11 December 2025
EMA/9518/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Anktiva

International non-proprietary name: nogapendekin alfa inbakicept

Procedure No. EMEA/H/C/006622/0000

Note

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

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

Table of contents

List of abbreviations

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT-803	N-803
ATC	Anatomical Therapeutic Chemical Code
BC	Bladder Cancer
BCG	Bacillus Calmette-Guerin
BLQ	Below the limit of quantitation
BTD	Preliminary Breakthrough Therapy Designation
CD	Cluster of differentiation
CI	Confidence Interval
CIS	Carcinoma in situ
C_{max}	Maximum observed concentration
COVID-19	Corona Virus Disease 2019
CPR	Central pathology review
CR	Complete response
CS	Chemical Structure
CSR	Clinical study report
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DoR	Duration of complete response
DSS	Disease-specific survival
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
FcRn	Neonatal Fc receptor
FDA	United States Food and Drug Administration
FICBT	First International Consultation on Bladder Tumors
GCP	Good Clinical Practice
HG	High grade
HLA-1	Human Leukocyte Antigen-1
HRQoL	Health-Related Quality of Life

Abbreviation or Specialist Term	Explanation
IBCG	International Bladder Cancer Group
ICH	International Conference of Harmonization
IFN	Interferon
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
IV	Intravenous
JAK	Janus kinase
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IL-2	Interleukin-2
IL-15	Interleukin-15
INN	International nonproprietary name
KM	Kaplan-Meier
LG	Low grade
LTF	Long-term follow-up
MA	Marketing authorisation
MAA	Marketing Authorisation Application
MTD	Maximum tolerated dose
NA	Not Applicable
NK	Natural killer (cell)
NKG2D	Natural killer group 2D
NMIBC	Non-muscle invasive bladder cancer
OS	Overall survival
PBS	Phosphate-buffered saline
PD-1	Programmed cell death protein 1
PE	Physiologic Effect
PFS	Progression-free survival
PK	Pharmacokinetic
RC	Radical cystectomy
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation or Specialist Term	Explanation
SCS	Summary of Clinical Safety
SMQ	Standardized MedDRA Queries
STAT	Signal transducer and activator of transcription
T1	Tumors invading the lamina propria
Ta	Tumors confined to the epithelial mucosa
t½	half-life
TEAE	Treatment emergent adverse event
TNF	Tumor necrosis factor
T reg	Regulatory T cell
TURB / TURBT	Transurethral resection of the bladder (tumor)
WOE	Weight of evidence

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Table 1 Information on the product

Product data	
Product name	Anktiva
Active substance	Nogapendekin alfa inbakicept
INN or common name	Nogapendekin alfa inbakicept
Applicant	ImmunityBio Ireland Limited 6th Floor, 2 Grand Canal Square Dublin 2, Ireland, D02 A342
EMA Product Number	EMEA/H/C/006622
ATC code and Pharmacotherapeutic group	L03AC03, Interleukins, Immunostimulants
Pharmaceutical form(s) and strength (s)	Intravesical solution, 400 µg
Packaging	Vial (glass)
Package size(s)	1 vial
Route of administration	Intravesical use
Orphan designation	N.A.
Type of marketing authorisation granted at opinion	Conditional Marketing Authorisation
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Anktiva in combination with Bacillus Calmette Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.
New active substance	Yes

1.2. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.3. Eligibility to the centralised procedure

The applicant Serum Life Science Europe GmbH submitted on 18 December 2024 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Anktiva, 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 June 2024. During the procedure, the applicant's name was changed from Serum Life Science Europe GmbH to ImmunityBio Ireland Limited.

The applicant applied for the following indication:

Anktiva in combination with Bacillus Calmette Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.

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, non-clinical and clinical data based on applicants' own tests and studies and/or 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) EMA/PE/0000182345 on the granting of a (product-specific) waiver.

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 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. Accelerated assessment request

The applicant requested accelerated assessment in accordance with Article 14(9) of Regulation (EC) No 726/2004. The CHMP did not grant this request, as it considered that the ability of Anktiva to address an unmet medical need, and the ability to identify the relevant target population, was insufficiently substantiated at the time of the request. This conclusion was based on several outstanding issues, including uncertainties regarding the methodology used to define complete responses and concerns about the potential risk of progression to metastatic disease due to delayed or omitted radical cystectomy (RC).

1.7.2. Conditional marketing authorisation (CMA)

The applicant initially sought a full marketing authorisation. However, during the assessment, in response to concerns raised by the CHMP regarding the non-comprehensiveness of the data submitted, the applicant requested that the application be considered under the provisions for a conditional marketing authorisation, in accordance with Article 14-a (1) of Regulation (EC) No 726/2004. Further details are provided in section 9.6.3.1.

1.7.3. New active substance status

The applicant requested the active substance nogapendekin alfa inbakicept 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.

1.7.3.1. CHMP recommendation on new active substance status

Based on the review of the data, it is considered that the active substance nogapendekin alfa inbakicept contained in the medicinal product Anktiva is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to the Appendix on new active substance status claim assessment report.

1.8. Steps taken for the assessment of the product

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

Rapporteur:	Filip Josephson
Co-Rapporteur:	Ingrid Wang

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

PRAC Rapporteur:	Jean-Michel Dogné
PRAC Co-Rapporteur:	Mari Thorn

The application was received by the EMA on	18 December 2024
An application for accelerated assessment was filed by the applicant. Accelerated assessment procedure was not agreed-upon by CHMP on	12 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was received on	9 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	16 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	28 April 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 May 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	22 September 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 October 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 October 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2025

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Anktiva as well as a report on New Active Substance (NAS) status of the active substance contained in Anktiva on	11 December 2025

1.9. Final CHMP outcome

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5. of this report.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6. of this report.

1.9.3. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Anktiva is favourable in the following indication: in combination with Bacillus Calmette Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.

The CHMP, therefore, recommends the granting of the conditional marketing authorisation subject to the conditions described in the following sections.

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder shall submit periodic safety update reports every 6 months.

1.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.9.7. Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a (1) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Table 2 Specific obligations

Description	Due date
In order to confirm the efficacy and safety of nogapendekin alfa inbakicept in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours, the MAH shall submit the results of the ongoing open-label randomized phase IIB QUILT-2.005 study to evaluate the efficacy and safety of intravesical BCG in combination with nogapendekin alfa inbakicept versus BCG alone in patients with BCG-naïve NMIBC.	30 June 2027
In order to confirm the efficacy and safety of nogapendekin alfa inbakicept in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS) with or without papillary tumours, the MAH shall submit the final results including the 5-years follow up period for patients of the ongoing open-label single-arm phase II/III QUILT-3.032 study.	31 December 2029

1.9.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic Context

In the European Union, bladder cancer (BC) is the fifth most common cancer, affecting over 200,000 people each year, with non-muscle invasive bladder cancer (NMIBC) comprising the majority of the cases (DeGeorge 2017). The incidence and mortality rates are four times higher in men, making this

the 6th most common and the 9th leading cause of cancer-related deaths among men. The highest incidence rates for both sexes are found in Southern Europe (especially Greece, Spain, and Italy), Western Europe (especially Belgium and the Netherlands), and Northern America. Notably, the two European countries with the highest sex-specific incidence rates globally are Greece for men and Hungary for women (Sung 2021). Moreover, many European countries such as Germany and Bulgaria, exhibit increasing bladder cancer rates, which are expected to rise even further due to a greater prevalence of the main risk factors, smoking and aging within the population (Saginala 2020). In the US, bladder cancer is the sixth most common cancer overall, and the fifth most common cancer in men (Cronin 2022). While the overall 5-year survival rate for bladder cancer is 77%, the frequency of recurrence and progression, accompanied by significant negative impacts on quality of life (QoL), act to increase disease burden (Saginala 2020).

The current standard of care in Europe for patients with intermediate or high-risk NMIBC is Transurethral Resection of Bladder Tumor (TURBT) followed by treatment with an induction course (6 weekly instillations) with or without maintenance therapy (3 weekly instillations at three and 6 months thereafter for 1 to 3 years) of BCG (Daniels 2020). In CIS, therapeutic options are limited and patients are treated based on a moderate- to low-level of evidence. Current guidelines recommend transurethral resection, followed by BCG as first-line therapy (Chang 2016, Gontero 2015). A high rate of tumors persists or recur despite treatment with BCG (Kamat 2017). In such cases, a radical cystectomy (RC) is usually performed. Post-operative mortality rate for radical cystectomy ranges from 0.8% to 8%, and its use is restricted due to the patient age or comorbidities (Zakaria 2014, Daniels 2020). Several categories of BCG failures, broadly defined as any high-grade disease occurring during or after BCG therapy, have been proposed. BCG-unresponsive is one subgroup of patients where additional BCG is unlikely to provide benefit, representing a serious condition with significant unmet medical need. The only current standard of care options are systemic immunotherapy, intravesical chemotherapy, and radical cystectomy with urinary diversion. Although radical cystectomy is considered curative for patients with high-risk NMIBC, it is associated with a high rate of perioperative morbidity and mortality and a clinically relevant negative impact on quality of life (Singer 2013, Smith 2018).

2.2. *Aspects of development*

The clinical development program includes clinical trials in BCG-naïve and BCG-unresponsive NMIBC as well as NMIBC CIS with or without Ta or T1 disease and NMIBC high-grade papillary disease (Ta/T1 only). The status, previous BCG treatment, cohorts, NMIBC population and treatment are shown in the table below for the four NMIBC clinical studies.

Table 3 NMIBC Development Program

Clinical Study	Status	BCG	Cohort	NMIBC Population	Treatment
QUILT-2.005 Phase 1b	Completed	Naive	NAP	CIS with or without Ta or T1 and High-grade papillary disease (Ta/T1)	BCG + N-803 100, 200, and 400 µg
QUILT-2.005 Phase 2b	Ongoing	Naïve Randomised by cohort	A	CIS with or without Ta or T1	BCG + N-803 400 µg
			A	CIS with or without Ta or T1	BCG only
			B	High-grade papillary disease (Ta/T1 only)	BCG + N-803 400 µg
			B	High-grade papillary disease (Ta/T1 only)	BCG only
QUILT-3.032	Ongoing	Unresponsive	A	CIS with or without Ta or T1	BCG + N-803 400 µg

Clinical Study	Status	BCG	Cohort	NMIBC Population	Treatment
			B	High-grade papillary disease (Ta/T1 only)	BCG + N-803 400 µg
			C	CIS with or without Ta or T1	N-803 400 µg only
QUILT-205	Ongoing	Naive	NAP	CIS with or without Ta or T1 and High-grade papillary disease (Ta/T1)	None

Since NMIBC is not a paediatric disease, the clinical program only includes adult subjects. The treatment schedule is the same for the studies in NMIBC. Clinical efficacy data supporting the application for N-803 in combination with BCG for BCG- unresponsive NMIBC (CIS) comes from a single study, the pivotal phase 2/3 QUILT-3.032 study. Clinical safety data supporting this application comes from 4 studies: the phase 1 QUILT-1.004 study, the QUILT-2.005 phase 1b study, the QUILT-2.005 phase 2b study, and QUILT-3.032.

The pharmacokinetic, pharmacodynamic, immunogenicity and safety data for the proposed indication is provided by the results of QUILT-2.005 phase 1b, QUILT-2.005 phase 2b, QUILT-3.032, and QUILT-3.032-2.005-PK. The QUILT-1.004 is included to provide pharmacokinetic, pharmacodynamic, and safety data after subcutaneous (SC) administration for comparison to the results after bladder instillation.

Table 4 Clinical Studies Supporting N-803 in NMIBC (CIS)

Protocol; Study Status Report Date (Cut-off)	Type of Study	Primary Study Objective	Population Number of Treated Subjects	Dose and Dosing Regimen	Data Collected
Healthy Subjects: N-803 Subcutaneous Administration					
QUILT-1.004; Complete 13 Mar 2018	Single-center, open-label	Determine PK profile after subcutaneous N-803 administration	Healthy adult volunteers 20 Subjects	10 µg/kg N-803, followed 15 days later by 20 µg/kg N-803	Safety PK PD
NMIBC: N-803 Bladder Instillation					
QUILT-2.005 Phase 1b; Complete 14 Aug 2017	Phase 1b dose-escalation, multi- center, open- label, single-arm	MTD and RD of N-803 plus BCG for BCG-naïve NMIBC	Adults with BCG-naïve NMIBC 9 Subjects	N-803 (100 µg, 200 µg, or 400 µg) plus BCG (50 mg) once weekly for 6 weeks	Safety Efficacy PD
QUILT-205; Ongoing QUILT-2.005 Phase 1b Follow-up 15 Jul 2024	LTF to assess yearly CR and DFS	Long-term follow- up	None; participated in QUILT-2.005 Phase 1b	None	Efficacy Survival
QUILT-2.005 Phase 2b; Ongoing 15 Jul 2024	Phase 2b, randomised, open-label, multicenter	CR rate (for CIS) or DFS (papillary) of N-803 plus BCG versus BCG alone	BCG-naïve NMIBC 195 total Cohort A (CIS ± Ta/T1): 120 Cohort B (HG Papillary): 75	N-803 (400 µg) plus BCG (50 mg) or BCG alone weekly for 6 weeks in induction and 3 weeks in maintenance	Safety Efficacy PD PK

Protocol; Study Status Report Date (Cut-off)	Type of Study	Primary Study Objective	Population Number of Treated Subjects	Dose and Dosing Regimen	Data Collected
QUILT-3.032-2.005-PK[a]; Complete 16 May 2024	Non-interventional PK sub-study of QUILT-3.032 and QUILT-2.005 phase 2	PK profile of N-803 after single dose of intravesical instillation of 400 µg N-803	Enrollment in QUILT-3.032 or QUILT-2.005 phase 2b 1 Subject	N-803 (400 µg) plus BCG (50 mg) or BCG alone weekly for 6 weeks in induction and 3 weeks in maintenance	PK Substudy
QUILT-3.032; Ongoing 15 Jul 2024	Phase 2/3, open- label, single-arm, three-cohort, multicenter	CR rate (Cohorts A and C) or DFR rate (Cohort B)	BCG-unresponsive high-grade NMIBC 190 total Cohort A (CIS ± Ta/T1): 100 Cohort B (HG Papillary): 80 Cohort C (CIS ± Ta/T1): 10	N-803 (400 µg) plus BCG (50 mg) (Cohorts A and B) or N- 803 alone (Cohort C) weekly for 6 weeks in induction and 3 weeks in maintenance	Safety Efficacy PD PK

2.3. *Description of the product*

N-803 is an interleukin-15 (IL-15) receptor agonist. It is a soluble complex consisting of (a) nogapendekin alfa (a human IL-15N72D variant, 114 amino acids) bound to (b) inbakicept [a dimeric human IL-15Rα sushi domain (65 amino acids)/human IgG1 Fc fusion protein (232 amino acids)]. Each fully assembled nogapendekin alfa inbakicept complex consists of a single inbakicept and two nogapendekin alfa components. Each IL-15N72D component is bound to one of the IL-15Rα sushi domains.

N72D substitution in IL-15 enhances activity in natural killer (NK) and cluster of differentiation $CD8^+$ T cell proliferation assays and favors beta over gamma chain IL-2/IL-15 receptor binding (Fujii 2018, Zhu 2009, Han 2011), thus does not activate T regulatory (Treg) cells. The bound IL-15Rα also contributes to enhanced activity (Rubinstein 2006, Stoklasek 2006). The Fc region stabilizes and increases half-life (t½) of the complex by its binding to the neonatal Fc receptor (FcRn).

2.4. *Inspection issues*

2.4.1. GMP inspection(s)

No GMP inspections were deemed necessary within the scope of this MAA evaluation procedure.

2.4.2. GLP inspection(s)

During the assessment, no specific issues to be addressed during a GLP inspection were identified.

2.4.3. GCP inspection(s)

During the assessment, no specific issues to be addressed during a GCP inspection were identified.

3. Quality aspects

3.1. Introduction

Anktiva is presented as a concentrate for intravesical suspension containing 400 micrograms of nogapendekin alfa inbakicept as active substance. Other ingredients are disodium phosphate (E339), potassium dihydrogen phosphate (E340), sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

The product is available in a glass vial with a serum stopper (chlorobutyl elastomer with a Flurotec B2-40 coating) and an aluminium alloy seal containing a yellow plastic polypropylene flip-off cap.

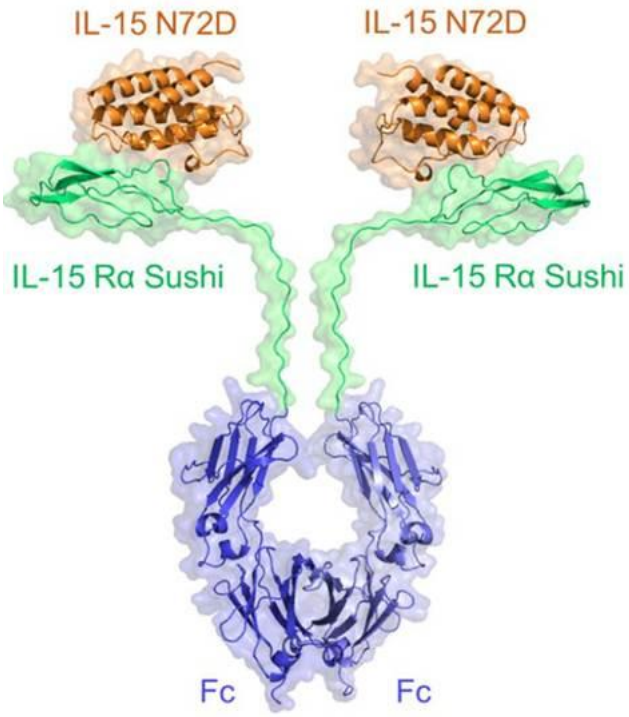
3.2. Active substance

3.2.1. General information

The active substance (AS), N-803 (INN: Nogapendekin alfa inbakicept) is a dimeric fusion protein complex acting as an interleukin-15 (IL-15) superagonist. This protein is produced in Chinese hamster ovary cells (CHO-K1) by recombinant DNA technology. N-803 is a soluble complex consisting of: nogapendekin alfa (a human IL-15N72D super agonist variant) bound with high affinity to inbakicept (a dimeric human IL-15Rα sushi domain/human IgG1 Fc fusion protein). Each fully assembled N-803 complex consists of a single inbakicept and two nogapendekin alfa components. Each IL-15N72D polypeptide is noncovalently associated with the IL-15RαSu/IgG1 Fc polypeptide. The IL-15RαSu/IgG1 Fc polypeptides form a covalent dimer through disulfide bonds in the Fc domains.

The simplified structure of nogapendekin alfa inbakicept is shown in Figure 1.

Figure 1 Structure of nogapendekin alfa inbakicept (N-803)



The primary structure of nogapendekin alfa inbakicept has been characterised with respect to its primary sequence, molecular weight of deglycosylated N-803 complex (92,106.2 Da) and individual sub-units (Fc domain: 66,565.6 Da; IL-15 domain: 12,770.45 Da), disulfide linkages and post-translational modifications, including glycosylation and attached glycan structures. Secondary, tertiary and higher-order structure have also been characterised by different analytical techniques.

The mode of action for nogapendekin alfa inbakicept is mediated by the biological activity of IL-15N72D, which includes lymphocytic activation of T cell and NK cell antitumor responses without initiating an adverse T regulatory (Treg) cell-mediated response. The activity exerted by nogapendekin alfa inbakicept in NK and CD8+ T cell proliferation assays is vastly enhanced by the engineered N72D substitution. In addition, the N72D substitution favours beta-over-gamma chain IL-2/IL-15 receptor binding, not activating Treg cells.

