increased severity or life-threatening consequences, are usually reversible and are manageable with usual standards of medical care:

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients in relation to the severity of the indication treated:

- constipation, diarrhoea, fatigue, pyrexia, amylase increased, lipase increased, decreased appetite, arthralgia, pruritus.
- injection site reactions

These risks represent general signs and symptoms / laboratory abnormalities which were mostly Grade 1 or Grade 2 in severity and non-serious and are manageable with standard medical care or have spontaneous resolution.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- immune thrombocytopenia (0.1%), sarcoidosis (0.3%), polymyalgia rheumatica (0.9%), rheumatoid arthritis (0.4%), Sjogren's syndrome (0.3%), psoriasis (1.4%), vitiligo (0.7%).

These reactions are associated with the mechanism of action and some may have potential to be serious but occurred at low frequencies (mostly < 1.0%) in clinical trials, were manageable with standard of care and have a low potential for severe consequences.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions

being part of standard clinical practice in each EU Member state where the product is authorised):

- none.

Known risks that do not impact the risk-benefit profile:

- none.

Other reasons for considering the risks not important:

Risks associated with the standard of care (intravesical BCG) and without increased frequency or severity when BCG was used in combination with sasanlimab:

- urinary tract infection, dysuria, haematuria, micturition urgency, pollakiuria.

These risks are known toxicities to intravesical BCG and are considered as adverse reactions for the sasanlimab + BCG combination, however, frequencies of these events were similar between patients treated with BCG only and those treated with sasanlimab in combination with BCG. Therefore, no increased risk associated with the addition of sasanlimab to the standard of care were observed. In addition, there is a low potential for severe events and these reactions are mostly manageable with standard of care and reversible.

The reasoning of the Applicant to identify the important identified risks is endorsed. The proposed important identified risks to be included in the RMP are also in line with those for the other approved PD-1 inhibitors and are thus agreed. However, the important identified risk should be limited to the umbrella term: "Immune-mediated adverse reactions". The specific PTs of the separate immune mediated reactions should be removed (**Rapp OC**).

PRAC rapporteur's comments on the list of safety concerns:

It is agreed with the CHMP Rapporteur that the important identified risk should be limited to "Immune-mediated adverse reactions" and that the specific PTs of the separate immune mediated reactions can be removed in the summary of safety concerns; however, detailed information provided in SVII is still endorsed by the PRAC Rapporteur.

Systemic BCG infection is an identified ADR with BCG treatment, and, although very rarely and reported as an uncommon ADR of BCG treatment in the EU SmPC for BCG (BCG Medac), can be life-threatening. It is agreed with the Co-Rapporteur that due to the limited size of the study, rare adverse events might not be seen. However, it is understood that increased risk of infections seen with PD-1 inhibitors are rather considered secondary to immune-related adverse events and their management by immunosuppressants. Therefore, "Increased risk for systemic infections, in particular systemic BCG infections" as suggested by the Co-Rapporteur is currently not supported by the PRAC-Rapporteur as important potential risk in the sasanlimab RMP.

However, the following should be noted: Based on the severity of a possible immune-mediated adverse reaction, sasanlimab should be withheld and corticosteroids administered. Upon improvement, to Grade ≤ 1, corticosteroids should be tapered over at least 1 month. If immune-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered (see recommendations section 4.4, SmPC). It is highlighted that BCG treatment might be contraindicated in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., positive HIV serology, leukaemia, lymphoma), cancer therapy (e.g. cytostatic medicinal products, radiation) or immunosuppressive therapy (e.g. corticosteroids) (e.g. BCG Medac EU SMPC, 4.3. Contraindications). Immune-mediated reactions and their management do not only affect

continuous treatment with sasanlimab, but also BCG treatment will have to be paused, if systemic immunosuppressants are necessary, to avoid increased risk of infections including systemic BCG infection.

Therefore, it is highly recommended that SmPC section 4.4 on immune-mediated adverse reactions will include recommendations for BCG treatment discontinuation and increased risk of infections including systemic BCG infection and a reference to the BCG SmPC for further information, taking into account the raised safety OC on increased risk for serious infections, in particular systemic BCG infections, in sasanlimab plus BCG treated patients receiving systemic corticosteroids and/or immunosuppressants.
Of note: A patient alert card for patients treated with BCG (BCG Medac) is already implemented for correct and early diagnosis and to avoid fatal consequences.