Sufficient information regarding the nomenclature, structure and general properties has been provided, as well as brief description of the mechanism of action.

3.2.2. Manufacture, characterisation, and process controls

Manufacturers

Name and address of the manufacturer of the biological active substance:

AGC Biologics, Inc.
21511 23rd Dr SE Bothell,
WA 98021
United States of America

Name and address of the manufacturer responsible for batch release

Bilthoven Biologicals
Antonie van Leeuwenhoeklaan 9
3721 MA Bilthoven
The Netherlands

All active substance manufacturing sites are GMP compliant.

Description of manufacturing process and process controls

A recombinant CHO-K1 cell line is used for the expression of the active substance, followed by an upstream cell culture and a downstream harvest and purification process. The upstream process begins with a working cell bank (WCB) vial and includes cell expansion steps, seed and production bioreactor steps, ending with a harvest of the cell culture fluid (bulk harvest). The bulk harvest is then purified through series of chromatographic purification steps and additional steps for virus removal/inactivation and formulation of bulk active substance.

The nogapendekin alfa inbakicept active substance manufacturing process has been sufficiently described in a detailed narrative together with flow-charts and tables presenting process parameters with normal operating ranges (NOR), proven acceptable ranges (PAR) and their criticality classification (key, KPP; non-key, nKPP; critical, CPP). The routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step and adequately set to control the process. No reprocessing is done for any step in the process. The active substance manufacturing process is considered acceptable.

Batch and scale definition

One batch of nogapendekin alfa inbakicept active substance refers to material derived from a single bioreactor cultivation using a single working cell bank vial. The batch numbering system is adequately described.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Nogapendekin alfa inbakicept is expressed in a recombinant CHO-K1 cell line. The source, history and generation of the cell substrate is sufficiently described in accordance with the recommendations of ICHQ5B and ICHQ5D. The N-803-expressing cell line was created using three plasmids, two encoding IL-15N72D and one encoding IL-15RαSu/IgG1 Fc fusion protein. The construction of the expression vectors and its genetic elements are described and illustrated in sufficient detail.

The cell bank system and the preparation of the cell banks are sufficiently described for the pre-master cell bank (MCB), MCB, WCB and end of production cells.

Comprehensive testing of MCB and WCB in line with ICHQ5A and ICHQ5D was performed (identification, mycoplasma, sterility, bacteriostasis/fungistasis and genetic stability). Brief description of methods used for the characterisation of cell banks has been provided. Historical stability data for MCB and WCB shows viable cells for six and four years, respectively.

No clear protocol for future WCB has been included in the documentation. However, in the release specification for the first WCB it is stated that for WCBs subsequent to the first WCB testing could be performed by either on WCB or cells at the Limit of In-vitro Cell Age (LIVCA). The Applicant has confirmed that introduction of future new WCBs will be managed via post-approval variation applications which was found acceptable.

To conclude a two-tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

Control of critical steps and intermediates

The manufacturing of nogapendekin alfa inbakicept is monitored and controlled by process parameters for each of the manufacturing process steps, together with in-process controls (IPCs). Process parameters with the corresponding NORs and their corresponding PARs where available, are presented. The identified process parameters are categorised according to their criticality as either a critical process parameter (CPP), a key process parameter (KPP), or a non-key process parameter (nKPP), where a CPP has greatest potential impact on critical quality attributes (CQAs). In-process controls (in-process specifications, IPS, and in-process limits, IPL) are established and used to assure acceptable product quality for individual unit operations in the manufacturing process. The presented definitions and classifications are appropriately justified.

The CPPs with the corresponding NORs and the impacted CQAs are provided in tabular form and this information is aligned with the process description. Tables providing summaries of the in-process specifications and limits for the active substance manufacturing process are provided.

A deviation management system in place, and the classification of deviations is explained. Any deviation from NOR for CPPs, KPPs, nKPPs, IPSs, and IPLs will trigger an investigation. A failure to meet specifications (product or in-process), or a failure to meet a CPP related to viral safety, will result in batch rejection.

The manufacturing process for the active substance does not include isolated process intermediates for long-term storage. Unprocessed bulk harvest is not stored prior to further processing.

The analytical methods for in-process control testing are adequately described and validated.

Overall, a comprehensive overview of critical in-process controls and critical in-process tests performed throughout the nogapendekin alfa inbakicept active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

Process validation of the commercial manufacturing process was performed at the commercial facility, Three consecutive commercial-scale process performance qualification (PPQ) batches were included in the study (upstream lots: 19-0157, 20-0086, 20-0091; corresponding downstream (DS) lots: 19-0161, 20-0090, 20-0095).

The pre-defined validation acceptance criteria for both process parameters and performance indicators were met for all three validation batches, apart from five deviations that were appropriately explained and for which it was shown that there was no impact on process performance or product quality.

An ongoing process verification program that will be used to assure that the manufacturing process remains in a state of control during commercial manufacture is outlined in the dossier and found acceptable. The program activities to collect and analyse product and process data include monitoring and reporting of process data for critical process parameters, selected key operating parameters, in-process limits, and in-process specifications. The activities will be performed for each manufacturing process step from each commercial-scale lot produced during the year.

The proposed hold times are sufficiently explained and justified based on process validation data. In addition, during process validation the number of re-use cycles for chromatography resins as well as testing and acceptance ranges for in-process mixing steps have been validated. Finally, the conditions for active substance shipping are adequately described and the validation strategy was found acceptable.

The nogapendekin alfa inbakicept active substance manufacturing process has been validated adequately.

Manufacturing process development

Manufacturing history and process change

Throughout development the active substance manufacturing process was performed at different sites and scales. The major changes implemented during manufacturing development have been clearly described and justified. They comprise a new manufacturing site (AGC Biologics), bioreactor scale-up, a new cell bank (working cell bank, WCB), change in upstream cell culture medium , change in the protein A resin, introduction of a hydrophobic interaction chromatography (HIC) step and depth filtration, and a change in order of the viral filtration and final UF/DF steps.

Analytical comparability

An analytical comparability exercise was performed to evaluate the comparability between the implemented changes in the processes for manufacturing of phase 1/2 material and phase 3/PPQ material. The analytical comparability exercise included comparisons of batch release data and extended characterisation data. The attributes and parameters compared are found acceptable and in line with ICH Q5E.

The comparability exercise was done directly on the finished product level. The selected finished product batches originate from four different active substance batches, including active substance batches from all three different manufacturing processes, and spanning all clinical materials (phase 1/2 and 3) produced. The approach for not including comparability assessment on the active substance level was justified given the straightforward manufacturing process for the finished product (i.e., active substance pooling and mixing, sterile filtration, filling, packaging).

Process characterisation and control strategy

Formal risk assessments were conducted for the upstream and downstream processes to develop the control strategy. A risk ranking approach was utilised to assess the severity of active substance quality attributes (QAs), followed by process parameter categorisation and characterisation. The CQAs for the active substance were identified in parallel to development of the manufacturing process, analytical development, and process characterisation. The identified list of CQAs include: identity by icIEF and peptide map, visual appearance (colour, clarity), pH, osmolality, protein concentration, fragments, partially occupied N-803 (single-arm variant), high molecular weight (HMW) species, IL-15 binding by anti-IL15 ELISA, IL-15 potency by cell-based bioassay, residual host cell protein, residual host cell DNA, residual protein A, bioburden and endotoxins.

Process parameters with impact on CQAs were classified as critical process parameters (CPPs), whereas parameters identified as important for process performance, but having no effect on CQAs, were classified as key operating parameters (KOP). The remaining parameters, not impacting product quality or process performance, are classified as non-KOPs. In-process limits (IPLs) or in-process specifications (IPSs) are introduced, in addition to the active substance specifications, to assess the process performance. The overall strategy described is found acceptable.

The study design, parameters, ranges and results of the process characterisation for the upstream and downstream manufacturing processes are provided. The information provided on process characterisation is considered acceptable and sufficiently justifying the classification of parameters and the corresponding NORs and PARs. Results and justifications for in-process limits and in-process specifications were also found acceptable.

Reduced-scale models were used during process characterisation were adequately qualified and, thus, representative of the corresponding process stage at manufacturing scale.

Characterisation

Elucidation of structure and other characteristics

The nogapendekin alfa inbakicept active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. Biological characterisation of nogapendekin alfa inbakicept indicates that this antibody has the ability to bind Fc receptor CD64 and IL-15Rβ expressing cells with high affinity. In summary, the characterisation is considered appropriate for this type of molecule.

Impurities

The impurities found in nogapendekin alfa inbakicept were adequately determined and include product-related impurities, process-related impurities and contaminants.

Active substance batches representative for the commercial process have been tested and the results observed for the different impurity categories are summarised. The results are consistent and demonstrate that the impurity levels in the active substance are sufficiently low to ensure drug safety.

Dedicated clearance studies were performed, confirming efficient removal of all process-related impurities. Safety assessments of the major process-related impurities show that there is adequate safety margin below the permissible daily exposure limit, and it is concluded that there is no safety risk. The information on process-related impurities and contaminants is acceptable.

3.2.3. Specification

The release and shelf-life specification for nogapendekin alfa inbakicept includes general compendial tests (colour, clarity, particulates, osmolality, pH), microbiological safety tests (endotoxin, bioburden, Mycoplasma), in-house tests for identity (peptide mapping by UPLC, charge variants by icIEF), strength (total protein concentration, IL-15 ELISA, CTLL-2 (IL-15 dependent proliferation assay for potency and effective concentration of active substance test samples), purity (charge variants by icIEF, CE-SDS, SE-UPLC, residual protein A by ELISA, Host cell protein by ELISA, host cell DNA) and safety tests (MMV PCR, IV adventitious agents).

The release specifications were established using data from 5 active substance batches and 6 finished product batches used for pivotal clinical trials and/or Process Performance Qualification (PPQ). The acceptance criteria were established based on statistical tolerance intervals, practical limits and compendial or established guidance. The proposed active substance acceptance criteria for icIEF, CE-SDS (reduced and non-reduced) and SE-UPLC were questioned in the first and second assessment round. Additional justification of the limits was based on the levels of the impurities in the batches used during clinical studies and considered satisfactory.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Validation summaries of all non-compendial methods have been provided including descriptions of validation approaches, parameters, results, and conclusions. Relevant calculations, acceptance criteria, description of results have been presented.

Since no degrading trends are observed for any of the quality attributes during shelf-life at the long-term storage temperature of 2°C to 8°C, the same specifications limits are proposed for active substance release and end-of-shelf life which is found acceptable.

Batch analysis

Batch analysis data (n=16) of the active substance were provided. The results were obtained from batches used for non-clinical, clinical, commercial use and developmental batches, and are within the specifications (valid at the time of testing) and confirm consistency of the manufacturing process.

Reference materials

The current primary reference standard (batch DC-10244-76) is used for clinical and commercial lot release and stability testing for active substance and finished product, and qualification for reference standards. The preparation of the current primary reference standard is found sufficiently described.

A two-tiered reference standard system is introduced, containing a primary reference standard PRS (lot DC-10244-76) and a working reference standard WRS (Lot 230046). The PRS is currently used for all biological and physicochemical routine release and stability testing of the productions lots, for assays that require a reference standard as a comparator. The introduced WRS has been qualified against the current PRS DC-10244-76 and will be implemented for all routine biological and physicochemical release and stability testing of production lots. Overall, the information on the implemented two-tiered reference standard system (PRS, WRS) is considered sufficient and acceptable, with an adequately qualified WRS (lot 230046).

With the proposed annual stability monitoring program, it is acceptable not to have any specified expiry date (shelf life) for the primary reference standard.

The strategy for qualification and requalification of future reference standards has been acceptably described with acceptance criteria provided. Protocols for qualification and requalification are presented in the dossier.

The internal control lot 3-FIN-3045 is qualified as an internal control for the CTLL-2 and IL-15 ELISA assays in the qualification and requalification process has been sufficiently described. Results from lot release and extended characterisation are presented.

Container closure system

The container closure system used for nogapendekin alfa inbakicept is a sterile 2000 mL Nalgene™ PETG Certified Clean Container. The active substance is filled and stored in the Nalgene containers at 2°C to 8°C.

The components of the Nalgene PETG container and the corresponding materials are clearly described. Confirmation is given that the container closure material is in compliance with Ph. Eur. 3.2.1.

The Applicant has performed an extractables and leachables study, including forced extraction data, with the conclusion that the Nalgene PETG containers are suitable for storage of active substance.

3.2.4. Stability

A shelf-life of 36 months is proposed for nogapendekin alfa inbakicept when stored at 2°C to 8°C long-term conditions.

The nogapendekin alfa inbakicept primary stability batches selected for stability studies according to ICH guidelines include one clinical phase 3 batch (17-0315) and two PPQ batches (19-0161, 20-0090) manufactured using the commercial-scale process and packaged in representative scaled-down PETG bottles (5 or 30 mL). The proposed selection of primary lots is found acceptable as the clinical phase 3 material is demonstrated to be comparable to the PPQ material.

Long-term stability data are obtained at recommended storage temperature of 2°C to 8°C, for one clinical phase 3 batch covering 48 months (ongoing, 48 of 60 months completed) and two PPQ batches covering 36 months (ongoing, 36 of 60 months). It is noted that the long-term stability studies for primary stability lots are planned to continue for up to 60 months.

A few OOS results have been registered during the stability studies. Regardless of these OOS against the specification at the time of testing, the primary stability results have remained within the proposed commercial release and shelf-life specifications as described in section 3.2.3. above, at the recommended storage temperature for at least 36 months.

Supportive forced degradation and stress stability studies were used to confirm the principal degradation pathways and to confirm the suitability of the analytical methods for detection and

quantitation of the primary active substance degradation products and thus shown to be fit for purpose as stability-indicating analytical methods. Stress results for one batch (17-0315) on 12-month storage at -70°C storage and multiple Freeze thaw studies of active substance from -70°C storage to room temperature show no significant changes in product quality on stability at frozen storage conditions even after 5 freeze thaw cycles.

Forced degradation study results that are common for the active substance and finished product are presented for three batches (one reference standard active substance batch and two finished product batches). The effects of photostability as per ICHQ1B (option II), agitation/shear, oxidation, elevated pH, reduced pH, and elevated temperature on the protein's degradation pathways were studied. Exposure of finished product material to thermal stress of 60°C for up to 7 days caused the most significant degradation observed by NR CE-SDS, SE-UPLC, icIEF, anti-IL15 ELISA, peptide map, and IL-15 Dependent Proliferation Assay analysis. Particles were observed visually in finished product samples exposed to high and low pH conditions, but changes were not observed by other utilized methods for pH stressed samples. Changes were observed in oxidation stressed samples by peptide map analysis only. No significant changes were observed in photostability (ICH Q1B option II), or agitation/shear stressed samples by any of the tested methods.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life of 36 months under refrigerated conditions (2°C to 8°C) in the proposed container.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

The finished product is presented as concentrate for intravesical suspension containing 400 microgram of nogapendekin alfa inbakicept as active substance.

Other ingredients are disodium phosphate (E339), potassium dihydrogen phosphate (E340), sodium chloride, sodium hydroxide, hydrochloric acid and water for injections

The components of the finished product are appropriately described. All the excipients used in the finished product comply with the Ph. Eur. requirements. No excipients of human or animal origin are used.

The primary packaging is a glass vial with serum stopper (chlorobutyl elastomer with a Flurotec B2-40 coating) and an aluminium alloy seal containing a yellow polypropylene flip-off cap, as described in section 6.5 of the SmPC. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Pharmaceutical development

Formulation development

All clinical studies were performed using N-803 finished product (FP) formulated in phosphate-buffered saline (PBS) at 1 mg/mL N-803 and formulated in PBS at 2 mg/mL N-803. The product concentration was increased to 2 mg/mL to allow for a more suitable subcutaneous injection volume for clinical trials performed with subcutaneous administration up to 20 µg/kg. An overview of finished product batches used in pivotal non-clinical studies and clinical trials is provided with the corresponding active substance batches listed.

Overages

There is no overage in N-803 finished product formulation. However, an overfill of 0.2 mL is applied to allow extraction of the nominal dose volume of 0.4 mL. The rationale for the overfill is justified and substantiated with studies on extractable volume which demonstrate that a range between 0.58-0.62 mL was required to yield the volume of 0.40 mL from each vial.

Manufacturing process development

Throughout clinical development N-803 finished product has been manufactured at three different sites,. The manufacturing steps during clinical development were the same at the three manufacturers who supplied clinical material. The process changes were all related to scale-up activities and changes necessary to support multiple routes of drug administration in clinical trials. Phase 1, Phase 2, and Phase 3 clinical trials included finished product in both the PBS 1 mg/mL and PBS 2 mg/mL formulations. The proposed commercial finished product uses the PBS 1 mg/mL formulation only.

The pharmaceutical development of the finished product contains QbD elements. A risk analysis has been done to identify the CQAs. The CQAs identified were: identity by cIEF and peptide map, visual appearance (colour, clarity, visible particles), pH, osmolality, protein concentration, fragments, partially occupied N-803 (single-arm variant), HMW Species, IL-15 binding by anti-IL15 ELISA, IL-15 potency by cell-based bioassay, bioburden, sterility, endotoxin, sub-visible particles, extractable volume, container closure integrity.

The development of the control strategy for the finished product has been sufficiently described. A risk analysis was performed using failure mode effect analysis (FMEA) method, along with characterisation studies, to define critical process steps and process parameters that may have an influence on the finished product quality attributes.

The comparability strategy supports active substance and finished product changes made during product development (The strategy was adopted to ensure that the finished product manufactured at different sites used in clinical trials were comparable). The overall comparability approach utilised both analytical comparability and pharmacokinetic studies. Based on the comparability study results, the N-803 finished product lots generated with the Phase 3 process (pre-change) and commercial (post-change) were found to be for most parts comparable.

For the stability comparability studies, the Applicant has presented updated long-term and accelerated comparability stability data. The results for 36 months show that the stability profile is largely the same although there are some minor differences for the iCEF profile and the low molecular weight (LMW) species but given the degradation profiles during the accelerated study are similar no concerns are raised.

Compatibility

A risk assessment was performed to evaluate the potential of materials (components) used during the production of N-803 finished product and in-use of the final finished product to contribute leachable compounds that may impact product quality. Satisfactory results were provided in case additional extractable and leachable studies were required.

One Major Objection (MO) was raised during the evaluation since the initial in-use compatibility was provided for finished product diluted in 0.9% saline but without Bacillus Calmette-Guérin (BCG), and therefore the compatibility study was not considered representative of the intended use. The Applicant has presented new in-use compatibility studies where the finished product is used in combination with two different BCG products intended for the EU market. The products selected account for approximately 70% of patients and 30% dosed in the EU with BCG. The in-use studies were done using three representative batches of finished product with maximum hold times of 2 hours for both

BCG products. Testing was performed to determine the impact on Weight Recovery, size-exclusion ultra-performance liquid chromatography with fluorescence detection (SEC-UPLC-FLD) for Purity and Content, Reduced and Non-reduced SDS-PAGE Silver Stain, Relative Potency by IL-15 Dependent Proliferation assay, Quantitation of N803 by Anti-IL-15 Detection ELISA and Bacterial Enumeration of BCG. The results show there is no impact following incubation with either BCG product. The studies cover the full dilution range of N-803 finished product that will be administered with BCG, covering a concentration range of 5.8-10.0 µg/mL. Three representative batches of N-803 1 mg/mL finished product were included in the studies. The in-use compatibility studies used the containers supplied with both BCG products and thus are representative of the syringes and solvent bags used in a clinical setting. Based on the provided additional information the MO was resolved.