Since sansalimab is indicated only as combination treatment with BCG, the proposed missing information "Use in subjects with autoimmune disease or in subjects already receiving systemic corticosteroids/immunosuppressants before starting sasanlimab" is currently not supported, in view of the restrictions of BCG treatment in case of immunosuppressants.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The applicant did not propose any routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

Having reviewed the submitted data, the PRAC Rapporteur is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks associated with the product. No additional pharmacovigilance activities are necessary.

Furthermore, the PRAC Rapporteur considers that routine pharmacovigilance remains sufficient to monitor the effectiveness of the implemented risk minimisation measure.

6.2.2.2. Additional pharmacovigilance activities

The applicant did not propose any additional pharmacovigilance activities, which is in line with other approved PD1-inhibitors and considered acceptable.

6.3. Plans for post-authorisation efficacy studies

Table 24: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

CHMP rapporteurs' position:
None, there are no plans for post-authorisation efficacy studies.

PRAC rapporteur's comments on the plans for post-authorisation efficacy studies:
None, the PRAC rapporteur agrees with the assessment by the CAT/CHMP rapporteur

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 25: Planned routine risk minimisation measures

Safety Concern	**Routine risk minimisation activities**
Important Identified Risk	
Immune-mediated adverse reactions including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies (thyroid disorders, adrenal insufficiency, hypophysitis/hypopituitarism, type 1 diabetes mellitus), severe rash, pancreatitis, and other immune-mediated adverse reactions (myocarditis, myositis, myasthenic syndrome/ myasthenia gravis, and uveitis)	Routine risk communication: SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 includes guidelines for withholding or permanent discontinuation of treatment for immune-mediated adverse reactions. SmPC Section 4.4 includes advice regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 lists and describes the immune-mediated adverse reactions PL Section 2 and PL Section 4 includes guidance to patients on how to early identify signs and symptoms and advice to seek medical care Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription

In addition, the applicant has proposed the following additional risk minimisation measures:

To increase understanding of the safe and effective use of sasanlimab, physicians should provide patients or their caregivers with the Patient Alert Card.

Objectives:

The patient alert card will promote awareness among patients and is intended to help minimise the risk in the following important identified immune-mediated risks: pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, pancreatitis, endocrinopathies (thyroid disorders, adrenal insufficiency, hypophysitis / hypopituitarism, type 1 diabetes mellitus), severe rash, and other immune-mediated adverse reactions (myocarditis, myositis, myasthenic syndrome/ myasthenia gravis, uveitis) in clinical practice.

Rationale for the additional risk minimisation activity:

This tool will provide the opportunity for reinforcing key messages of early recognition and appropriate management of important identified risks of immune-related adverse reactions to maintain favorable benefit-risk profile of sasanlimab with postmarketing use.

Target audience and planned distribution path:

Patients via healthcare professionals (HCPs), will receive a patient alert card for their education about the signs and symptoms of important identified immune-mediated adverse reactions and the need to report them immediately to their health care provider. Additional instructions will be provided to the patient on the importance of carrying the patient alert card with them at all times and showing it to any HCP who may treat them. In addition, the patient alert card will be available electronically to allow continuous access to updated information on risks and actions to be taken for risk minimisation as well as support dissemination of risk minimization measure (RMM) messages for knowledge adoption.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Process indicators: distribution metrics of the patient alert cards through the internal risk management plan implementation process will be measured.

Outcome indicators: through routine pharmacovigilance activities, information, observations, findings, and outcomes of immune-mediated adverse reactions will be presented regularly in the Periodic Safety Update Reports including the review of reported rates for serious instances of the important identified immune-mediated risks: pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, pancreatitis, endocrinopathies (thyroid disorders, adrenal insufficiency, hypophysitis / hypopituitarism, type 1 diabetes mellitus), severe rash, and other immune-mediated adverse reactions (myocarditis, myositis, myasthenic syndrome/myasthenia gravis, uveitis).

Direct evaluation of the patient population is not planned due to known barriers to recruiting patients for survey research in the EU. The patient card will be judged effective if patient access and adherence to the digital patient cards is observed through distribution metrics and no negative trends or worsening outcomes in immune-mediated risks are identified through ongoing routine pharmacovigilance.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The important identified risk "Immune-mediated adverse reactions" is well reflected in the proposed SmPC sections 4.2, 4.4., and 4.8. with information and advice regarding withholding or permanent discontinuation of treatment as well as monitoring and management of the adverse event. The PL sections 2 and 4 include guidance on identification of signs and symptoms as well as advice to seek medical care.

The proposed routine risk minimisation measures are considered acceptable.

6.4.2.2. Additional risk minimisation measures

The applicant proposed a Patient Alert Card as additional risk minimization measure in line with other approved PD-1 inhibitors.

The PRAC Rapporteur, having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

6.4.2.3. <Patients engagement on the risk minimisation activities>

N/A

6.5. RMP summary and RMP annexes overall conclusion

The RMP summary (Part VI) and the RMP Annexes are currently not acceptable and requires revision in line with the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2).

The following information is currently missing and shall be added:

- The RMP details important risks of <invented name>, <how these risks can be minimised>, **and how more information will be obtained about <invented name>'s risks and uncertainties (missing information).**
- In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, **including PSUR assessment,** so that immediate action can be taken as necessary.
- Identified risks are concerns for which there is sufficient proof of a link with the use of <invented name>. **Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);**
- **Annex 1 – EudraVigilance Interface**

6.6. Overall conclusion on the Risk Management Plan

☒The CHMP and PRAC consider that the risk management plan version 0.1 could be acceptable if the applicant implements the changes to the RMP requested in the list of questions.

The applicant is reminded that in case of a positive opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

7.1. Pharmacovigilance system

☒ The CHMP rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The scientific opinion holder shall submit periodic safety update reports for this product in alignment with the requirements for the centrally authorised product as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines web-portal.

☒The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

8. Benefit-risk assessment

8.1. Therapeutic context

8.1.1. Disease or condition, proposed therapeutic indication

Initially proposed indication – Sasanlimab, in combination with Bacillus Calmette-Guérin (BCG), is indicated for the treatment of adult patients with BCG-naïve, high-risk, non-muscle invasive bladder cancer (NMIBC).

Initially proposed posology – The recommended dose of sasanlimab is 300 mg every 4 weeks (Q4W) administered as a single 2 mL subcutaneous injection. Treatment with sasanlimab should be given in combination with BCG induction and maintenance, and should be continued until recurrence of HG disease, disease progression, persistence of carcinoma in situ (CIS), unacceptable toxicity or up to 24 months. No dose reductions of sasanlimab are recommended. Sasanlimab should be withheld or discontinued to manage adverse reactions.

Mode of action – Sasanlimab is a monoclonal antibody (mAb) that binds to the programmed cell death protein-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

Disease Background – Bladder cancer is the 9th most common cancer type worldwide, with approximately 614,300 cases and 220,596 deaths reported in 2022 (Globocan), of which 224,777 and 70,383, respectively, in Europe. Approximately 75% of newly diagnosed cases of bladder cancer are non-muscle invasive disease, papillary tumours confined largely to the mucosa (Ta) (70%-75%) or, less often, to the lamina propria (T1) (20%-25%) or flat high-grade (HG) lesions (CIS, 5%-10%) (NCCN guidelines).
To facilitate treatment recommendations, clinical guidelines recommend the stratification of patients into risk groups based on their probability of progression to muscle-invasive disease. Based on the WHO 2004/2016 risk group definition, NMIBC is classified as low, intermediate, high, and very high risk (HR) and the probability of progression within 1 to 10 years of diagnosis ranges respectively from 0.06-3.7%, 1.0-8.5%, 3.5-14%, and 16-53%, respectively (EAU guidelines).
Patients with HR NMIBC represent a challenging patient population to treat, with a 2-year rate of

recurrence or progression of 30% and 10%, respectively (Frau et al. Arch Esp Urol. 2016; Cambier et al. Eur Urol. 2016; Shore et al. Urol Oncol. 2021). The 5-year survival rate is around 90% (Knowles et al. Nat Rev Cancer. 2015).

8.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1. of this document.

Optimal treatment of NMIBC is the complete removal of all visible lesions in the bladder, followed by intravesical instillations (with chemotherapy or BCG) or early radical cystectomy (RC), according to risk stratification (ESMO guideline). For patients with HR NMIBC, **the current SOC is** transurethral resection of bladder tumour (**TURBT**) **followed by** intravesical instillations of **BCG**, typically induction followed by maintenance therapy (EAU guidelines). BCG therapy will, however, eventually fail in up to 60% of patients with NMIBC resulting in recurrence or progression to more advanced disease (Shore et al. Urol Oncol. 2021; Knowles et al. Nat Rev Cancer. 2015; Babjuk et al. Eur Urol. 2017). At the time of BCG treatment failure, limited bladder-sparing therapeutic options exist. An **unmet medical need**, therefore, remains for new, effective and safe treatment options to improve the treatment outcome in patients with HR NMIBC, i.e., to delay HG tumour recurrence and progression into MIBC or advanced disease, which would require RC (and/or systemic therapy).