3.3.2. Manufacture of the product and process controls

Manufacturers

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

Description of manufacturing process and process controls

The finished product manufacturing process is summarised in a flow chart and detailed in a written narrative.

The manufacturing process is a common process for aqueous sterile finished products which cannot be subjected to terminal sterilisation. It consists of buffer formulation and filtration, finished product formulation and first filtration, sterile filtration and aseptic filling in vials.

The stoppered vials are capped, and 100% manually, visually inspected. The capped vials are stored at 2-8°C before further handling. A brief description of the batch numbering system has been provided. No reprocessing has been described in the dossier.

Process duration times and hold times for the commercial manufacturing process of N-803 solution are clearly presented and classified according to their criticality. The processing and holding times proposed for bulk sterile filtration (NMT 24 hours), sterile filtered bulk finished product (NMT 24 hours) and aseptic filling (NMT 12 hours) are adequately justified and validated.

A batch size range for the commercial finished product manufacture is declared.

Control of critical steps and intermediates

The Applicant conducted a failure modes and effects analysis (FMEA) of the manufacturing process to identify the critical manufacturing steps. The CPPs, nCPPs, and IPCs established for preparation of the Formulation Buffer, preparation of the active substance pooling, dilution, aseptic filtration, filling, stoppering, and sealing have been provided as well as NORs and they have overall been acceptably justified by data presented in development and validation dossier sections.

The control strategy consists of process parameters (PPs) which are categorised as either critical (CPP) or non-critical process parameters (nCPP). CPPs are PPs which impact a CQA while nCPPs do not impact CQAs. The process control strategy also includes IPCs, as checks to ensure the process is performing consistently and to allow adjustments if appropriate to ensure the product meets its specifications. The Applicant has updated the control strategy to include PARs for the CPPs and some of the nCPPs. The lack of a PAR for all other nCPPs can be accepted since they are not deemed to impact the quality of the product and the remaining nCPPs are still controlled with a NOR around a target set-point. The overall proposed control strategy is justified.

Process validation

The commercial manufacturing process has been validated using four commercial scale production lots during Process Performance Qualification (PPQ, two 5.000 vial scale and two 20.000 vial scale).

Overall, the results of IPCs and process characterisation samples met their predefined acceptance criteria, and all CPPs were controlled within their predefined ranges (NOR). All release results met finished product release specification, and all process validation batches demonstrated consistent quality profiles, demonstrating that the finished product can be consistently manufactured within predefined processing parameters.

Post-PPQ execution, the finished product specification was revised under change control IB-CC-21-124 and is reflected in Module 3.2.P.5.1 Specifications. It has been clarified that both the PPQ and earlier batches meet the revised, more stringent specifications. Thus, the process remains fully validated under the new specifications.

The presented filter validation comprises filter compatibility including filter extractables, viability and filter flush, bacterial retention validation (*B. diminuta*), and bubble point including forward flow test determination. All results met the acceptance criteria. Also, the results from the filter extractables/leachables study have been presented with acceptable results.

The aseptic process validation of the filling line was initially performed with media fills. and the results provided in the dossier are satisfactory. The media fills also support the maximum sterile filtered bulk hold (NMT 24 hours) and the maximum fill duration (NMT 12 hours) as defined in the manufacturing description section.

Single use sterile bags and assemblies are used during production to collect and hold sterile filtered bulk finished product. They are sterilised by gamma irradiation. The Applicant has confirmed that the reference absorbed dose is ≥ 25 kGy and that the specifications for the bags are in compliance with the Note for Guidance "The use of Ionization Radiation in the Manufacture for Medicinal Products" and in compliance with Ph. Eur. chapter 5.1.1.

Shipping validation studies have been presented for commercial bulk finished product manufacturing sites, with acceptable results. Shipping validation in compliance with EU GMP Annex 15 and EU GDP guidelines will be completed before commercial batches are shipped to and within the EU. All shipping systems are pre-qualified to maintain 2–8°C and are periodically requalified.

The finished product manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product intended quality in a reproducible manner.

3.3.3. Product specification

The finished product release and shelf-life specifications include general compendial tests (colour, clarity, visible and sub-visible particles, osmolality, pH, extractable volume), gross volumetric content (IPC), compendial microbiological safety tests (endotoxin, bioburden), container closure integrity test, in-house tests for identity (peptide mapping by UPLC, charge variants by icIEF), strength (total protein concentration, IL-15 ELISA, CTLL-2), and purity (charge variants by icIEF, CE-SDS, SE-UPLC).

The specifications are based on the performance of analytical methods, severity of impact on safety and efficacy, clinical experience, manufacturing process capability, regulatory and compendial requirements, and stability trends. The acceptance criteria have been set to be aligned with the active substance for specifications that are common between both and it is referred to S.4.5 for further discussion on the justification for these specifications.

It is noted that no degrading trends are observed for any of the quality attributes during shelf-life at the long-term storage temperature of 2°C to 8°C. Therefore, the same specifications limits are proposed for finished product release and end-of-shelf life which is justified.

Analytical methods

The majority of methods are used to control both the active substance and finished product. Additional methods are used due to testing for gross content (in-process test) container closure integrity. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines and the compendial methods have been verified according to the appropriate compendial chapters

Batch analysis

Batch analyses data has been provided for finished product batches from development batches to commercial scale batches used in clinical trials and in PPQ/Stability studies. Information for these batches include manufacturing batch number, production date, active substance batch(es) used, manufacturer of active substance(es) used, formulation and use of the batch and batch size.

The provided batch analysis data originates from four PPQ batches, two GMP batches and one commercial batch. The batch results comply overall with the limits in the proposed finished product release specification in place at the time of manufacture and confirm process and product consistency.

In conclusion, the batch data provided demonstrate reproducible manufacturing of the finished product provided that acceptable responses to the questions raised are received from the applicant.

Characterisation of impurities

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity control***.*** The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Reference materials

The same reference standard(s) is used for testing of both active substance and finished product, information is provided in module 3.2.S.5 Reference Standards or Materials.

3.3.4. Stability of the product

The proposed shelf-life for the finished product vial presentation is 36 months when stored at the recommended storage condition of 2°C to 8 °C and protected from light.

Stability data has been provided for up to 48 months at 2 to 8 °C. The primary stability batches and the PPQ batches are comparable as justified in P.2.3, and then there are additionally supporting

stability studies that are completed. The specifications are the same for release and stability (see 1.2.2.3 above). The stability studies are performed in accordance with ICH Q5C and the container closure system used in the stability studies is identical with the proposed container closure system. Furthermore, comparability has been demonstrated between vial presentation manufactured at minimum (~5,000) and maximum (~20,000 vials) batch sizes.

The on-going stability program includes to date 48 months data for 1 batch and 36 months for two batches, all part of the primary stability studies. 48-, 36- and 24-months data for three PPQ batches. Additional data for supporting stability studies for four finished product batches, 1-3 months and 21-66 months stability are presented. All stability results for the vial presentation stored at 2 to 8 °C for up to 36 months comply with the release and shelf-life specifications (see 1.2.2.3 above) without any significant trends. Only the IL-15 ELISA shows a slight decrease in potency.

Accelerated storage temperature of 25 ± 2°C has been assessed for two batches up to 12 months and three batches up to 6 months, and one supporting stability study has been assessed up to 6 months. Most stability results comply with the stability specifications. For purity there are some data out of trend for 6, 9 and 12M, also the IL-15 ELISA potency shows decrease on a batch.

In addition, stability data has been provided at stressed temperatures for one batch at -70°C, and 20°C for up to 3 months and accelerated conditions (40 ± 2 °C) for 1 month. These data support the wording in section 6.3 and 6.4 of the SmPC that the finished product should only be stored at 2°C to 8 °C.

One primary stability batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Active substances and Products. The results showed that the vial presentation is photosensitive and, in addition, that the intended commercial pack with secondary packaging material is able to protect the finished product from photodegradation, in-line with the wording reflected in section 6.4 of the SmPC.

The suitability of the container closure system to protect the content in the vial from microbial contamination during storage has been demonstrated during long-term stability results. The Applicant has clarified that the start of shelf life is in accordance with the "Note for guidance on start of shelf-life of the finished dosage form".

At least one commercial batch will be placed annually on stability studies at long-term conditions (2 to 8 °C) as per the proposed stability protocol. The stability protocol for the primary batches and PPQ batches has also been presented, and testing will continue up to 60 months. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA".

The stability results justify the proposed shelf life of 36 months when stored at 2°C to 8°C in the proposed container and protected from light. The compatibility studies in the development section have demonstrated the chemical and physical in-use stability of the admixture of Anktiva finished product with OncoTICE (2 hours at 2°C to 8°C, protected from light) and BCG-medac (24 hours at 2°C to 8°C, protected from light).

3.3.5. Adventitious agents

Materials of animal origin

No animal- or human-derived raw materials are used in the manufacture of active substance or finished product. The production cell substrate was adapted to animal-serum-free growth medium prior engineering to express the N-803 proteins. A pre-master cell bank (ALT-803 3.18.2.6), a GMP master cell bank (ALT-803-26 clone T3.18.2.6 MCB), and a GMP working cell bank (ALT-803-26 Clone

T3.18.2.6 WCB) were manufactured, using protein-free medium. The transfectants were initially grown in medium containing 10% FBS. EDQM CEP certificates for these materials are provided. It is acknowledged that the risk of TSE is negligible.

Non-viral adventitious agent testing

Microbial controls testing for bioburden and endotoxin is part of the control strategy and is outlined in S.2.4 controls of critical steps and intermediates. Mycoplasma is also tested for on the unprocessed bulk harvest. It is acknowledged that microbial agents are sufficiently controlled with this test programme

Testing of unprocessed bulk

The unprocessed bulk harvest is tested for mycoplasma, bioburden, endotoxin, MMV (PCR) and an in vitro adventitious agents assay as part of routine release testing. The highest TEM results found by the Applicant (n=5) was 1.6×10^7 retrovirus like particles (RVLPs) per mL.

Virus clearance studies

The viral clearance studies were performed with the potential worst-case conditions on scale down model (SDM) representative of full-scale manufacturing process. Low pH and nanofiltration are dedicated steps for viral clearance. Protein A and AEX chromatography contribute to viral clearance. Model viruses used is in accordance with ICH Q5A and are Murine Leukemia Virus (MLV), Pseudorabies Virus (PRV), Reovirus 3 (Reo-3) and MMV. The viral inactivation kinetics was performed at worst-case conditions and significantly effective inactivation kinetics was observed.

From the purification process steps evaluated for virus clearance, low pH inactivation, AEX chromatography and nanofiltration were confirmed to be effective and low pH inactivation and nanofiltration being orthogonal viral clearance steps.

Carryover study was performed to support the reuse of the chromatography resins. Information about cytotoxicity and interference testing has been provided.

The calculation of the retrovirus risk is performed in accordance with the ICH Q5A guideline and the calculated virus safety factor for retrovirus like particles (RVLPs) is 9.7 $\log_{10}$ per dose.

The information provided is sufficient and acceptable and demonstrate that adventitious agents' safety including TSE have been sufficiently assured.

3.4. Discussion on chemical, pharmaceutical and biological aspects

3.4.1. Drug substance

The drug substance manufacturing process is adequately described. Characterisation of the drug substance was performed using an extensive panel of appropriate methods. The control of drug substance is found acceptable, with acceptably justified acceptance limits in the drug substance specifications. The provided data to support the shelf-life claim for the drug substance is considered acceptable and justified

3.4.2. Drug product

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner.

One Major Objection (MO) was raised during the evaluation since the initial in-use compatibility was provided for finished product diluted in 0.9% saline but without BCG, and therefore the compatibility study was not considered representative of the intended use. The Applicant provided new in-use compatibility studies where the finished product is used in combination with two different BCG products intended for the EU market. The Major Objection was adequately addressed by the applicant and section 6.6 of the SmPC has been updated to include instructions for the preparation and administration of Anktiva in combination with BCG admixture based on the in-use stability studies that were performed for Anktiva in combination with OncoTICE® and BCG-Medac®. During the procedure a new standard term for the pharmaceutical form was requested to the EDQM. The Applicant received the notification and accepted the new standard term 'concentrate for intravesical suspension' which is also added to the Standard Terms database at EDQM. The product information is amended accordingly.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed.

The results of tests carried out indicate consistency and uniformity of important quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

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

3.6. Recommendation for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

N-803 is to be used in combination with BCG to treat BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). N-803 (400 µg) and BCG are combined in one syringe and administered directly into the bladder (intravesical) through a catheter once a week for six weeks, followed by optional maintenance treatments up to 37 months. BCG (attenuated vaccine of Mycobacterium bovis) activates innate immunity responses. In patients relapsing on BCG therapy, T-cell exhaustion and loss of HLA-1 have been proposed to contribute to the transient BCG effect. N-803 would enable a synergistic immunotherapeutic effect by acting as a booster to the BCG immune effects.

The non-clinical program consists of in vitro/in vivo pharmacology studies in rats, mice and monkeys. Studies determining the anti-tumor activity of intravesical N-803 in combination with BCG in rodent bladder cancer models were provided.

A limited toxicology program in accordance with ICH S6 and ICH S9 was conducted with pivotal repeat dose toxicity studies performed in rats and monkeys. No toxicology study has been performed with the clinical route of administration (intravesical).

4.2. Analytical methods

N-803 was quantified in mouse, rat and cynomolgus serum using enzyme-linked immunosorbent assays (ELISAs). Toxicokinetic samples from the non-clinical GLP 13-week SC rat toxicology study (20328204) were analysed in compliance with GLP using a validated ELISA.

The toxicokinetic analysis from the IV study in monkeys (YLP-1203) was not performed in compliance GLP and the assay was not validated, but qualified by evaluating precision, accuracy/recovery, effect of interfering substances, quantification range, standard curve linearity, and sample dilution linearity. Selectivity and stability of N-803 in cynomolgus monkey serum were not evaluated. The assays used for mice were only informative and not validated.

For the detection of antibodies against N-803 (ADAs) in rat serum, an electrochemiluminescence (ECL) method was developed and validated. For ADA detection in cynomolgus monkey serum, a bridging ELISA was developed and qualified.

Overall, the assays are considered suitable for quantification of N-803 and ADA in mouse, rat and monkey serum.

4.3. Pharmacology

N-803 (INN: nogapendekin alfa inbakicept also known as ALT-803) is a first in class IL-15 receptor agonist that is a fusion protein made up of two units of an IL-15 mutein (N72D) (nogapendekin alfa) fused to a dimeric IL-15 receptor alpha subunit sushi domain/IgG1 Fc region (inbakicept). It is designed to activate the immune system by promoting activation and proliferation of NK, CD4+, CD8+ and memory T-cells without activating immunosuppressive regulatory T-cells.

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

In vitro binding studies

The binding and agonistic effects of N-803 to the IL-15 receptor were assessed and compared to wild type IL-15 in *in vitro* studies.

N-803 exhibited higher binding affinity to IL-15 receptor when compared to human IL-15 in vitro. N-803 incubation lead to a 4-5 fold increase in biological activity when compared to wild type IL-15, measured as proliferation and JAK/STAT signalling in the IL-15 depended mouse 32Dβ cell line and CTLL-2 cells. Results from cells with (murine 32Dβ cells) and without (human TF-1β cells) the IL-15 receptor alpha chain, also indicate that this was mediated by improved interactions with the human IL-15Rβ chain rather than the IL-15Rα chain. Based on the cytokine-dependent cell proliferation assays, the EC50 values for N-803 were 39,9 pM and 4,8 pM in 32Dβ cells and TF-1β cells, respectively. A competive binding assay in TF-1β cells indicated about an 8-fold greater competetive binding activity for N-803 compared to IL-15 (IC50 = 0.48 pM for N-803 vs. 3.8 pM for human IL-15).

Interaction of N-803 to IL-15 receptor subunits, IL-15Rβ and IL-15RγN-803 was measured by surface plasmon resonance (SPR) and by Bio-layer interferometry, respectively and results showed that N-803 binds to IL-15Rβ, with the strongest affinity (KD of 1.36 nM). N-803 has a weak binding affinity to the other common receptor chain, IL-15Rγ (KD = 136 nM) and was only capable of binding IL-15Rγ in the presence of IL-15Rβ. Moreover, N-803 bound with high affinity to CD64 (Fc-gamma receptor 1) Fc receptor (KD=9,28 nM) and with lower affinity to other FC receptors.

Human and monkey IL-15 present 97% sequence identity, while human and murine IL-15 have 73% sequence identity. The applicant performed a comparative binding study in mouse splenocytes and monkey and human PBMC cells. N-803 was found to bind to the IL-15 receptor (βc and γc) on NK cells from monkeys, mice and humans in vitro when evaluated by flow cytometry. There were differences in NK cell binding where the lowest EC50 value was observed with mouse cells (203 nM), intermediate EC50 value in human cells (412 nM) and highest EC50 value in monkey cells (1127 nM). In these experiments, there were lower levels of binding of N-803 to CD8+ T-cells in mouse and human samples, and no binding was detected in monkey T-cells possibly indicating a lower expression of IL-15 receptor in the CD8+ cell population.

In vitro efficacy studies

In vitro effects of N-803 on human blood lymphocyte proliferation were determined. Following a 7-day culture period of human PBMCs (n=7 donors), N-803 (0,5 nM) or human IL-15 increased the number of CD4+/CD8+ T-cells and NK-cells compared to control when analyzed by flow cytometry. While IL-15 increased the number of regulatory T- cells compared to control, N-803 did not significantly increase the number of regulatory T-cells, although a trend towards an increase was noted.

N-803 induced expression of the lymphocyte activation markers CD25 and CD69 on PBMCs and increased the cytotoxicity of human PBMCs against Daudi B lymphoma cells and K562 myelogenous leukemia cells. This correlated with an increase in the expression of granzyme B and perforin on CD8+T-cells/NK-cells and the results support that N-803 leads to functional immune-cell activation in vitro.

Results from an in vitro cytokine release study indicate that N-803 primarily induces human and mouse lymphocytes to release IFN-gamma with higher levels produced after 4-day of PBMC cultures. There were milder increases in TNF-alpha, IL-6 and IL-2 after 4 days in human PBMCs and in TNF-alpha in mouse PBMCs. Data do not indicate that N-803 results in a broader cytokine response.

CDC and ADCC

The ability of N-803 to induce Complement-Dependent Cytotoxicity (CDC) and Antibody-Dependent Cellular Cytotoxicity (ADCC) was investigated in vitro. N-803 did not activate CDC against human PBMCs and there was no significant N-803-mediated ADCC against human PBMCs when using a high affinity FC receptor-engineered NK-cell line as effector cells.

In vivo efficacy of N-803

The Applicant refers to two publications (*Gomes-Giacoia, 2014 and Furuya, 2019*) in which the anti-tumour effect of intravesical N-803, alone or in combination with BCG was studied in a rat and a mouse model of bladder cancer. In these rodent models, chemically-induced (N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN)) bladder cancer was studied. The BBN-induced model is a well-established rodent model of bladder cancer.