8.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

The single pivotal Study B8011006 (CREST; Shore et al. Nat Med. 2025) is a randomized, open-label Phase 3 study of sasanlimab (300 mg SC Q4W) in combination with intravesical BCG in patients with BCG-naïve, HR NMIBC (i.e., HG Ta and/or T1 papillary tumours and/or CIS). Prior to randomisation, all patients had undergone TURBT to remove all resectable papillary disease (Ta and T1). Residual CIS not amenable to complete resection was allowed. Randomisation was stratified by presence of CIS at randomisation (CIS vs no CIS) and geography (US vs Western Europe + Canada vs Rest of World). Patients were randomised (1:1:1) to one of the following treatment arms (with Arm B not being relevant for this application) (Figure 8):

- Arm A (n=352): sasanlimab in combination with BCG induction and maintenance (IND+MNT);
- Arm B (n=352): sasanlimab in combination with BCG IND; or
- Arm C (n=351): BCG IND+MNT.

The BCG induction period included 6 weekly doses of BCG. The BCG maintenance period included 5 cycles of 3 weekly doses of BCG at 3, 6, 12, 18, and 24 months. Treatment with sasanlimab continued until recurrence of HG disease, disease progression, persistence of CIS, unacceptable toxicity, or a maximum of 24 months.
Assessment of disease – by cytology and cystoscopy, followed by biopsy and imaging (CT/MRI) when needed – was performed at baseline and then every 12 weeks for 2 years from randomisation and then every 24 weeks thereafter.
The primary endpoint was investigator-assessed event-free survival (EFS) for the comparison of Arm A vs Arm C. A key secondary endpoint was overall survival (OS) for Arm A vs Arm C.

8.3. Favourable effects

Primary objective – investigator-assessed EFS – The median (95% CI) time of follow-up for

investigator assessed EFS was 36.4 (36.1, 37.7) months in Arm A and 36.7 (36.1, 41.2) months in Arm C. **The study met its primary objective.** A statistically significant improvement in EFS per investigator assessment was shown for sasanlimab + BCG (IND+MNT) compared with BCG (IND+MNT): HR 0.68 (95% CI: 0.489, 0.941); medians not reached; 2-sided p-value 0.0191.

Key secondary objective – OS – The median (95% CI) time of follow-up for OS was 40.8 (39.1, 41.3) months in Arm A and 41.2 (39.8, 41.3) months in Arm C. **The study did not meet this key secondary objective.** No (statistically significant) improvement in OS was shown for sasanlimab + BCG (IND+MNT) compared with BCG (IND+MNT): HR 1.13 (95% CI: 0.681, 1.865); medians not reached; 2-sided p-value 0.6419.

8.3.1. Uncertainties and limitations about favourable effects

Very late in the pivotal study CREST, i.e., <6 months before the primary completion date (PCD)/DCO date of 02-Dec-2024, protocol amendment 5 (PA5, dated 17-Jun-2024) was performed. With PA5, the initially planned, event-driven IA2 (based on 272 EFS events) for the primary endpoint of investigator-assessed EFS was removed and instead the EFS FA based on a calendar-based data cut-off date was planned (while the EFS FA was initially event driven, to be based on 389 EFS events). Additionally, the Applicant removed the dual primary endpoint of EFS for Arm B vs Arm C (downgraded it to a key secondary endpoint) with equal alpha allocation (1-sided 0.0125 for each test) and instead considered only one primary endpoint (EFS for Arm A vs Arm C) with an alpha of 0.025 (1-sided).

With Protocol Amendment 5 (PA5) the Applicant implemented major changes to the protocol (and SAP) of a fully enrolled, ongoing, open-label study where a considerable amount of information was already available. Moreover, following PA5 the main hypothesis was to be tested with a higher alpha (0.025 instead of 0.0125 [both 1-sided]), therefore, having a higher chance for CREST to be declared positive. As a result, the study integrity is seriously questioned (**joint Rapps MO on PA5**).