In the rat model, intravesical N-803 alone or in combination with BCG showed decreased bladder wall thickness/bladder weights (used as surrogate for tumour burden) compared to control and BCG alone indicating increased anti-tumour activity of N-803 in combination with BCG compared to BCG alone. As a single treatment agent, N-803 reduced tumour burden by 35% compared to control whereas BCG

alone reduced tumour burden by 15%. The combination of N-803 plus BCG reduced tumour burden by 46% compared to control.

Tumour infiltration of immune cells, 1 week after last treatment, was investigated by histological staining of immune cells in the bladder. The number of CD3+ T-cells were increased with N-803+BCG compared to BCG alone. The combination N-803+BCG did however not result in increased staining of CD4+ or CD8+ T-cells when compared to BCG or N-803 alone. The number of NK-cells stained increased with the combination N-803 + BCG compared to control, BCG or N-803 alone. No changes in macrophage infiltration were noted in any groups. N-803+BCG was associated with increased serum levels of IL-1 alpha and IL1-beta when compared to control, N-803 or BCG alone, when assessed 2 weeks after the last treatment. In urine samples, RANTES was significantly increased with N-803+BCG when compared to BCG or N-803 alone. The cytokine profile is supportive of NK cell activation.

Tumour angiogenesis was found to be reduced when N-803 was combined with BCG (76 % reduction compared to BCG alone (40% reduction) or N-803 alone (59% reduction). The proliferative index (Ki67) was reduced and the cleaved caspase-3 staining was increased in the N-803+BCG group, compared to BCG or N-803 alone.

In a mouse model of BBN-induced bladder cancer using intravesicular administration, a 28% reduction in bladder weight was seen with BCG alone or N-803 alone compared to control whereas 36% reduction in bladder weight was seen with BCG plus intravesical N-803 compared to control. Subcutaneous administration of N-803 together with BCG resulted in a 44% reduction. No differences in infiltrating T-cells were noted in any groups compared to control 2 weeks after last treatment. Intravesicular N-803+BCG resulted in an increase in CD8+ T-cells in circulation when compared to control and BCG treatment alone whereas no changes in NK-cells were detected. Again, subcutaneous administration of N-803 appeared more potent in inducing CD8+ T-cells and NK-cells. Similar results were noted when analysing splenic tissue, although a trend towards an increase in NK-cell induction could be detected with intravesicular N-803+BCG.

Intravesical N-803+BCG did not induce an increase in serum or urine cytokines when compared to control or BCG alone. Instead, addition of intravesical N-803 led to a decrease in serum cytokines when compared to BCG treatment alone, supporting that intravesical N-803 has milder systemic effects.

In samples from healthy monkeys from the repeat dose toxicity study, four weekly IV injections of N-803 resulted in a transient dose-related increase in the NK and T-cell population when compared to control. The results support that IV administration of N-803 is able to induce immune responses in cynomolgus monkeys supporting that N-803 is pharmacological active in monkeys.

In rat and mice models of BBN-induced bladder cancer, intravesical (clinical route) N-803 alone or together with BCG had anti-tumour effects when bladder weight or bladder wall thickness was used as a surrogate for tumour burden. In rats, lymphocytic infiltration was noted with intravesical administration of N-803+ BCG in the bladders demonstrating the local immunostimulatory activity with intravesical administration. A synergistic effect of N-803+BCG was noted since the combination N-803+BCG showed larger reduction in tumour burden than BCG alone, possibly coupled to an increase in tumour infiltrating NK-cells, reduction in tumour angiogenesis and increase in apoptotic markers.

In mice, the additive effect of intravesical N803+BCG was weaker than in rats when compared to BCG alone and no significant increase in tumour/bladder immune cell infiltration was seen in mice 2 weeks after the last treatment.

4.3.1.2. Secondary pharmacodynamics

The applicant did not include any specific studies evaluating secondary pharmacodynamics of N-803 and therefore, there is no information on the potential binding of N-803 to receptors other than the IL-15 receptor. N-803 is a fusion protein and key elements of the pharmacology, as described in ICH S6, was investigated including binding to target/specificity and biological activity in vitro and in vivo. Moreover, there is no or negligible systemic exposure of N-803 after intravesical administrations in human. The lack of secondary pharmacology screen is therefore acceptable.

4.3.1.3. Safety pharmacology

No stand-alone safety pharmacology studies were conducted. No Cardiovascular (CV), respiratory or Central Nervous System (CNS) abnormalities were detected in rat or monkey repeat-dose toxicity study.

4.3.1.4. Pharmacodynamic drug interactions

No studies investigating pharmacodynamic drug-drug interactions were performed. N-803 is administered intravesical with BCG. Since systemic N-803 absorption was not demonstrated in clinical studies, this is acceptable.

4.3.2. Pharmacokinetics

The intravesical clinical route was not examined in any of the non-clinical PK studies. All non-clinical PK data were derived from SC or IV administration. The non-clinical PK package characterized the PK of SC or IV administered N-803 in C57BL/6 and CD-1 mice, Sprague Dawley rats, and cynomolgus monkeys. In vivo biodistribution was assessed in C57BL/6 mice following IV administration. An in vitro cellular distribution study was also conducted.

Toxicokinetic samples from the non-clinical GLP 13-week rat toxicology study (20328204) were analysed in compliance with GLP whereas the toxicokinetic analysis from the 1-month study in monkeys (YLP-1203) was non-GLP.

4.3.2.1. Absorption

PK after repeated dosing of N-803 was studied in rats dosed once every 2 weeks via SC injection at dose levels of 0,1, 0,3, and 1,0 mg/kg for up to 13 weeks. The TK of N-803 was evaluated in serum samples collected on Days 1 and 85. N-803 was quantifiable 7 days after the first dose and up to 14 days after the last dose in Sprague Dawley rats. N-803 exposure was sex independent on Day 1 but on day 85 exposure was greater in females. The half-life in rats was around 14-20 hours. The AUC levels increased with dose on the first day whereas systemic exposure to N-803 in male and female rats decreased following repeated administration, likely due to the development of ADAs.

In cynomolgus monkeys, the TK profile of N-803 from the 1-month cynomolgus monkey toxicology study was determined. Data from IV administration after the first dose, indicate a more than dose dependent increase in systemic exposure. The half-life of N-803 was 7-8 hours which is similar to the mouse but less than in rat. Systemic exposure increased more than dose-proportional, based on AUC. The low dose-level resulted in pharmacological relevant systemic exposure.

4.3.2.2. Distribution

Typical distribution studies of N-803 were not conducted. In vivo biodistribution was assessed in mice following intravenous (IV) administration of radiolabelled N-803 or IL-15. An in vitro cellular distribution study was also conducted.

N-803 is a fusion protein consisting of amino acids, to be administered directly into the bladder via a catheter. Systemic injection of N-803 resulted in a broad biodistribution pattern including, blood, liver, kidney, lymph nodes, lung, spleen, thymus with a rapid clearance pattern for most organs. The N-803 signal was persistence in the lymph nodes for at least 70 hours. The in vitro kinetics of internalization, efflux, and surface binding of N-803 and IL-15 was studied in 32Dβ cells and results indicate rapid internalization of N-803 and lower efflux rate and higher stability when compared to IL-15.

4.3.2.3. Metabolism

No metabolism studies with N-803 were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1) and is agreed with.

4.3.2.4. Excretion

No dedicated excretion studies were conducted, which is agreed. Data from the intravenous mouse biodistribution study indicate that N-803 predominantly is cleared via the hepatobiliary pathway.

4.3.2.5. Pharmacokinetic drug interactions

No studies investigating pharmacokinetic drug-drug interactions were performed. N-803 is administered intravesical with bacillus Calmette-Guérin (BCG). Since systemic N-803 absorption was not demonstrated in clinical studies, this is acceptable.

4.3.2.6. Other pharmacokinetic studies

None.

4.4. Toxicology

Six repeated-dose toxicology (RDT) studies have been performed of which 4 were non-GLP studies in mouse (1 month duration, 4 weekly SC or IV administrations) and 2 were pivotal GLP studies in rat (13-week duration, 7 SC administrations) and Cynomolgus monkey (1-month duration, 4 IV administrations). In addition, a WOE assessment for DART, and 2 immunogenicity evaluations (i.e. ADA analyses) have been performed. As per ICH S6(R1), genotoxicity and carcinogenicity studies have not been conducted with N-803.

4.4.1. Single-dose toxicity

No single dose studies have been performed. This is considered acceptable as relevant single dose information can be identified in repeated-dose toxicity studies.

4.4.2. Repeat-dose toxicity

Non-pivotal

The Applicant has performed 2 non-GLP 4-week studies in C57BL/6 mouse where N-803 was administered by the intravenous route of exposure. The high dose of 4mg/kg was lethal whereas 1mg/kg induced clear and adverse toxicities. Both studies identified effects related to marked immune stimulation which were characterised by a shift from erythropoiesis to leukocyte production in the bone marrow, resulting in anemia. Toxicities included increased organ weights correlating with lymphoplasmacytic hyperplasia and/or infiltration in several organs (e.g. lymph nodes, spleen, thymus, liver, kidneys, lungs, salivary gland) and inflammatory lesions. Most toxicities identified remained after recovery periods. No TK is available from the studies.

An additional 4-week study in BALB/c mouse evidenced a similar toxicity profile as seen in C57BL/6 mouse. The Applicant has also referenced a published article, where a 4-week study in C57BL/6 mouse using SC administration of 1 mg/kg N-803 resulted significantly increased liver weights and increased levels of AST in addition to the toxicities identified with IV administration (doi: 10.1016/j.cyto.2017.12.003). A NOAEL of 0.1mg/kg was overall identified in the studies.

Pivotal

The pivotal RDT studies have been performed by Charles River Laboratories Inc. (US) and Yunnan Laboratory Primate, Inc. and are claimed to be in accordance with US FDA GLP regulations. However, the Applicant could not confirm the GLP designation of the monkey study and the study is therefore only considered supportive.

In both species, haematology effects were noted already from the lowest doses. In the rat there were dose-related increases in monocytes, eosinophils, lymphocytes and basophils with large individual differences. The changes in leukocytes were suggestive of N-803-mediated immune stimulation and the effects on lymphocytes correlated with increased cytotoxic lymphocytes in immunophenotyping. A similar haematology trend was seen in monkey.

Cmax and AUC in rats increased dose-dependently in males and more than dose-dependently in females on SD1, but due to extensive ADA formation (94-100% of animals) at SD85 in almost all animals, exposure decreased in both sexes.

In the rat, non-significantly increased levels of IL-1β, IL-2, IL-10, and MIP-1α values were noted in both sexes on SD28, SD56, and 85. Dose-dependent increases in spleen-weight and size which correlated microscopically with lymphoid cellularity, histiocytic infiltrates in red pulp and/or extramedullary haematopoiesis. Dose-dependent microscopic injection site findings were evident in both sexes, and consisted of mixed cell infiltrates, mixed cell inflammation (mild-moderate). 4 female rats also had minimal-mild oedema. It is noted that these findings are a result of SC treatment Q2W, and that mixed-cell infiltrates remained after recovery.

Liver

Liver effects in rat included increased mixed cellularity in portal triads (minimal-moderate) and bile duct hyperplasia, with increased incidence and severity of biliary hyperplasia at 1.0 mg/kg. In monkey, multifocal inflammation was seen around hepatic portal areas with accumulation of lymphocytic and myeloid cells (in 1/6, 3/6 and 5/6 animals) and scattered mild liver necrosis (in 1/6, 3/6 and 5/6 animals at 0, 0.03 and 0.1 mg/kg respectively). These findings remained after recovery in both species and are considered adverse from 0.03mg/kg.

Kidney

Kidney toxicities were only identified in monkey and consisted of microscopic mild multifocal interstitial inflammation of renal parenchyma, serosa, and hilar areas with accumulations of lymphocytic cells (in 1/6, 1/6, 4/6 animals at 0, 0.03 and 0.1 mg/kg respectively). These findings remained in 4/8 animals after recovery and is considered adverse at 0.1mg/kg.

Lung

Lung toxicities only identified in monkey included mild multifocal interstitial infiltration of pulmonary parenchyma with accumulations of lymphocytic cells (in 1/6, 4/6, 2/6 animals at 0, 0.03 and 0.1 mg/kg respectively). Remained in 1/4 low-dose animals at recovery and is considered adverse at 0.03 mg/kg.

Bone marrow

Bone-marrow hyperplasia (moderate hyperplasia of the lymphoid and myeloid series) was identified in 2/6, 4/6 and 6/6 monkeys at 0, 0.03 and 0.1 mg/kg respectively. It is unclear why hyperplasia was seen in control animals.

Reproductive organs

No microscopic findings were evidenced in reproductive organs of rats and monkeys treated with N-803. However, as the monkeys used in the study were not considered reproductively mature, the lack of effect observed in this study cannot be regarded as conclusive.

4.4.3. Genotoxicity

No genotoxicity studies have been performed with N-803 in accordance with ICH S6.

4.4.4. Carcinogenicity

No carcinogenicity studies have been performed with N-803.The lack of carcinogenicity studies is acceptable, since standard carcinogenicity studies are generally not appropriate for biotechnology-derived pharmaceuticals according to ICH S6.

4.4.5. Developmental and reproductive toxicity

Microscopic examination of male and female reproductive organs in the 13-week study in rats did not identify any toxicities related to N-803 administration, suggesting that no effects on fertility are anticipated.

No standard DART studies according to ICH S5 were performed. The Applicant has evaluated the reproductive- and developmental toxicity risks with a Weight of Evidence (WoE) approach based on a systematic literature search and results from the Applicant's non-clinical and clinical data.

IL-15 is abundant and tightly regulated in the uterus during pregnancy and evidence suggest that homeostasis of IL-15 must be maintained to ensure the health of the mother and fetus (https://doi.org/10.3390/ijms222011094). Based on the provided literature data, IL-15 has been shown to be a key component of decidualization (via uNK cell proliferation in vivo in the secretory endometrium and early decidua) and the embryo implantation process. Therefore, given the main systemic effect of N-803 on expansion/activation of NK cells and CD8+ T cells, maternal exposure to N-803 can lead to effects on the early pregnancy via a direct IL-15-mediated effect on uNK cell

proliferation in the endometrium and the resultant proinflammatory impact on the maternal immune system. It has also been referenced that elevated IL-15 levels are associated with clinical fertility complications (e.g., endometriosis and implantation failure) and pregnancy loss. Thus, while no DART studies have been performed, the data presented show that the IL-15 agonist effects of Anktiva may cause embryofoetal harm if sufficient systemic exposure to the substance would occur in a pregnant woman which is reflected in sections 4.6 and 5.3 of the SmPC.

Breast milk

No data have been presented regarding the levels of N-803 in breast milk. Given that the systemic levels of N-803 are very low in patients receiving Anktiva intravesically, it is anticipated that the levels in breast milk will also be very low.

4.4.6. Toxicokinetics and exposure margins

See Pharmacokinetics (Section 4.3.2. .Regarding margins from non-clinical NOAELs to clinical exposure, given that there is no systemic exposure of N-803 after intravesical use, and the non-clinical studies have used SC and IV administration, the exposure-margin calculations are not useful for this indication.

4.4.7. Local tolerance

No local tolerance studies with N-803 have been performed by the Applicant..

4.4.8. Other toxicity studies

Antigenicity (ADA development)

The Applicant evaluated ADA development in the pivotal GLP studies in rat and monkey. The immunogenicity of the rat samples was performed as part of the RDT study. Part of the study was not performed in accordance with GLP. N-803 was highly immunogenic in the rat with 94%, 94% and 100% of the animals developing ADA following administration of N-803 at 0.1, 0.3, and 1.0 mg/kg, respectively. N-803 systemic exposure decreased as a consequence of the ADA formation.

In the monkey, a total of 40% (8/20) of the N-803 treated animals developed ADA. Since TK data from the monkey study has only been presented from SD1, it is unclear if the ADA formation had an impact on the levels of N-803.

4.4.9. Ecotoxicity/environmental risk assessment

Anktiva (N-803) is a protein without non-natural amino acids. Thus, the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, N-803 is not expected to pose a risk to the environment.

4.5. *Overall discussion and conclusions on non-clinical aspects*

4.5.1. Discussion

Considering that there was no systemic exposure of N-803 following intravesical administration in humans, N-803 immunostimulatory effects are expected to be mostly local within the bladder. In addition to the in vitro binding data indicating that N-803 binds to the IL-15 receptor with higher affinity than IL-15 resulting in increased in vitro biological activity when compared wild type IL-15. N-803 favoured beta over gamma chain IL-2/IL-15 receptor binding, the applicant provided evidence that N-803 promotes activation and proliferation of NK-cells and T-cells in vitro.

Data from supportive studies performed in mouse models of multiple myeloma using IV administration suggest that N-803 is able to induce memory T-cells in mice and increase serum IFN-gamma levels. In a dose-relationship study in human PBMCs (n=2 donors), dose-dependent effects on CD8+ T-cell proliferation were noted from 0,07 nM N-803, corresponding to 6,4 ng/ml. No significant increases in CD4+ T-cells or NK-cells were detected in the dose-relationship experiments.

The intravesical clinical route was not examined in any of the non-clinical PK studies. All non-clinical PK data were derived from SC or IV administration. The methods used for the TK analysis were not fully validated and the analysis of the samples were not conducted under GLP compliance**.** Moreover**,** TK data following repeated administration from the 1-month cynomolgus monkey toxicology study (YLP-1203) has not been presented since only data from day 1 was included in the TK reports *(report PC-ALT- 803-01-13*, PC-ALT-803-01-13 Amendment). The exposure of N-803 after repeated dosing is therefore missing**.** Human PK data from intravesical administration indicates that N-803 remains confined to the bladder and that there is no systemic N-803 exposure. Given that the clinical route was not studied in the non-clinical PK package, the value and clinical relevance of the non-clinical PK data is limited but may be informative when it comes to toxicological findings in the non-clinical studies

The applicant has performed a limited toxicology program to support the evaluation of Anktiva, which is indicated in combination with BCG for the treatment of adult patients with BCG-unresponsive NMIBC CIS with or without papillary tumours.

The development program has been performed in accordance with the principles of ICH guidelines S6(R1). Although ICH S9 was considered, it was not considered applicable to the proposed indication, as treatment with Anktiva is intended for the treatment of NMBIC, an earlier-stage, non-metastatic malignancy, in a bladder-sparing setting, rather than advanced or metastatic disease considered by ICH S9. This is also in line with previous CHMP positions for products developed for curative and local treatment of NMBIC.Therefore, the preclinical documentation was assessed in line with the principles outlined in ICH S6(R1), with ICH M3(R2) considered where applicable. Based on the product characteristics, administration pathway and treatment regime, no additional studies are requested.

Repeat-dose toxicity

The species selected for the toxicology assessment were mice, rats and monkeys, which were considered relevant species to assess toxicity of N-803 based on its PK/PD activity. Six (6) repeated-dose toxicology (RDT) studies have been performed of which 4 are non-GLP studies in mouse (1 month duration, 4 weekly SC or IV administrations) and 2 are pivotal GLP studies in rat (13-week duration, 7 SC administrations) and Cynomolgus monkey (1-month duration, 4 IV administrations). In addition, a WOE assessment for DART, and 2 immunogenicity evaluations (i.e. ADA analyses) have been performed. As per ICH S6(R1), genotoxicity and carcinogenicity studies have not been conducted with N-803. The drug lots used in non-clinical studies are claimed to be the same or similar to those used in clinical studies, but no evidence has been provided to substantiate this.