Even though CREST met its primary objective showing a statistically significant improvement in investigator-assessed EFS for Arm A compared with arm C, i.e., adding sasanlimab to BCG (IND+MNT), efficacy has not sufficiently/convincingly been demonstrated (**part of merged Rapps MO on the B/R**), as:

- for an open-label study, investigator-assessed EFS is not considered appropriate as primary endpoint;
    -
- the EFS FA results are considered too immature;
    - This is a direct consequence of PA5. Median EFS has not been reached in either study arm and only a relative risk in terms of a HR is currently available for assessment. The EFS FA was performed with 150 events which is little more than one third (150 / 389 x 100% = 38.6%) of the number of EFS events initially planned for the EFS FA. It is, therefore, highly uncertain whether the observed immature effect is representative of the real treatment effect, with patients with a poorer prognosis being over-represented. In addition, the interpretation of subgroup analyses is hampered by the limited number of events in each one of the comparisons of interest.
- the clinical relevance of the observed treatment effect magnitude is uncertain;
    - The difference in EFS events (17.3% vs 25.1%) is considered rather small. The IBCG of clinical experts considers a difference of 10% at 2 years as a clinically meaningful magnitude of effect (Kamat et al. J Clin Oncol. 2016; Kamat et al. J Clin Oncol. 2023). The observed difference of <5% at 24 months does not meet this bar.
      In addition, EFS is a composite endpoint comprised of events of varying clinical

meaningfulness. The type of EFS events driving the difference between Arm A and Arm C is recurrence of HG disease (7.4% vs 15.1%), while the rates of other types of EFS events (i.e., progressive disease, persistence of CIS, and death) are (more) similar. Events of disease progression which would require cystectomy (instead of further intravesical therapy) and/or deaths are considered more clinically relevant than recurrence of HG disease *per se* which could be treated by, e.g., (repeated) TURBT and further BCG treatment.

- the result is not considered robust; and
    - Statistical significance is lost for two (very) important sensitivity analyses.
      Firstly, the censoring rule for the primary analysis of investigator-assessed EFS is not in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). A sensitivity analysis was performed though, not censoring events after ≥2 missing or inadequate post-baseline disease assessments (i.e., counting all events), which *is* in line with EMA guidance. For this sensitivity analysis, i.e., when following EMA-preferred censoring rules, the EFS result was not/no longer statistically significant: HR 0.75 (95% CI: 0.551, 1.029); medians not reached; 2-sided p-value 0.0732.
      Secondly, the BICR-assessed EFS result was not statistically significant: HR 0.75 (95% CI: 0. 523, 1.063); medians not reached; 2-sided p-value 0.1035 (Shore et al. Nat Med. 2025). This is important since in the open-label study CREST, the BICR-assessed EFS result is assumed to be less biased than the investigator-assessed EFS.
      Thirdly, the result of the investigator-assessed primary analysis is not considered particularly compelling with respect to statistical significance in the light of an application with a single pivotal study (CPMP/EWP/2330/99).
- there is no support from secondary endpoints (e.g., OS, time to cystectomy).
    - In particular, the estimated treatment effect on OS cannot ensure that there are no relevant negative effects on this endpoint (EMA/CHMP/205/95 Rev.6).

The majority of the included participants had papillary tumour (Ta/T1) at baseline, whilst only 25% had CIS with or without Ta/T1. This study population is considered heterogeneous regarding the risk for progression (to MIBC), with the lowest risk in patients with HG pTa disease without CIS and the highest risk in patients with HG pT1 disease with CIS (who in fact have very HR NMIBC). At progression, CIS and papillary tumours without CIS are met with different treatment approaches.

No specific information on clinical efficacy studies in special populations, e.g., in the elderly, and in patients with renal or hepatic impairment, could be located in the application dossier. Justification for the proposed recommendations/information in the subsection 'Special populations' in section 4.2 of the SmPC is, therefore, lacking (**Rapp OC**).

No justification has been provided for the in CREST used (and proposed) maximum duration of sasanlimab treatment up to 25 cycles (2 years) (**Rapp OC**).

While the mode of action as a PD-1 inhibitor on T-cells is acknowledged, there are no available non-clinical data from relevant PD models supporting beneficial effects of sasanlimab on BCG-naïve, early-stage NMIBC.

The impact of body weight on sasanlimab exposure is not fully explored, especially in respect to patients in the lower and higher ends of the weight range. Additional information is needed to support the rationale for a flat dose and to characterise the expected differences in sasanlimab exposure with the proposed dose across body weights.

8.4. Unfavourable effects

The sasanlimab + BCG (IND+MNT) cohort consisted of 350 patients included in the safety analysis set. The BCG (IND+MNT) control arm cohort consisted of 349 patients. The median duration of exposure to sasanlimab was 80.3 weeks in the sasanlimab + BCG (IND+MNT) arm and 98.9 weeks in the BCG (IND+MNT) arm.

Overall, 97.4% of patients in the sasanlimab + BCG (IND+MNT) arm and 88.8% in the BCG (IND+MNT) arm experienced **TEAEs of any grade**. The most common (≥20%) all-causality TEAEs of any grade for sasanlimab + BCG (IND+MNT) were dysuria (33%), haematuria (28%), urinary tract infection (26%), pollakiuria (24%), lipase increased (22%), and pyrexia (21%). The most common (≥20%) all-causality TEAEs of any grade for **BCG (IND+MNT**) were dysuria (36.1%), haematuria (25.8%), urinary tract infection (23.5%), pollakiuria (21.2%).

Overall, 48.9% of patients in the sasanlimab + BCG (IND+MNT) arm and 25.8% in the BCG (IND+MNT) arm experienced **TEAEs of grade ≥3**. The most common (≥3%) all-causality TEAEs of Grade ≥3 were lipase increased (7.7%) and haematuria (5.7%) in the sasanlimab + BCG (IND+MNT) arm and haematuria (3.4%) in the BCG (IND+MNT) arm.

Treatment related TEAEs were reported in 87.1% of patients in the sasanlimab + BCG (IND+MNT) arm and 70.2% in the BCG (IND+MNT) arm. The most common (≥10%) **treatment-related TEAEs of any grade** were for **sasanlimab + BCG** (IND+MNT) were: dysuria (29.4%), pollakiuria (22.9%), haematuria (20.9%), urinary tract infection (19.1%), lipase increased (17.4%), pyrexia (15.4), hypothyroidism (14.3), amylase increased (11.7%), alanine aminotransferase increased (10.9%), cystitis (10.9%), aspartate aminotransferase increased (10.6%), micturition urgency (10.3%), and fatigue (10.0%).

The most common (≥10%) **treatment-related TEAEs of any grade** were for **BCG (IND+MNT)**: dysuria (32.1%), haematuria (20.1%), urinary tract infection (20.1%), pollakiuria (18.9%), pyrexia (11.7%), and micturition urgency (10.6%).

The most common (≥1%) **treatment-related TEAEs of Grade ≥3** for sasanlimab + BCG (IND+MNT) were: lipase increased (6.0%), haematuria (4.0%), amylase increased (2.3%), alanine aminotransferase increased (2.3%), aspartate aminotransferase increased (2.0%), urinary tract infection (2.0%), pancreatitis (1.7%), gamma-glutamyltransferase increased (1.4%), diabetes mellitus (1.1%), adrenal insufficiency (1.1%).

The most common (≥1%) treatment-related TEAEs of grade ≥3 for BCG (IND+MNT) was haematuria (3.4%).

Serious TEAEs or higher TEAEs were reported in 34.3% the patients in the sasanlimab + BCG (IND+MNT) arm versus 14.0% in the BCG (IND+MNT) arm.

TEAEs leading to discontinuation of BCG occurred in 26.3% the patients in the sasanlimab + BCG (IND+MNT) arm and in 8.6% in the BCG (IND+MNT) arm.

All causality TEAEs leading to death were reported in 6 (1.7%) patients in the sasanlimab + BCG (IND+MNT) arm, 4 (1.1%) patients in the sasanlimab + BCG (IND) arm, and 2 (0.6%) patients in the BCG (IND+MNT) arm.

All causality TEAEs leading to death were reported in 6 (1.7%) patients in the sasanlimab + BCG (IND+MNT) arm, 4 (1.1%) patients in the sasanlimab + BCG (IND) arm, and 2 (0.6%) patients in the BCG (IND+MNT) arm. Two **deaths were attributed to study treatment**. The grade 5 events included myocarditis on Study Day 26 and pneumonia bacterial on Study Day 64 (which occurred in a patient with ongoing myocarditis), both occurring within 30 days after the last dose of study

treatment, and immune-mediated hepatic disorder on Study Day 476, beyond 30 days after the last dose of study treatment in the sasanlimab + BCG (IND) arm.

8.4.1. Uncertainties and limitations about unfavourable effects

The open-label design of the pivotal study B8011006 combined with the prior knowledge of PD-1 receptor blockers and local BCG therapy could induce bias during the safety data collection of the combination therapy.

Based on Figure 11: Participant flow 131 out of 350 (37%) patients withdrew from overall treatment with reason adverse event in arm A versus 37 out of 349 (11%) patients in arm C (**Rapp OC**).

More patients discontinued due to treatment-related TEAEs in arm A sasanlimab + BCG (IND+MNT) versus arm C the BCG, 26.3% versus 8.6% respectively. The primary efficacy outcome measure was investigator-assessed event-free survival (EFS) in an open label study design. Information bias is introduced as the investigator is aware of discontinuation due to AE while the patient continues to evaluation of the other study objectives. Patients in arm B who all discontinued BCG after the induction period had the worst treatment outcome in the study. The median EFS (95% CI) was 50.1 months (47.1, NE). The median EFS had not been reached in the other treatment arms. Discontinuation of BCG treatment induces an unfavourable prognosis for patients.