In the clinical study QUILT 2.005 (see clinical section), referenced by the Applicant in the non-clinical overview, there was no evidence of systemic exposure to N-803 after bladder instillation. None of the toxicity studies (pivotal or non-pivotal) in the program have been performed with the clinical route of administration (i.e. intravesical route). The rat study used SC administration as this is the intended route of human exposure for tumour types other than bladder cancer. No clear justification has been given for the use of IV administration in the study in Cynomolgus monkey, but the Applicant noted that a longer-term intravesical study would be difficult to perform given the technical challenges and animal welfare concerns involved (i.e., complications due to repeated anaesthesia). However, the administration pathways used (SC in rat and IV in monkey) have led to clinically unrealistic systemic exposure for this indication and systemic toxicities which do not reflect the clinical situation. While the data gives a good understanding of the systemic toxicity profile of N-803, we have no non-clinical information about the local toxicities in kidneys, ureter, bladder and urethra related to the intravesical administration pathway. The Applicant did not justify the lack of intravesical administration in the RDT studies with N-803, nor the lack of local tolerance studies and did not provide a discussion about specific safety aspects of the intravesical administration pathway compared to IV or SC. However, given that the clinical safety profile of the product is driven by BCG and no new safety concerns with the administration pathway has been identified in the clinical section, the non-clinical aspect of this issue is considered to be of limited relevance.

Based on the lack of systemic exposure in the clinical studies, and the fact that the AEs identified clinically are related to the local administration, the toxicities identified in the general toxicology program for Anktiva are not considered relevant for this indication. The pivotal RDT studies in rat and monkey have been performed by Charles River Laboratories Inc. (US) and Yunnan Laboratory Primate, Inc. (China), respectively.

Based on submitted GLP inspection records from Charles River Laboratories, the 13-week rat study can be considered GLP compliant.

The Chinese test facility / test sites have not been inspected by an EU monitoring authority. The 13-week monkey study (YLP-1203) can therefore not be considered as GLP compliant. Furthermore, lack of TK data following repeated dosing, non-validated analytical methods and the lack of three dose groups lead to additional concerns regarding the validity of this study. The Applicant could not confirm the GLP designation of the study and agreed that the study can only be considered supportive. Since the clinical safety data are considered sufficient and the safety profile in studies with the combination is driven by BCG, the lack of GLP compliance for this study was considered acceptable. In line with this reasoning, the lack of TK data from repeated dosing in the study was also not further pursued.

The repeated-dose toxicity studies with N-803 resulted in clear adverse toxicities in the non-pivotal findings in mouse, including effects related to marked immune stimulation, anaemia, increased organ weights, lymphoplasmacytic hyperplasia, and inflammatory lesions. These toxicities remained after recovery, suggesting enduring immune activation. A No Observed Adverse Effect Level (NOAEL) of 0.1mg/kg was identified in the studies. In the pivotal studies in rats and monkeys, dose-related hematology effects, including increases in monocytes, eosinophils, lymphocytes, and basophils, suggestive of N-803-mediated immune stimulation were identified. Organ-specific toxicities were observed, including liver effects (increased mixed cellularity and bile duct hyperplasia in rats, and multifocal inflammation and liver necrosis in monkeys), kidney toxicities (mild multifocal interstitial inflammation in monkeys), and lung toxicities (mild multifocal interstitial infiltration in monkeys). A NOAEL can be identified at 1 mg/kg in the rat. However, at this dose, the exposure was low due to ADA formation, therefore there is considerable uncertainty.

No NOAEL was identified in the monkey study, due to adverse inflammation noted in several organs. If there is a correlation between these inflammations and ADA formation, it is possible that the

inflammations are related to an immune-complex mediated reaction. This has not been discussed by the Applicant. The liver and lung inflammations noted at 0.03 mg/kg are considered adverse, why no NOAEL can be identified in the study. The lack of a NOAEL was not further pursued.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies have been performed with N-803. While N-803 remains localized in the bladder, minimizing systemic interaction with other organs, the absence of RD-toxicity studies with sufficient duration leaves a gap in histopathological data regarding potential local inflammatory effects in the bladder. Chronic immune stimulation, even localized, could theoretically result in inflammatory stress or immune cell proliferation, which may be relevant to carcinogenicity. During the procedure, the Applicant submitted an acceptable Weight-of-Evidence (WoE) assessment addressing the carcinogenicity potential of N-803, in accordance with the ICH S1B(R1) Addendum. The assessment included the mechanism of action, immunomodulatory effects, toxicological and local data of N-803, and relevant published literature on the safety profile of IL-15 superagonists. Based on the provided WoE, N-803 is considered to have low carcinogenic potential.

Developmental and reproductive toxicity

No DART studies have been performed; the data presented show that the IL-15 agonist effects of Anktiva may cause embryofoetal harm if sufficient systemic exposure to the substance would occur in a pregnant woman. While no systemic exposure is expected after intravesical administration of N-803, there can be accidental systemic exposures in relation to procedures such as cystoscopies and biopsies. In addition, pro-inflammatory cytokines such as IFN-γ can enter the bloodstream to activate systemic immune cells. The Applicant has revised the SmPC to address the potential IL-15 related embryo-foetal harm and has included in section 4.6 the statement that, in murine models of pregnancy, IL-15 pathway increases uterine natural killer cells, whereby producing interferon-gamma (IFN-γ). This disrupts maternal tolerance to the foetus and results in an increase in embryofoetal loss. Therefore a recommendation has been added that treatment is not recommended during pregnancy or in women of childbearing potential who are not using effective contraception. In addition, a recommendation has been included to extend contraception use for an extra week after the last dose based on the N-803 half-life of 20-21 hours (following SC administration). Thus, if systemic exposure were to occur with the use of Anktiva, the end of relevant systemic exposure is considered to be five half-lives. This corresponds to approximately 5 days and can be communicated in the SmPC as one week. This has been reflected in SmPC section 4.6 and in the package leaflet, indicating that women of childbearing potential must use effective contraception during treatment with Anktiva and for one week after the last dose.

The rational for generating a WoE evaluation instead of studies has not been specified. According to the Applicant, there is no systemic exposure of the API based on referenced clinical data from the study program. While this can to some extent be agreed, the planned cystoscopies and repeated biopsies constitute risks for systemic exposure.

Regarding breastfeeding, based on the negligible systemic exposure (below the LLOQ) observed in the clinical program following intravesical administration of Anktiva, no effects on the breastfed child are anticipated. Although no data are available on the presence of Anktiva in human milk or on possible effects on the breastfed child, breastfeeding may be continued during treatment with Anktiva. This has also been reflected in the SmPC section 4.6.

Regarding fertility, no effects are expected since systemic exposure to Anktiva following intravesical administration is below the LLoQ. This has been reflected in the SmPC section 4.6.

No local tolerance studies with N-803 have been performed by the Applicant. The RDT studies performed with the substance were performed with IV or SC administration, which means that we have no toxicity data supporting the safe use of the intravesical formulation.

Local tolerance studies to evaluate the toxicities of ureter, urethra and bladder after intravesical use should have been useful to support clinical trials with the product. It is further noted that in the rat 13-week study, there were remaining mixed cell infiltrates in SC injection sites after a 2-week recovery period, supporting that there have indeed been local tolerance findings identified. The lack of dedicated environmental risk assessment studies is agreed. N-803 is a protein without non-natural amino acids and is therefore not expected to pose a risk to the environment.

4.5.2. Conclusions

The non-clinical data supports that N-803 binds to the IL-15 receptor. Intravesical administration of N-803 stimulated local immune responses in the bladder leading to antitumor efficacy in rodent NIMBC models. The non-clinical pharmacology studies support that the rat, monkey and mouse are relevant species from a toxicological point and provide support for synergistic immunological contribution of N-803 to BCG therapy in NMIBC.

All non-clinical PK data were derived from SC or IV administration. Human PK data from intravesical administration indicate that N-803 remains confined to the bladder, with no detectable systemic exposure. Given that the clinical route was not studied in the non-clinical PK package, the value and clinical relevance of the non-clinical PK data is limited but may be informative when it comes to toxicological findings in the non-clinical studies. The Applicant has submitted a limited non-clinical program based on S6 and S9 to support the use of Anktiva for BCG-unresponsive NMIBC with CIS with or without papillary tumours. However, the NMIBC indication is not within the scope of ICH S9. The general toxicology studies submitted are of limited relevance for the intended clinical use of Anktiva, as no toxicity studies were performed using the intravesical administration route. However, given that no systemic exposure to N-803 is observed during clinical use, the toxicities identified in the non-clinical studies following systemic administration are not considered reflective of the AEs reported clinically.

There are no genotoxic concerns for Anktiva, and based on the provided WoE, Anktiva is considered to have low carcinogenic potential. A WoE to support the use in fertile and pregnant women has identified potential reproductive risks based on the mechanism of action, and these risks have been described adequately in section 4.6 of the SmPC.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

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

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

The submitted FDA GCP inspection reports did not indicate any critical findings.

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for further GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table 5 Clinical Studies Supporting N-803 in NMIBC (CIS)

Protocol; Study Status Report Date (Cut-off)	**Type of Study**	**Primary Study Objective**	**Population Number of Treated Subjects**	**Dose and Dosing Regimen**	**Data Collected**
Healthy Subjects: N-803 Subcutaneous Administration					
QUILT-1.004; Complete 13 Mar 2018	Single-center, open-label	Determine PK profile after subcutaneous N-803 administration	Healthy adult volunteers 20 Subjects	10 µg/kg N-803, followed 15 days later by 20 µg/kg N-803	Safety PK PD
NMIBC: N-803 Bladder Instillation					
QUILT-2.005 Phase 1b; Complete 14 Aug 2017	Phase 1b dose-escalation, multi- center, open- label, single-arm	MTD and RD of N-803 plus BCG for BCG-naïve NMIBC	Adults with BCG-naïve NMIBC 9 Subjects	N-803 (100 µg, 200 µg, or 400 µg) plus BCG (50 mg) once weekly for 6 weeks	Safety Efficacy PD
QUILT-205; Ongoing QUILT-2.005 Phase 1b Follow-up 15 Jul 2024	LTF to assess yearly CR and DFS	Long-term follow- up	None; participated in QUILT-2.005 Phase 1b	None	Efficacy Survival
QUILT-2.005 Phase 2b; Ongoing 15 Jul 2024	Phase 2b, randomized, open-label, multicenter	CR rate (for CIS) or DFS (papillary) of N-803 plus BCG versus BCG alone	BCG-naïve NMIBC 195 total Cohort A (CIS ± Ta/T1): 120 Cohort B (HG Papillary): 75	N-803 (400 µg) plus BCG (50 mg) or BCG alone weekly for 6 weeks in induction and 3 weeks in maintenance	Safety Efficacy PD PK
QUILT-3.032-2.005-PK[a]; Complete 16 May 2024	Non-interventional PK sub-study of QUILT-3.032 and QUILT-2.005 phase 2	PK profile of N-803 after single dose of intravesical instillation of 400 µg N-803	Enrollment in QUILT-3.032 or QUILT-2.005 phase 2b 1 Subject	N-803 (400 µg) plus BCG (50 mg) or BCG alone weekly for 6 weeks in induction and 3 weeks in maintenance	PK Substudy
QUILT-3.032; Ongoing 15 Jul 2024	Phase 2/3, open- label, single-arm, three-cohort, multicenter	CR rate (Cohorts A and C) or DFR rate (Cohort B)	BCG-unresponsive high-grade NMIBC 190 total Cohort A (CIS ± Ta/T1): 100 Cohort B (HG Papillary): 80 Cohort C (CIS ± Ta/T1): 10	N-803 (400 µg) plus BCG (50 mg) (Cohorts A and B) or N- 803 alone (Cohort C) weekly for 6 weeks in induction and 3 weeks in maintenance	Safety Efficacy PD PK

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; DFR, disease-free rate; DFS, disease-free survival; EOS, end of study; HG, high-grade; LTF, Long-term follow-up, MTD, maximum tolerated dose; NMIBC, non-muscle invasive bladder cancer; PK, pharmacokinetic; RD, recommended dose.

[a] Enrollment in the PK substudy QUILT-3.032-2.005-PK was superseded by a protocol amendment of QUILT-3.032, leading to closure of the former study. The patient enrolled in QUILT-3.032-2.005-PK was treated in QUILT-3.032.

5.2. Clinical pharmacology

5.2.1. Methods

Determination of N-803

A commercial ELISA kit developed for detection of IL-15 has been used as the basis in the method to quantify N-803 in plasma. The first bioanalytical method (LLOQ of 23,4 pg/ml) used in two phase1-studies (QUILT-1.004 and QUILT-2.005 Phase 1b) is not validated in accordance with the ICHM10 guideline and while none of the provided validation data indicate that the method is not adequate the missing aspects are too many. For subsequent clinical studies the bioanalytical method was further developed, using the same commercial kit as a basis. The validation of the developed method is adequate but with a substantially higher calibration range with a LLOQ of 100 pg/ml.

Determination of anti-drug antibodies (ADAs) in human serum

A three-tiered immunogenicity assay strategy was used for the detection of ADA responses. Two methods (VQ-ALT-803-01-15 and MN20093) were used to evaluate presence of ADAs in study QUILT-1.004, QUILT-2.005 1b, QUILT-2.005 2b and QUILT-3.032.

Method VQ-ALT-803-01-15 (used for study QUILT-1.004 and QUILT-2.005 1b)

In this bridging ELISA assay ALT-803 was used as the capture reagent following immobilization in a microtiter well and horseradish peroxidase (HRP) labelled ALT-803 (which is same as N-803) was used as detection reagent.

Method MN20093 (used for study QUILT-2.005 2b and QUILT-3.032)

In this bridging ELISA assay N-803 was coated onto standard 96-well Nunc Maxisorp® microtiter plate. The assay wells were blocked with 1% bovine serum albumin (BSA) in phosphate buffered saline (PBS). Human serum test samples (PC and NC samples, study samples, etc.) were diluted to a minimum required dilution (MRD) in assay diluent (1% BSA in PBS) and added to the assay wells. After incubation and wash steps, detection of bound human ADA was achieved with HRP-N-803. After another set of incubation and wash steps, 3',3',5',5'-Tetramethylbenzidine (TMB) was added to the assay wells to react with the bound horseradish peroxidase (HRP) complex. When the HPC sample signal reached approximately 1.0 - 1.2 optical density (OD), the plate was quenched with stop solution (2N H2SO4). The color intensity that developed was proportional to the amount of bound anti-N-803 antibodies in the wells. The positive control antibody used in this study was mouse anti-human interleukin 15 (IL-15) monoclonal antibody (mAb).

This method was cross validated due to site transfer (BAL-SAN to BAL-DUR). A partial re-validation was performed using anti-N-803 affinity-purified polyclonal antibody positive control.

Determination of neutralising antibodies (nAbs) in human serum

IL-15 Bioassay Cells were plated onto a white, flat bottom 96-well microtiter plate (assay plate). PC, NC and test samples were incubated with N803 in polypropylene dilution tubes. The treated samples were then transferred to the assay plate coated with IL-15 Bioassay Cells, and the samples together with the cells were incubated. At the end of the incubation, Bio-GloTM Reagent was added and the intensity of the luminescence was measured by reading the plate on the Molecular Devices SpectraMAX M5e plate reader. PC antibody for this assay was mouse anti-human IL-15 monoclonal

antibody.

This method was cross-validated due to site transfer (BAL-SAN to BAL-DUR). A partial re-validation was performed using anti-N-803 affinity-purified polyclonal antibody positive control.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The role of the pharmacokinetics in this application is very limited. The active substance is a protein with largely predictable metabolism and elimination properties. The product is administered locally at the intended site of action. No systemic concentrations (above 100 pg/ml) were detected in the performed clinical studies after intravesical administration.

5.2.2.2. Evaluation and qualification of models

No models have been submitted in this application.

5.2.2.3. Absorption

After intravesical administration all samples were below the limit of quantification. There appears to be no significant absorption of N-803 over the uroepithelium.

5.2.2.4. Bioequivalence

The same formulation has been used throughout the studies. Drug substance (DS) process changes and bridging data for clinical DS lots are assessed based on quality aspects.

5.2.2.5. Distribution

No data available after intravesical administration.

5.2.2.6. Metabolism

As a protein, N-803 is expected to be degraded by proteases.

5.2.2.7. Elimination

The main elimination pathway for any absorbed N-803 is predicted to be catabolism by proteolysis.

5.2.2.8. Dose proportionality and time dependency

No data available after intravesical administration.

5.2.2.9. Pharmacokinetics in the target population

In the target population all PK-samples were reported BLQ.

5.2.2.10. Special populations

No data available.

5.2.2.11. Pharmacokinetic interaction studies

As N-803 is a protein standard PK-interactions with CYP enzymes or transporter proteins are not expected. A slight elevation in serum IL-6 levels (<80 pg/mL) were observed following intravesical administration of N-803 in combination with BCG. There was minimal or no change observed in the serum levels of IL-2, IL-4, IL-10, TNF-α, and IFN-γ.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

N-803 functions as a selective immunomodulator that enhances the activation, proliferation, and cytotoxicity of effector lymphocyte subsets, primarily through interaction with the IL-15 receptor.

In vivo PD studies on the mechanism of action of N-803 showed that N-803 is an IL-15 super-agonist that enhances immune responses by stimulating CD8+ T cells and NK cells. It primarily activates CD8+CD44high memory T cells to produce IFN-γ via an antigen-independent pathway,

As demonstrated by clinical data, N-803 alone has limited activity against NMIBC. It does restore responsiveness to BCG and may also act synergistically with the bacteria.

Table 6 Comparison of Pharmacodynamic Results in QUILT-2.005 Phase 1b, Cohort B of QUILT-3.032, and QUILT-1.004

Study	Indication	N-803 Dose[a]	Route of N-803 Administration	Pharmacodynamic Results
Healthy Subjects				
QUILT-1.004	Healthy volunteers	1st dose: 10 µg/kg 2nd dose: 20 µg/kg	Subcutaneous	Induced proliferation of NK cells and to a lesser degree and $CD8^+$ T cells and $CD4^+$ T cells.
Non-muscle invasive bladder cancer				
QUILT-2005 Phase 1b	BCG-naïve NMIBC	100 µg, 200 µg, 400 µg (3 subjects in each group)	Intravesical	9/9 subjects had either a CR or lack of recurrence/progression beginning at or before month 12, and none of the subjects had disease recurrence through 24 months.
QUILT-3.032 – Cohort B	BCG-unresponsive high-grade Ta or T1 papillary NMIBC	400 µg	Intravesical	DFS rate at 12 months of 56.7% based on Kaplan-Meier analysis; median DFS of 24.9 months based on Kaplan-Meier analysis.

DFS, disease-free survival; NK, natural killer

[a] In QUILT-2.005 phase 1b and for Cohort B in QUILT-3.032, N-803 was administered in combination with 50 mg BCG.

5.2.3.2. Primary and secondary pharmacology

Regarding the primary pharmacology, please see above on the mechanism of action.

Small elevations in serum IL-6 were observed after SC administration in QUILT-1.004 and following

intravesical administration of N-803 in combination with BCG in QUILT-2.005 phase 1b.

Elevations in urine cytokines were observed following intravesical administration of N-803 in QUILT-2.005 phase 1b and QUILT-3.032. Elevation of Th1 cytokines implicated in BCG responses was seen in both studies. However, cytokine levels were highly variable at all time points measured.