The safety profile in older patients needs further clarification as the safety data is presented based on age <65 years and age ≥65 years (**Rapp OC**).

No analysis of the duration of all causality or treatment-related SAEs were provided by the Applicant, however, at least 14 SAEs related to sasanlimab were reported as Not recovered at data cut-off. In addition, the prolonged duration of irAEs with 60% of irAEs recorded as ongoing at the current data cut-off indicates potential long-term negative effects of sasanlimab. Thus, a more detailed analysis is requested.

8.5. Effects table

Table 45: Effects Table for Zumrad, in combination with BCG, for the treatment of adult patients with BCG-naïve, high-risk, non-muscle invasive bladder cancer (data cut-off: 02-Dec-2024)

Effect	*Short description*	*Sasanlimab + BCG (I+M)*	*BCG (I+M)*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects		**N=352 vs N=351 – Full Analysis Set**			
Investigator-assessed Event-Free Survival	Patients with event, n (%)	61 (17.3)	89 (25.4)	**SoE:** PE; randomized, controlled, Phase 3 study vs SoC comparator **HR** (95% CI) 0.68 (0.489, 0.941) 2-sided p-value 0.0191 **Unc:** unblinded investigator assessment in open-label study; immaturity of data; clinical relevance highly uncertain; result not robust; no support from KSE	CREST Table 23; Figure 12
Median	Months (95% CI)	NE (NE, NE)	NE (NE, NE)		

Effect	Short description	Sasanlimab + BCG (I+M)	BCG (I+M)	Uncertainties/ Strength of evidence	Ref
Overall survival	Patients with event, n (%)	32 (9.1)	29 (8.3)	**SoE:** KSE; randomized, controlled, Phase 3 study vs SoC comparator **HR** (95% CI) 1.13 (0.681, 1.865) 2-sided p-value 0.6419 **Unc:** (severe) immaturity of data; HR >1; no support from KSE for PE	CREST Table 27; Figure 15
Median	Months (95% CI)	NE (NE, NE)	NE (NE, NE)		
Unfavourable effects		**N=350**	**vs N=349**	**– Safety Analysis Set**	
TEAEs (%)	All causes (treatment related)	97.4 (87.1)	88.8 (70.2)	**SoE:** randomized, controlled, Phase 3 study **Unc:** open-label study design	CREST Table 33
Most frequent TEAEs (%)	dysuria haematuria urinary tract infection pollakiuria lipase increased	33 (29.4) 28 (20.9) 26.3 (19.1) 23.7 (22.9) 21.7 (17.4)	36.1 (32.1) 25.8 (20.1) 23.5 (20.1) 21.2 (18.9) 8.0 (0)		Table 34
Grade ≥3 TEAEs (%)	All causes (treatment related)	48.9 (29.1)	25.8 (6.3)		CREST Table 33
Serious TEAEs (%)	All causes (treatment related)	34.3 (17.7)	14.0 (1.4)		CREST Table 33
TEAEs leading to death (%)	All causes (treatment related)	1.7 (0)	0.6 (0)		CREST Table 33
TEAEs leading to discontinuation of sasanlimab (%)	All causes (treatment related)	30.9 (26.3)	NA		CREST Table 33
TEAEs leading to discontinuation of BCG (%)	All causes (treatment related)	22.0 (16.9)	10.0 (8.6)		CREST Table 33
irAEs (%) - Hepatitis - Rash - Thyroid disorders		42.6 4.1 13.1 17.7	1.4 0 0 1.4		CREST Table 33; Table 37
Patients with ongoing irAEs	n (% of patients with irAEs)	88 (59.1)	2 (40)		

Abbreviations: BCG: Bacillus Calmette-Guérin; HR: hazard ratio; irAEs: immune-related adverse events; I+M induction and maintenance; KSE: key secondary endpoint; NA = not applicable; NE: not estimable; PE: primary endpoint; Ref: reference; SoC: standard-of-care; SoE: strength of evidence; TEAEs: treatment-emergent adverse events; Unc: uncertainties.

8.6. Benefit-risk assessment and discussion

8.6.1. Importance of favourable and unfavourable effects

With PA5, the Applicant– implemented major changes to the protocol (and SAP) of a fully enrolled, ongoing, open-label study where a considerable amount of information was already available. Moreover, following PA5 the main hypothesis was to be tested with a higher alpha, therefore, having

a higher chance for CREST to be declared positive. As a result, the study integrity is seriously questioned (as are the reported results).
The Applicant is, therefore, requested to thoroughly justify that these decisions were taken without any knowledge of the results by treatment arm and that only the global rate of progression triggered the decision, thereby maintaining the integrity of the study. This justification should at minimum include data providing convincing support for the Applicant's rationale for PA5, i.e., data showing that EFS events were accumulating at a much slower rate than originally projected, together with an increasing rate of patients dropping out from EFS observation.
Additionally, the Applicant is requested to confirm that the *entire* study team remained fully blinded to aggregate/cumulative data summaries by treatment arm until the PCD (**joint Rapps MO on PA5**).

The proposed target population consists of patients with early stage disease with an established SOC (i.e., BCG) which is generally well tolerated, and the short term risk for serious disease related morbidity/mortality is low. Adding a systemic therapy with clinically relevant toxicity to this SOC for an extended period of time could only be justified by a clearly positive benefit risk ratio.

Even though CREST met its primary objective showing a statistically significant improvement in investigator-assessed EFS for adding sasanlimab to BCG (IND+MNT), efficacy has not sufficiently been demonstrated (**part of merged Rapps MO on the B/R**), as:

- for an open-label study, investigator-assessed EFS is not considered appropriate as primary endpoint;
- the EFS FA results are considered too immature;
- the clinical relevance of the observed treatment effect magnitude is uncertain;
- the result is not considered robust; and
- there is no support from secondary endpoints (e.g., OS, time to cystectomy).

The **safety profile** of sasanlimab in combination with BCG for the treatment of adult patients with BCG-naïve, HR NMIBC resembles the expected safety profile of a systemically administrated PD-1 inhibitor in combination with a locally administered BCG. The combination therapy results in a worse safety profile due to partly non-overlapping toxicities. The immune-related AEs did not resolve for the majority of the patients at the time of database lock. This confirms the persistence of long lasting immune-related AEs. Furthermore, a large part of the patients required treatment with systemic corticosteroids or other immunosuppressants, often in high doses and over longer periods. The incidence of Grade ≥3 TEAEs and SAE doubled in patients treated with sasanlimab in combination with BCG induction and maintenance therapy. More patients discontinued with BCG treatment due TEAEs and can no longer have benefit from BCG treatment. The added toxicity of sasanlimab to BCG (IND+MNT) could result in a loss of chance for patients to benefit from the current standard of care in this treatment setting. In conclusion, the addition of sasanlimab to standard of care BCG results in a non-negligible safety profile (**part of merged Rapps MO on the B/R**).

8.6.2. Balance of benefits and risks

Even though CREST met its primary objective showing a statistically significant improvement in investigator assessed EFS for adding sasanlimab to BCG (IND+MNT), **efficacy has not sufficiently been demonstrated**.
The addition of sasanlimab to standard of care BCG treatment resulted in **clinically relevant extra toxicity**, which is reflected by higher rates of TEAEs (both any Grade and Grade ≥3), serious TEAEs, TEAEs leading to discontinuation, TEAEs leading to death, immune-related AEs (both any Grade and Grade ≥3), and serious immune-related AEs. Immune-related AEs, in particular, may be irreversible and require treatment with systemic corticosteroids or other immunosuppressants, and it is noted

that the majority of immune related AEs were ongoing (had not resolved) at the time of database lock.
As a result, the **B/R is considered negative**.
The Applicant is, therefore, requested to justify a positive B/R (**merged Rapps MO on the B/R**).

In addition, due to very late, major changes to the protocol (and SAP) of the open-label, pivotal study CREST, the study integrity is seriously questioned (as are the reported results) (**joint Rapps MO on PA5**).

There are no Quality MOs affecting this assessment and discussion. An MO is raised on the NAS status.

8.6.2.1. Areas for further treatment optimisation

Table 46: Areas for further development

Problem statement	*Objectives of study or further research*
The Applicant had not conducted any dedicated dose response study(ies) before initiating the pivotal study with the sasanlimab dose regimen of 300 mg SC Q4W which is also the proposed posology. It is also noted that the Applicant used data from this pivotal study with a single dose regimen to explore the E-R efficacy relationship.	The Applicant is encouraged to further investigate and optimize the sasanlimab dosing.

8.6.3. Joint Rapporteurs' conclusions

The overall benefit risk balance of Zumrad in combination with BCG for the proposed indication is **negative**.