Urine cytokines

Urine samples were collected to analyse urine biomarkers of IL-2, IL-4, IL-6, IL-10, IFN-y, and TNF-a for all enrolled subjects on study day 1 immediately prior to treatment instillation, and 4 hours after the start of instillation. Urine samples were also collected before instillation on study day 15, 29 and 36. The cytokine population included all enrolled subjects. All 9 subjects had samples collected and analysed for all time points during the study. Mean urine levels of IL-2, IL-4, IL-6, IL-10, TNF-a, and IFN-y following administration of ALT-803 plus BCG are presented in Figures 1-6 below.

Figure 2 Mean (+/- SD) in Urine Cytokines over time Safety Population

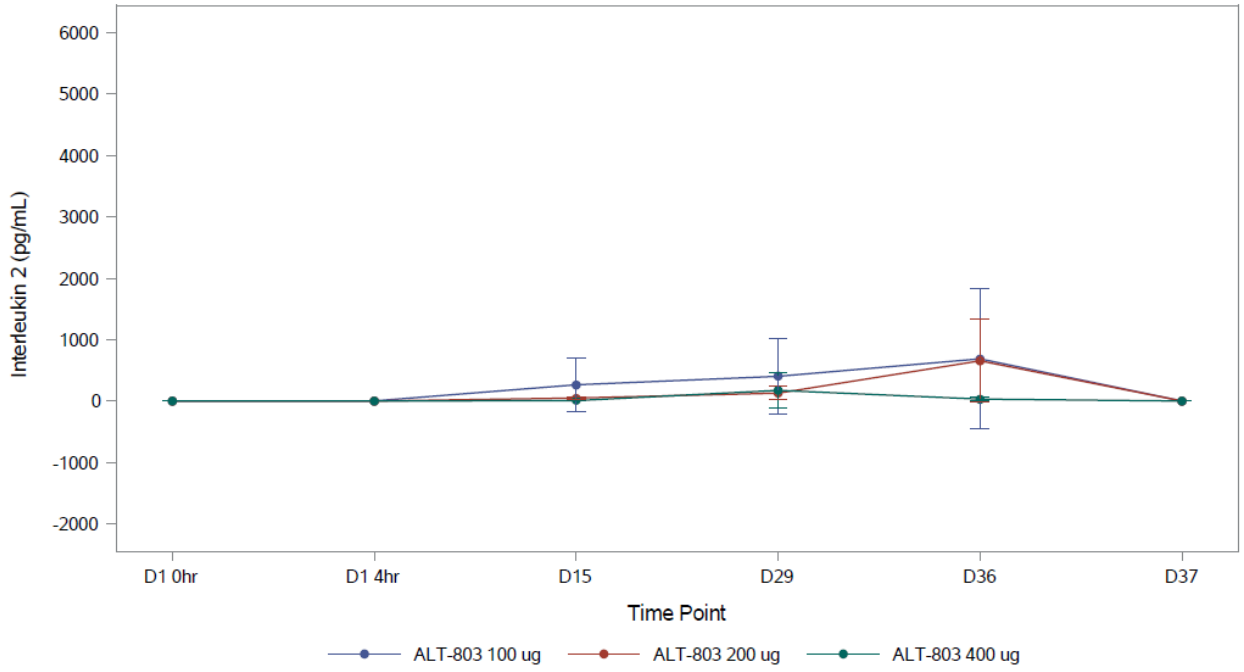


Figure 3 Mean (+/- SD) in Urine Cytokines over time Safety Population

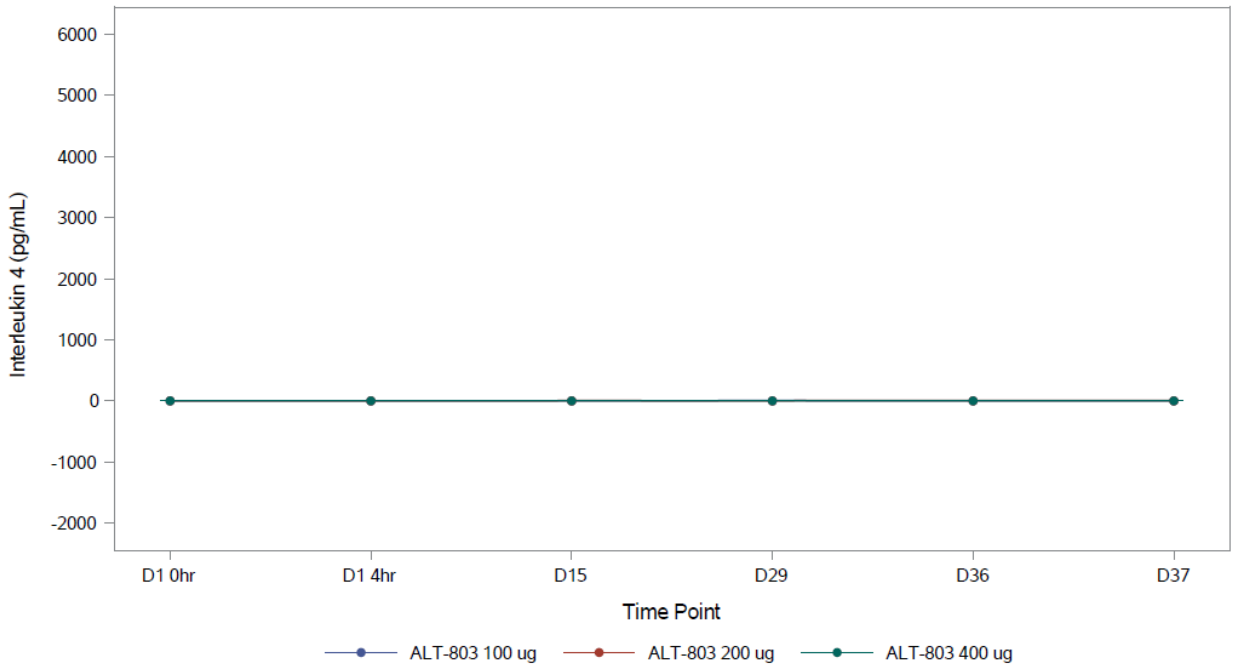


Figure 4 Mean (+/- SD) in Urine Cytokines over time Safety Population

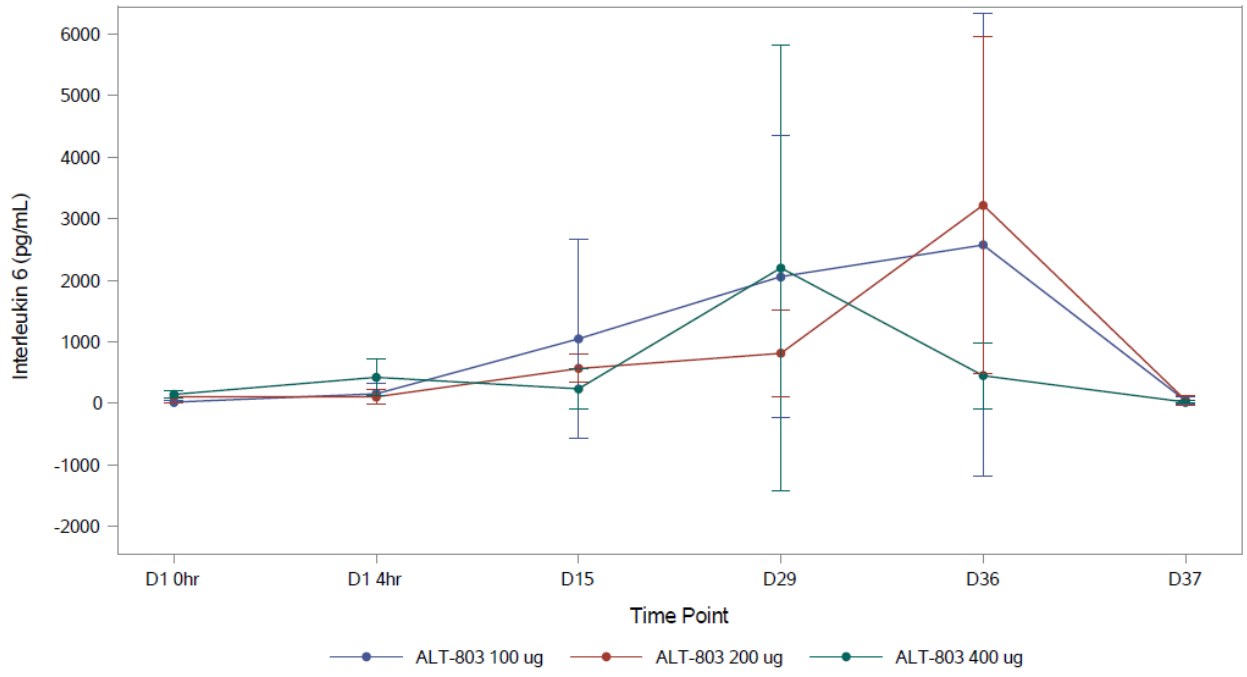


Figure 5 Mean (+/- SD) in Urine Cytokines over time Safety Population

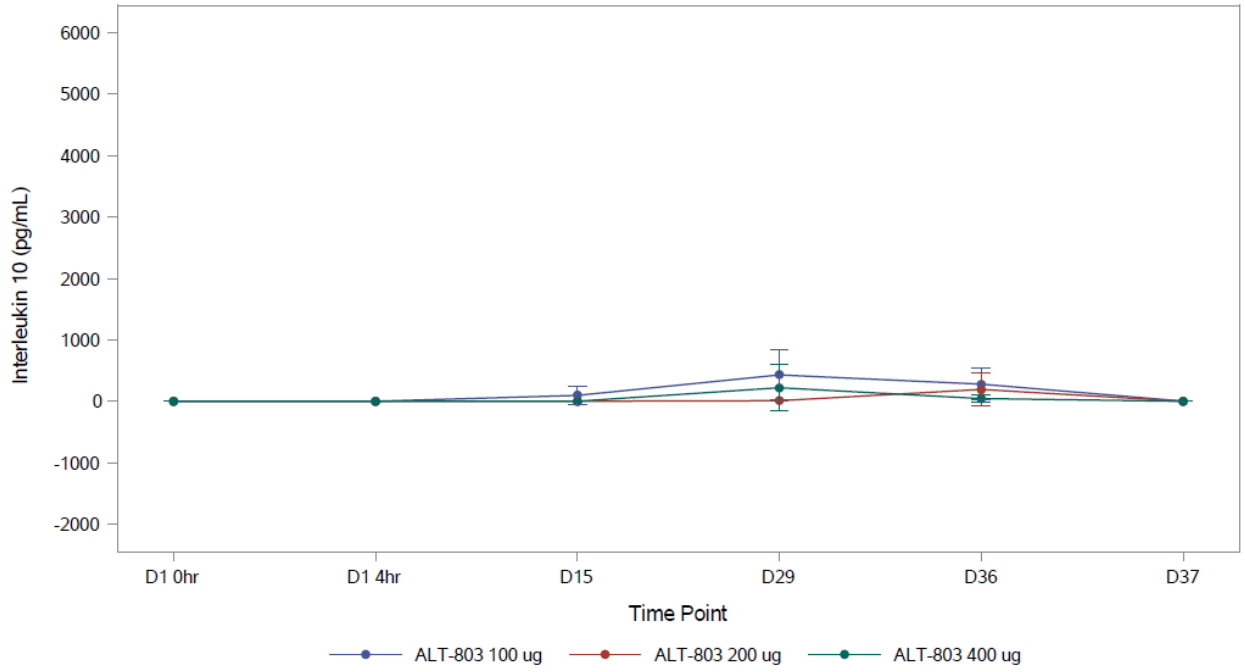


Figure 6 Mean (+/- SD) in Urine Cytokines over time Safety Population

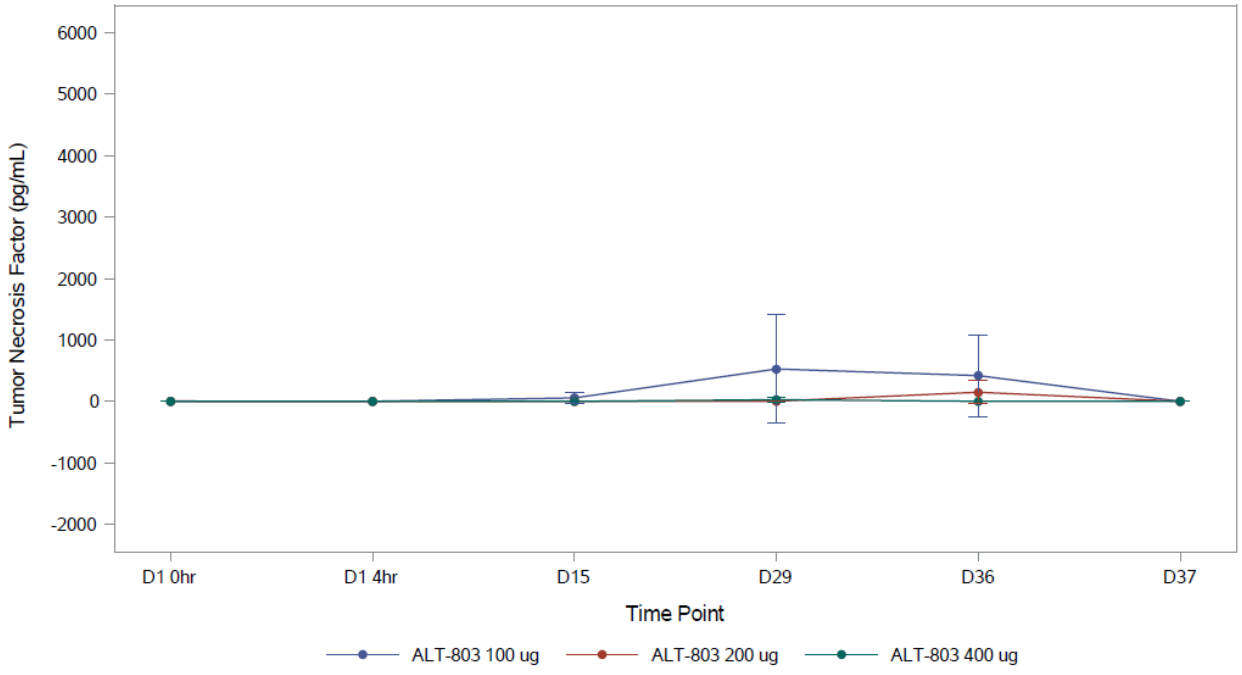
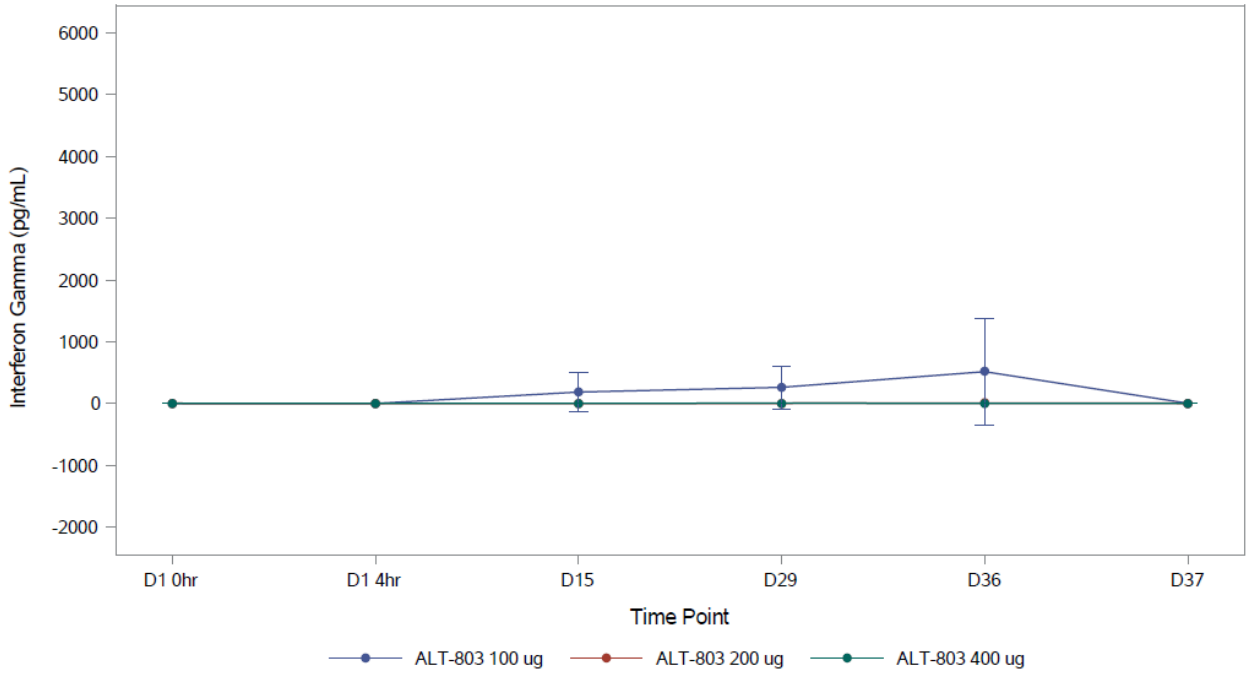


Figure 7 Mean (+/- SD) in Urine Cytokines over time Safety Population



An apparent increase in urine levels of IL-6 (mean peak concentration [mean ± SD] of 3223 ± 2747 pg/mL on day 36 in subjects receiving 200 µg N-803) was evident after intravesical administration of N-803 in combination with BCG. Urine IL-6 levels showed high variability at each time point measured. Similar trends in urine IL-6 levels were evident in subjects receiving 100 µg or 400 µg of N-803 per instillation (mean peak concentrations of 2572.81 ± 537.08 on day 36 and 2200.21 ± 3630.87 on day 29, respectively). Peak urine cytokine levels in QUILT-2.005 Phase 1b are presented in Table 7.

Table 7 Peak Urine Cytokine Levels in QUILT-2.005 Phase 1b

Study	Indication	N-803 Dose	Route of N-803 Administration	Cytokines: Peak Concentration (Mean ±SD) (pg/mL)	Study Day/Week on Which Peak Cytokine Occurred
QUILT-2005 phase 1b	BCG-naïve NMIBC	100 µg, 200 µg, 400 µg (3 subjects in each group)	Intravesical	IL-2: 687.16± 1143.30	Day 36
				IL-6: 3222.94 ± 2747.38	Day 36
				IL-10: 429.23 ± 411.61	Day 29
				IFN-γ: 515.34 ± 866.65	Day 36
				TNF-α: 526.76 ± 885.09	Day 29

IL-6 was the cytokine that showed the largest change in urine concentrations. Smaller changes in urine IL-2, IL-10, TNFα, and IFN-γ were observed. All urine cytokines showed high variability at each time point measured. There was no apparent increase in IL-4 levels.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

N-803 has been reported to restore sensitivity to BCG and may act synergistically when used in combination with it.

5.2.3.4. Genetic differences in PD response

None known.

5.2.3.5. Immunological events

Immunogenicity was assessed in studies QUILT-1.004, QUILT-2.005 phase 1b and 2b and QUILT-3.032.

In QUILT-1.004, treatment-induced ADAs were observed in 1 out of 15 subjects (7%), at D15. No subjects were ADA positive at baseline. The ADA-positive patient was not tested for nAbs. In QUILT-2.005 phase 1b, 0/9 (0%) patients had treatment-induced ADAs. No subjects were ADA-positive at baseline.

Table 8 Summary of ADA incidence (QUILT-2.005 2b)

	QUILT-2.005 Phase 2b					
	Cohort A (CIS +/- Ta/T1)		Cohort B (HG Papillary)		All Subjects	
Variable Category	BCG (N=61)	BCG+N-803 (N=59)	BCG (N=37)	BCG+N-803 (N=38)	BCG (N=98)	BCG+N-803 (N=97)
Baseline						
POSITIVE	0/3	2/48 (4%)	0/1	1/34 (3%)	0/4	3/82 (4%)
NEGATIVE	3/3 (100%)	46/48 (96%)	1/1 (100%)	33/34 (97%)	4/4 (100%)	79/82 (96%)
Subjects with Baseline Negative and Negative at All Post-baseline Assessments	2/2 (100%)	41/44 (93%)	1/1 (100%)	31/32 (97%)	3/3 (100%)	72/76 (95%)
Subjects with Baseline Negative and Changed to Positive at Any Post-baseline Assessments	0/2	3/44 (7%)	0/1	1/32 (3%)	0/3	4/76 (5%)
Subjects with Baseline Positive and Positive at Any Post-baseline Assessments	0/0	2/2 (100%)	0/0	1/1 (100%)	0/0	3/3 (100%)
Subjects with Baseline Positive and Changed to Negative at All Post-baseline Assessments	0/0	0/2	0/0	0/1	0/0	0/3
Last Post-Baseline Assessment						
POSITIVE	0/4	3/50 (6%)	0/2	1/37 (3%)	0/6	4/87 (5%)
NEGATIVE	4/4 (100%)	47/50 (94%)	2/2 (100%)	36/37 (97%)	6/6 (100%)	83/87 (95%)

The titer values were low (<9). Of 30 confirmed ADA positive samples, 27 samples were evaluated for presence of nAb. None of the samples were nAb positive.

Table 9 Summary of ADA incidence (QUILT-3.032)

	QUILT-3.032: BCG + N-803			QUILT-3.032: N-803 Alone
Variable Category	Cohort A (CIS +/- Ta/T1) (N=100)	Cohort B (HG Papillary) (N=80)	Cohorts A and B (N=180)	Cohort C (CIS +/- Ta/T1) (N=10)
Baseline				
POSITIVE	3/83 (4%)	4/73 (5%)	7/156 (4%)	0/9
NEGATIVE	80/83 (96%)	69/73 (95%)	149/156 (96%)	9/9 (100%)
Subjects with Baseline Negative and Negative at All Post-baseline Assessments	78/80 (98%)	66/68 (97%)	144/148 (97%)	9/9 (100%)
Subjects with Baseline Negative and Changed to Positive at Any Post-baseline Assessments	2/80 (3%)	2/68 (3%)	4/148 (3%)	0/9
Subjects with Baseline Positive and Positive at Any Post-baseline Assessments	3/3 (100%)	4/4 (100%)	7/7 (100%)	0/0
Subjects with Baseline Positive and Changed to Negative at All Post-baseline Assessments	0/3	0/4	0/7	0/0
Last Post-Baseline Assessment				
POSITIVE	5/89 (6%)	4/77 (5%)	9/166 (5%)	0/10
NEGATIVE	84/89 (94%)	73/77 (95%)	157/166 (95%)	10/10 (100%)

The titer values were low (<9) for majority of the confirmed ADA positive samples. 3 samples (from subject) showed titer of 27, 2 samples (from subject) showed titer of 81 and 1 sample (from subject) showed titer of 729.

Of 93 confirmed ADA positive samples, 56 samples were evaluated for presence of nAb. 9 samples (3 subjects) were nAb positive.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

The product is locally administered in the bladder. There is no relation between plasma concentrations and effects.

5.2.5. Dose selection and therapeutic window

In the phase 1b portion of QUILT-2.005, 9 patients (2 with CIS and 7 with high-risk papillary NMIBC) received intravesical N-803 at either 100 µg, 200 µg, or 400 µg per instillation in conjunction with BCG weekly for 6 consecutive weeks. Safe and durable responses (> 24 months) were observed in 9 out of 9 subjects. No dose-limiting toxicities (DLTs), serious adverse events (SAEs) or adverse events (AEs) > grade 3 were experienced by any subjects. Based on these results, the 400 µg dose was selected as the dose for the intravesical route of administration.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The role of the pharmacokinetics in this application is limited. The active substance is a protein with largely predictable metabolism and elimination properties. The product is administered locally at the intended site of action. No systemic concentrations (above 100 pg/ml) were detected in the performed clinical studies after intravesical administration. The dose is not based on PK and no dose adjustments are proposed in the SmPC (not due to toxicity nor PK). It is not considered likely that any special population would have different systemic concentrations of clinical relevance. The assessment of the PK-data in the dossier has been done with these facts in mind.

Nogapendekin alfa inbakicept (N-803) is an IL-15 receptor agonist which upon receptor binding results in proliferation and activation of NK, CD4+, CD8+, and memory T cells without proliferation of immuno-suppressive Treg cells. It is a soluble complex consisting of nogapendekin alfa (a human IL-15 variant) bound to inbakicept (a dimeric human IL-15Rα sushi domain/human IgG1 Fc fusion protein). Nogapendekin alfa inbakicept is a large (113 kDa) molecule that is negatively charged upon instillation into the bladder in a buffered solution which may explain its seemingly impermeability of the uroepithelium. Dissociation of the subunits in vivo appears non-significant from non-clinical studies.

A commercial kit developed for detection of IL-15 has been used as the basis in the method to quantify N-803 in plasma. The first bioanalytical method (LLOQ of 23,4 pg/ml) used in two phase1-studies is not validated in accordance with the ICH M10 guideline. Further, no bioanalytical report describing method performance, storage times and ISR was found in the dossier. Together with the limited validation this renders the data from the study unreliable. While there are uncertainties with the method, N-803 was detected in plasma after subcutaneous administration but not after intravesical administration indicating a low likelihood of systemic exposure after the intended

posology. The clinical consequences of the earlier method not being properly validated are thus considered minimal.

For subsequent clinical studies the bioanalytical method was further developed, using the same commercial kit as a basis. While the validation of the developed method is adequate, it does however use substantially higher calibration range with a LLOQ of 100 pg/ml compared to 23,4 pg/ml in the earlier method. Considering that all samples were BLQ already using a method with a LLOQ of 23,4 pg/ml the reason to use 4 times higher LLOQ is not understood. Given the limited role of the pharmacokinetics in this application, this was not further pursued. The bioanalytical reports from study samples applying method MN20092 has been submitted, the method performance was adequate and the lack of incurred sample reanalysis due to all samples being BLQ is acceptable.

After the intended intravesical administration, all PK-samples from all studies were below the LLoQ. Blood samples for PK assessment were drawn (for subjects enrolled under protocol version 7 or later) at time points where Cmax theoretically could be expected, thus the PK sampling is considered sufficient. There appears to be no absorption of nogapendekin alfa inbakicept over the uroepithelium which is in line with its size and negative charge. In one submitted study using subcutaneous administration of nogapendekin alfa inbakicept to healthy volunteers plasma concentrations were measurable, however the data is considered unreliable due to bioanalytical issue and also not relevant to the intended posology. Publications included in the submission mentions several other studies with nogapendekin alfa inbakicept administered subcutaneously. These might have provided more information on the basic pharmacokinetic properties of nogapendekin alfa inbakicept but are not requested as it will not affect the use of the product in the intended population in this application.

Dose finding was investigated in QUILT-2.005 phase 1b, in which subjects received intravesical administration of 100 µg (n=3), 200 µg (n=3), or 400 µg (n=3) of N-803 in combination with a fixed 50 mg dose of BCG. The maximum tolerated dose (MTD) was not reached, and no correlation between dose and efficacy or between dose and safety was found. Based on this, 400 µg N-803, in combination with 50 mg BCG, was selected for intravesical administration for further studies.

The number of patients in the dose finding study was small (n=9), and it is not known whether 400 µg N-803 is the most well-balanced dose. However, given that doses from 100 µg to 400 µg did not seem to affect safety and efficacy (although limited data) and that the systemic absorption of N-803 after intravesical administration appears to be minimal, the dose of 400 µg does not raise any concern. The dose is primarily supported by data on efficacy and safety from study QUILT-3.032.

No detailed discussion of PK and special populations has been provided. Given the absence of detectable systemic exposure, this is considered acceptable for a large therapeutic protein.

Serum cytokines have been measured in two clinical studies. A slight elevation in serum IL-6 levels (<80 pg/mL) were observed following intravesical administration of N-803 in combination with BCG, there was minimal or no change observed in the serum levels of IL-2, IL-4, IL-10, TNF-α, and IFN-γ. From an interaction point of view the slight increase in IL-6 is not considered relevant and may be caused by BCG.

From a PK point of view, no dose modifications are needed in special populations (including elderly patients and patients with hepatic and/or renal impairment) and no drug-drug interactions are expected, since the systemic exposure is negligible.

Immunogenicity

Method VQ-ALT-803-01-15 cannot be used to evaluate presence of ADAs in studies QUILT-1.004 and QUILT-2.005 1b due to the method not being adequately validated. However,as the subjects included

in the studies QUILT-1.004 and QUILT-2.005 1b are not the intended patient population and as sufficient data has been obtained in QUILT-2.005 2b and QUILT-3.032 this issue didn't raise concerns.

Method MN20093 used to measure ADAs in studies QUILT-2.005 2b and QUILT-3.032 is considered adequately validated for the intended purpose. Cross-validation was conducted due to the change in analytical site. The ADA assays were successfully cross-validated, with comparable performance between the two sites.

Method MN20094 used to measure NAbs in studies QUILT-2.005 2b and QUILT-3.032 is not considered adequately validated. Nevertheless, these issues will not be further pursued as ADA incidence was low after administration of N-803. Cross-validation was conducted due to the change in analytical site. However, the submitted data only showed data from the San Diego facility. Thus, it cannot be concluded that comparable performance has been shown in both sites. However, this issue was not further pursued as ADA incidence was low after administration of N-803.

ADAs were not evaluated between baseline and week 6, thus any early, transient immunogenicity would have been missed with the sampling scheme employed. However, given that no data is available for the early time period in the current study, the issue was not further pursued.

It is also noted that 15/97 subjects in QUILT-2.005 Phase 2b and 25/190 subjects in QUILT-3.032 were not evaluated for immunogenicity testing, thus ADA results are missing for a substantial number of patients in the safety population, constituting a further uncertainty. However, since majority of the included subjects were evaluated for ADA, any available data from these missing subjects is not considered to change the immunogenicity assessment.

Given that Anktiva has endogenous counterparts, there is potential for cross-reactivity against these endogenous proteins. The binding sites of the observed ADAs, cross-reactivity and any functional impact of any such cross-reactivity have not been characterized. However, no issues are raised given the low ADA incidence and no evidence for impact on efficacy or safety.

Only a few patients developed ADAs in the clinical studies, this hampers the evaluation of ADAs' effect on PK, PD, efficacy and safety.

Pharmacodynamics

N-803 is an IL-15 superagonist designed to enhance immune responses by stimulating $CD8^+$ T cells and NK cells. It primarily activates $CD8^+CD44^{high}$ memory T cells to produce IFN-γ via an antigen-independent pathway, but also induce proliferation and activation of NK cells, upregulating markers like NKG2D and granzyme B. Studies in vivo demonstrate that N-803 significantly increases IFN-γ levels, white blood cell counts, spleen weights, and cytotoxic activity against tumour cells. Its effects are dose-dependent, with higher doses showing diminished responses and potential toxicity. Both intravenous (IV) and subcutaneous (SC) administration routes are effective, yielding comparable immune activation. No dedicated in vitro or in vivo non-clinical pharmacodynamic studies have been performed with intravesical route of administration to assess mechanism of action of N-803.

Induction of NK cell proliferation has solely been examined in healthy volunteers in study QUILT-1.004. N-803 administration strongly induced proliferation of NK cells in study period 1 and increased NK cell frequency (significantly increased on days 4 to 8 relative to baseline). NK cell numbers in study period 2 were significantly increased on days 5 to 8 relative to baseline.

In both QUILT-2.005 phase 1b and QUILT-3.032, urine samples were examined for levels of a selection of cytokines (IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ). Additionally, levels of the same cytokines were measured in serum samples from study QUILT-2.005. According to the Applicant, the elevation of Th1 cytokines, particularly including IFN-γ and IL-2, in the urine of subjects in QUILT-2.005 phase 1b and QUILT-3.032 is consistent with anticancer activity of N-803 plus BCG, and

consistent with efficacy seen in these studies.

In serum, only a small increase in IL-6 levels was observed. Increased level of IL-6 was also observed in urine samples in both QUILT-2.005 and QUILT-3.032. In QUILT-2.005, smaller changes in urine IL-2, IL-10, TNF-α, and IFN-γ were observed; however, variability was high at each time point measured. In QUILT-3.032, changes in IL-4, IL-10 and TNF-α were minimal. However, the Applicant refers to an apparent increase in urine levels of IL-2, IL-6 and IFN-γ, but without clear time-dependent trends.

Given the substantial variability in the provided results, the claimed increases and their proposed correlation with anticancer activity and effect of N-803 + BCG are not justified. Given the proposed mechanism of action, measurement of immune cells, and NK cells in particular, would be valuable. However, these measurements failed both in serum and urine. Based on the above, no apparent biomarkers were identified.

5.2.6.2. Conclusions

The available pharmacokinetic information is limited, which is considered acceptable for a large therapeutic protein with no detectable systemic exposure in the target population following the recommended posology.

No apparent biomarkers were identified in the clinical pharmacodynamics studies.

Although based on limited dose-finding data, the proposed dose of 400 µg N-803 is acceptable. Only a few patients developed ADAs in the clinical studies, this hampers the evaluation of ADAs' effect on PK, PD, efficacy and safety.

The ADA incidence from QUILT-2.005 phase 2b and QUILT-3.032 is reflected in section 5.1 the SmPC. The NAb assay is however not considered adequately validated and therefore no NAb incidence is reflected in the SmPC.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

The dosing recommendation for intravesical N-803 is based on results from QUILT-2.005 phase 1b in patients with high-risk BCG-naïve NMIBC.

In QUILT-2.005 phase 1b, BCG-naïve NMIBC subjects were treated with 50 mg BCG plus 100 µg (n = 3), 200 µg (n = 3), or 400 µg (n = 3) N-803 administered via a urinary catheter into the bladder. N-803 plus BCG were administered weekly for 6 consecutive weeks in an initial induction treatment phase. Subsequent maintenance treatment consisted of 3 consecutive weeks of N-803 plus BCG every 3 months for up to 12 months and then every 6 months for up to 24 months. There was no observed dose-dependence in the frequency or seriousness of AEs, or in other measures such as immunogenicity, and the MTD was not reached. The dose level of 400 µg N-803 per instillation was considered safe and therefore was selected as the recommended dose (RD) for future studies.

The proposed dosing regimen, in line with the widely-adopted SWOG dosing regimen (Lamm 2000), consists of an induction treatment of 6 consecutive weeks followed by maintenance treatment administered over 3 consecutive weeks at months 4, 7, 10, 13, and 19, with additional optional doses to 3 years. The duration of dosing is planned to be 3 years since BCG can be administered for up to 3 years.

Subjects with high-grade Ta and/or residual CIS after the induction treatment were eligible for a re-induction course of treatment with Anktiva and BCG. This approach aligns with available evidence showing a favourable benefit-risk balance for BCG re-induction in patients who did not achieve a complete response after initial induction treatment (Catalona 1987). Thus, subjects with residual CIS and/ or high-grade Ta at month 4 received a re-induction course of therapy (6 weekly instillations of BCG plus 400 µg N-803).

5.3.2. Main study(ies)

5.3.2.1.1. Study title

QUILT-3.032 study (CA-ALT-803-01-16): A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination With ALT-803 (N-803) in Patients With BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer

ClinicalTrials.gov Identifier: NCT03022825t

5.3.2.1.2. Study design

Study QUILT-3.032 is a phase 2/3, open-label, single-arm, three-cohort, multicenter US-based study of intravesical N-803 plus BCG (cohort A and B) or N-803 alone (cohort C) in subjects with BCG-unresponsive high-grade NMIBC.

For the current application, the efficacy assessment is focused on the Cohort A and C including patients with histologically confirmed presence of BCG-unresponsive NMIBC CIS (with or without Ta/T1 papillary disease).

As Cohort B enrolled patients with histologically confirmed BCG-unresponsive high-grade NMIBC (Ta/T1 papillary disease), the efficacy data of Cohort B is not included in the efficacy evaluation, since this cohort does not fall within the scope of the sought indication in this MAA.

Treatment

Subjects in Cohorts A and B received N-803 plus BCG combination treatment.

Subjects in Cohort C received N-803 monotherapy.

Dose and mode of administration

N-803 plus BCG combination

Each instillation of combination therapy (administered to Cohorts A and B) consisted of 400 µg N-803 plus 50 mg BCG. N-803 was mixed with reconstituted TICE-BCG to a final volume of 50 mL using sterile saline and instilled together at the same time into the bladder through a urinary catheter. The study treatment dose was to remain in the bladder for 2 hours (at minimum for 1 hour, but 2 hours was the optimum retention time) during which time subjects were to be monitored for TEAEs. Dose reduction of up to one third dose of 50 mg BCG (i.e., 16.7 mg) was allowed at the discretion of the investigator to address concerns of subject safety. No dose reductions were permitted for N-803.

N-803 monotherapy

Each instillation of N-803 monotherapy (administered to Cohort C) consisted of 400 µg N-803, which was mixed with sterile saline to a final volume of 50 mL and administered as described above.

Duration of treatment

The initial treatment period (induction treatment) consisted of 6 weekly treatments followed by 6 weeks of rest. After the week 12 response assessment, subjects with residual CIS or high-grade Ta could receive an additional 6 weeks of re-induction treatment, while those with no evidence of disease or low-grade Ta could receive 3 weeks of maintenance treatment. Subjects with no disease or low-grade Ta disease at their month 6-36 response assessments could receive maintenance therapy (i.e., 3 weekly instillations) at 3-month intervals through month 12, and then at 6-month intervals through month 36. The maximum duration of treatment was 3 years. After treatment discontinuation, subjects were to be followed for disease progression, post-treatment therapies, and survival through month 60. The planned total study duration is 5 years.

Induction Treatment Period (Months 1 - 3)

All subjects received either N-803 plus BCG or N-803 monotherapy via a urinary catheter in the bladder, weekly for 6 consecutive weeks after enrolment followed by 6 weeks of rest. This treatment period occurred prior to the first response assessment.

Response evaluation

Response assessments were completed every 3 months through month 24, and then every 6 months through month 60.

Second Treatment Period (Months 4 - 6)

Re-induction therapy

Subjects with presence of high-grade Ta and/or residual CIS received a re-induction course of therapy (6 weekly instillations of either N-803 plus BCG or N-803 monotherapy). Presence of Ta disease required a TURBT procedure before instillation.

Maintenance therapy

Based on the first response assessment at week 12 (i.e., the end of month 3), any subject who showed no disease or low-grade Ta disease received a maintenance course of therapy (3 weekly instillations of either N-803 plus BCG or N-803 monotherapy). Presence of low-grade Ta disease required a TURBT procedure before instillation.

No response

Subjects with new CIS and/or any T1 disease or greater (including disease progression) were considered treatment failures, received no further study treatment, and were followed for disease progression, post-therapies, and survival status through 60 months.

Third Treatment Period (Months 7 - 24)

Maintenance therapy

Subjects in all cohorts with no disease or low-grade Ta disease at response assessments occurring in months 6-18 were eligible to receive continued maintenance treatment, which consisted of 3 weekly instillations of N-803 plus BCG (Cohorts A, B, and E) or N-803 monotherapy (Cohorts C).

For subjects with ongoing no disease/low grade Ta disease, maintenance therapy was administered in months 7, 10, 13, and 19.

Ineligibility for additional treatment/ intolerance

If a subject became ineligible for additional treatment, the subject was to be followed for disease recurrence, progression, post-therapies, QoL, and survival according to the scheduled response assessments every 3 months through month 24, then every 6 months through month 60.

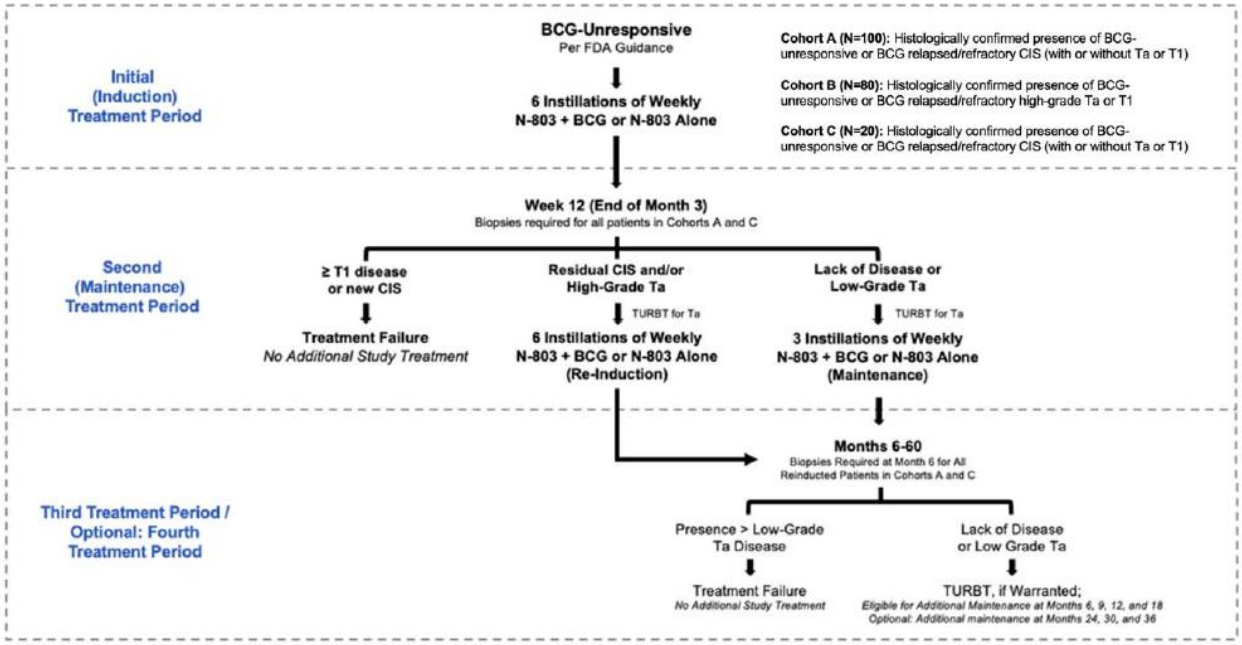
At the discretion of the investigator and with Sponsor approval, subjects who became intolerant to BCG could be treated with N-803 monotherapy.

Fourth Treatment Period (Optional; Months 25 - 36)

Subjects in all cohorts with no disease or low-grade Ta disease at months 21, 24, 30, and 36 response assessments were eligible for additional optional maintenance treatment of BCG plus N-803 or N-803 monotherapy, by investigator's discretion. Presence of low-grade Ta disease required a TURBT procedure before instillation.

For participating subjects with ongoing no disease/low grade Ta disease, maintenance therapy could be administered in months 25, 31, and 37.

Figure 8 Schema of interventions in QUILT-3.032



Prior and Concomitant Therapy

With the exception of FDA-authorised treatments for the treatment of COVID 19, no investigational or commercial anticancer agents or anticancer therapies other than BCG, N-803, and supportive care therapies were to be administered while the subject continued to receive N-803. A single postoperative dose of Mitomycin C or gemcitabine treatment was permitted prior to study entry but was prohibited during the study. Subjects who had a diagnostic biopsy or tumor resection should have waited at least 2 weeks before the first treatment instillation.

Treatment Compliance

Study treatment was administered by intravesical instillation by the investigator at the study site. If the study treatment instillation was held or interrupted for any reason, a single dose delay of up to one week was permitted.

Randomisation and Blinding

This is an open label, single-arm study and as such, randomization and blinding are not applicable.

Patients were enrolled into one of three study cohorts based on the histologically confirmed presence of BCG-unresponsive CIS (with or without Ta/T1 papillary disease).

Cohorts A, B and C are independent study cohorts and were evaluated for efficacy separately.

Patient population

This is a multi-center study conducted in the US. From 31 July 2017 (first subject enrolled) to 15 July 2024 (data cutoff), a total of 190 subjects were enrolled at 22 clinical sites (out of 32 total sites; 10 sites did not enrol subjects).

A total of 238 subjects were screened, and there were 48 screen failures. Cohort A enrolled 100 subjects with histologically confirmed BCG-unresponsive and BCG-refractory or BCG-relapsed CIS (with or without Ta or T1 disease). Cohort B enrolled 80 subjects with histologically confirmed BCG-unresponsive high-grade Ta or T1 disease. Cohort C enrolled 10 subjects with histologically confirmed BCG-unresponsive CIS (with or without Ta or T1 disease).

Selection of Study Population

Key Inclusion Criteria

1. Male or female subjects 18 years of age or older.
2. Histologic confirmation of NMIBC of the transitional cell carcinoma high-grade subtype (mixed histology tumors allowed if transitional cell histology is predominant histology):
    a. Cohort A (N = 100): Histologically confirmed presence of BCG-unresponsive CIS (with or without Ta/T1 papillary disease).
    b. Cohort B (N = 80): Histologically confirmed presence of BCG-unresponsive high-grade Ta or T1 papillary disease.
    c. Cohort C (N = up to 20): Histologically confirmed presence of BCG-unresponsive CIS (with or without Ta/T1 papillary disease).
3. Absence of resectable disease after TURBT procedures (residual CIS acceptable; subjects with T1 tumors must undergo repeat resection and biopsy [inclusive of muscularis propria] if initial biopsy did not include muscularis propria). Subjects with high-grade Ta and/or T1 disease should have complete resection before study treatment.
4. BCG-unresponsive disease, as defined as:
    a. Persistent or recurrent CIS (± recurrent Ta/T1 disease) within 12 months of receiving adequate BCG (at least 5 of 6 doses of an initial induction course plus either at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of a second induction course); or
    b. Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG (at least 5 of 6 doses of an initial induction course plus either at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of a second induction course); or
    c. T1 high-grade disease at the first evaluation following an induction BCG course alone

(at least 5 of 6 doses of an initial induction course).

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
6. Voluntary written informed consent and HIPAA authorization and agree to comply with all protocol-specified procedures and follow-up evaluations.

Key Exclusion Criteria

1. Recurrence of BCG-unresponsive Ta/T1 disease (without presence of CIS) >6 months after last BCG instillation or BCG- unresponsive CIS >12 months after last BCG instillation.
2. Life expectancy <2 years.
3. History of or evidence of muscle-invasive, locally advanced, metastatic and/or extravesical bladder cancer (inclusive of the prostatic urethra); or any other cancer within the past 5 years that is progressing or requires active treatment. Exceptions are adequately treated basal cell or squamous cell skin cancer that has undergone potentially curative therapy or in situ cervical cancer; and adequately treated stage I or II cancer or stable prostate cancer from which the patient is currently in complete remission and is under active surveillance or hormone control.

Removal of Subjects from Therapy or Assessment

Subjects could have been discontinued from therapy for any of the following reasons:

- Development of new CIS or ≥ T1 disease at the week 12 response assessment.
- Presence of disease > low-grade Ta disease at any response assessment after and including the month 6 response assessment.
- Development of unacceptable toxicity.
- Pregnancy.

Subjects who discontinued treatment because of bladder cancer presence or progression or toxicity were followed for disease recurrence, progression, post-therapies, QoL, and survival through 60 months.

5.3.2.1.3. Objectives and estimands

Primary objective

Cohort A: To assess the antitumor activity of intravesical BCG in combination with N-803 in subjects with BCG-unresponsive high-grade NMIBC as determined by CR rate (for BCG-unresponsive CIS [with or without Ta/T1 papillary disease]) using cystoscopy, confirmatory bladder biopsy, and urine cytology. CR at any time was exploratory endpoint for the Cohort C.

To determine the incidence of CR at any time, a decision algorithm was provided to assist the investigator in the CR assessment. The CR assessment at any time was based on procedures including cystoscopy by the investigator, biopsy by the local pathology review, cytology by local pathology review and the handling of suspicious or missing cytology results.

The investigator decision criteria for CR assessment based on the results of the procedures performed are as follows below:

Table 10 Definition of Complete Response (CR)

Primary Endpoint	Cystoscopy Evaluation by Local Urologist	Cytology Evaluation by Local Cytologist Pathologist	Biopsy Evaluation by Local Pathologist(s)	CR is Determined by Investigator and Local Pathology Review
Complete response is defined in Section 3.1				
a. Negative cystoscopy and negative (including atypical) urine cytology; or	Negative	Negative / Atypical	Not Required	✓ = CR Section 3.1
b. Positive cystoscopy with biopsy-proven benign or low-grade Ta NMIBC and negative cytology; or	Positive	Negative / Atypical	Negative	✓ = CR Section 3.1
c. Negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative.	Negative	Positive	Negative ↓ Upper Tract Section 7.1.7: Upper Tract Evaluation	✓ = CR Section 3.1
d. A visit where a negative cystoscopy with one or more consecutive missing, suspicious, or malignant urine cytologies, and the subsequent urine cytology is negative or atypical and normal cystoscopy (or negative biopsy if cystoscopy is suspicious or abnormal) is considered a complete response.	Negative	Missing / Suspicious / Positive ↓ Negative / Atypical	Negative (if cystoscopy is suspicious or abnormal)	✓ = CR Section 3.1

If the urine cytology is indeterminate (either suspicious for disease or not performed) or positive (along with no lesions on cystoscopy or negative biopsy results) for a visit and the patient has subsequent urine cytology assessments that are negative or atypical at the next visit, the patient will be considered as having CR for both visits.

If the last recorded cytology assessment is indeterminate or positive (despite no lesions on cystoscopy or negative biopsy results), then the patient will not be considered as having CR at the last study visit.

When one or more consecutive missing, suspicious, or malignant urine cytologies are reported, and subsequent urine cytology is negative or atypical and normal cystoscopy (or negative biopsy if cystoscopy is suspicious or abnormal) the assessment is considered a CR.

When the definitive cytology result is obtained, the response status for all prior consecutive, suspicious cytology results will be backdated with the investigator response assessment.

If a patient has consecutive suspicious cytologies and during a subsequent visit has a biopsy-confirmed recurrence in the bladder, or a positive cytology is found without alternative non-bladder source identified, the date of recurrence should be backdated to the date of the original suspicious cytology.

Primary endpoint assessment

For cohort A, the primary efficacy endpoint was the incidence of CR at any time. CR at any time was exploratory endpoint for the Cohort C. The procedures required to collect the key parameters required to determine the incidence of CR at any time included cystoscopy by the investigator, biopsy by the local pathology review, cytology by local pathology review and the handling of suspicious or missing cytology results.

Participants with (a) negative cystoscopy and negative (including atypical) urine cytology, also had random biopsies of 5 areas of the bladder to confirm CR even when no visible disease was seen. This is a more rigorous methodology to determine CR than routine standard of care. Random biopsies were not required to confirm CR later than 6 months on study.

The rigor in which the CR rate at any time is determined by the protocol relating to biopsies is as follows:

- At the time of visualization at 3 months or at 6 months, a biopsy is performed. The performance of the biopsy exceeds the standard of care where the cystoscopy visualization and urine analysis are used to determine CR.
- The biopsy performed at the time of CR is reviewed locally, in most instances, by 2 pathologists who confirm the results of a CR.
- The local analysis is further confirmed by an independent blinded central review.
- Finally, a concordance analysis is performed between local and central review, affirming the validity and rigor of the finding of CR.

Estimand for the primary objective

No estimands or intercurrent events were defined by the Applicant in this study. The table below was created by the assessor, based on available protocol and analysis information.

Table 11 Estimand for the primary objective

Population	Patients with BCG-unresponsive High-grade non-muscle invasive bladder cancer (NMIBC) with Carcinoma in situ (CIS) with or without Ta or T1 disease.
Treatment condition	Assignment to intravesical N-803 plus BCG combination, regardless of discontinuation, under the hypothetical scenario of no use of additional anticancer medications.
Endpoint (variable)	Complete Response (CR) at any time.
Population-level summary	Proportion of patients achieving CR at any time.
Intercurrent events and strategy to handle them	
Discontinuation of treatment	Treatment policy
Use of additional medications	Hypothetical

The clinical question of interest was to assess the antitumor activity of intravesical BCG in combination with N-803 in patients with BCG-unresponsive high-grade NMIBC with Carcinoma in situ (CIS) with or without Ta or T1 disease, as measured by Complete Response (CR) rate at any

time. The estimand targets the rate of CR based on cystoscopy, confirmatory bladder biopsy, and urine cytology, regardless of treatment discontinuation (treatment policy strategy) and under the hypothetical scenario of no use of additional anticancer medications.

Statistical methods for estimation and sensitivity analysis on primary estimand

The data cutoff date for this application was 15 July 2024. The final analysis for each cohort was to be conducted once all enrolled patients in a cohort have completed the study.

All analyses were to be conducted without adjustments for multiple testing.

Analysis populations

Cohorts A, B and C are independent study cohorts and were to be evaluated separately for efficacy. The primary efficacy population were to include all patients who met the definition of BCG-unresponsive and BCG-refractory or BCG-relapsed NMIBC and who had reached the 3-month response assessment or discontinued treatment prior to the 3-month response assessment at the time of data cutoff. The secondary efficacy population were to be the safety population. The safety population (SAF) were to include all patients in that cohort who received at least one instillation of BCG plus N-803 or N-803 alone. The SAF is the population that will be used for all safety analyses.

Main analysis methods

Descriptive statistical methods were to be used to summarize the data from this study. Confidence intervals (CIs) were to be presented as 2-sided 95% CIs.

Biopsy assessments for the primary, key secondary and other secondary endpoints were to be based on local pathology review if not specified otherwise. All endpoints for Cohort C were exploratory. The primary efficacy endpoint for Cohorts A and C was the incidence of complete response (CR) of CIS at any time.

The CR rate at any time (overall CR rate) were to be calculated as the ratio of the number of patients who have CR at any time divided by the number of patients in the analysis population of Cohort A and C, respectively. The primary endpoint for Cohorts A and C (exploratory) were to be analyzed using a two-sided exact 95% confidence interval (CI). The exact CI were to be calculated using the Clopper-Pearson method. For the primary endpoint to be successful for Cohort A, the lower limit of the 95% CI should be >20%.

Handling of Missing data

Disease response or recurrence assessments at some visits may not be determined for various reasons. For example, assessments may have not been performed or assessment results may be inconclusive due to indeterminate cytology or cystoscopy assessments (if biopsy was not performed). If missing or inconclusive response assessments occurred after the patient's initial CR and the patient had subsequent assessments that were deemed CR, then the patient in Cohorts A and C would have been considered as having CR from the date of his/her initial CR to the date of the last known CR. CR rate was to be presented at each assessment visit. If missing or inconclusive response assessments occurred, CR rate was to be estimated including the imputed response assessments as described above.

Efficacy Sensitivity Analyses

Sensitivity analyses were to be performed for CR at any time, duration of CR and progression-free survival. These analyses were to be performed by including new malignant lesions that were found only in the upper tract or prostatic urethra as evidence of disease.

Further sensitivity analyses were to be performed for CR at any time and duration of CR where subjects with persistent malignant cytology and a negative biopsy/biopsies without documented upper tract disease were also to be included as if they have upper tract disease.

A sensitivity analysis for the primary and/or key secondary efficacy endpoints were also to be performed based on subjects' baseline disease type regardless of which cohort the subjects were assigned to. The analysis was to be performed for subjects with any CIS [with or without Ta/T1 papillary disease] and subjects with papillary disease [Ta/T1] only.

Subgroup Analyses

Analyses of CR at any time, duration of CR, and time to recurrence delayed cystectomy were presented for the following subgroups: Age (<65 years, ≥65 years); Gender (male, female); Race (white, non-white); Baseline disease type (Cohort A: CIS only, CIS with T1, CIS with Ta.), ECOG status (0, 1-2); Subjects with re-induction versus subjects without re-induction; Number of prior BCG doses (≥12 doses, Heavily pretreated subjects with additional prior BCG and other therapies after BCG- unresponsive diagnosis, <12 doses.); Prior cancer therapy (BCG only, BCG plus other therapy); Number of prior TURBT; Subclassification of BCG Failure (Refractory or Relapsed); Time from last prior BCG to study entry; Time from last prior BCG to first recurrence of CIS disease; Other intravesical or systemic therapies after last prior BCG but before study entry; and Site (each individual clinical site).

Secondary objective

Duration of complete response (DoR): To assess the duration of CR (for BCG-unresponsive CIS [with or without Ta/T1 papillary disease]). Loss of response is defined as no longer fulfilling CR criteria.

According to the Study QUILT 3-302 protocol the absence of response /no response was defined as follows: subjects with new CIS and/or any T1 disease or greater (including disease progression) were considered treatment failures, received no further study treatment, and were followed for disease progression, post-therapies, and survival status through 60 months.

Additional Secondary Objectives (Cohort A only)

- To assess CR rate per Central Pathology Review (CPR), CR rate and duration of CR (where disease is defined as all recurrent bladder cancer, including low grade Ta disease). CR rate was evaluated at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months
- To confirm the baseline pathologic diagnosis by CPR, to assess PFS, OS, Disease-specific survival (DSS), time to disease worsening, time to cystectomy, safety, characterization of the immunogenicity profile of BCG in combination with N 803, and QoL as assessed by the EORTC questionnaires for patients with cancer (QLQ-C30) and for patients with NMIBC (QLQ-NMIBC24).

Exploratory Objective

- Cohort C: To assess the antitumor activity of intravesical N-803 alone in subjects with BCG-unresponsive high-grade NMIBC as determined by CR rate (for BCG-unresponsive CIS [with or without Ta/T1 papillary disease]) using cystoscopy, confirmatory bladder biopsy, and urine cytology.

- Cohort C: To assess the duration of CR (for BCG-unresponsive CIS [with or without Ta/T1 papillary disease]).
- Cohort C: Safety, characterization of the immunogenicity profile of N-803, and QoL.
- All Cohorts (exploratory; subset of subjects): To evaluate systemic N-803 exposure after single and multiple intravesical instillations of 400 µg N-803.
- All Cohorts: To determine the PK profile of N-803 after a single intravesical instillation of 400 µg N-803 (QUILT-3.032-2.005-PK).
- All Cohorts: To determine the PK profile of N-803 after multiple intravesical instillations of 400 µg N-803 (QUILT-3.032-2.005-PK).

Statistical methods for estimation and sensitivity analysis on the secondary estimand

Analysis of Key Secondary Efficacy Endpoints

Duration of CR, DFS, and disease-free rates were to be assessed using Kaplan-Meier (KM) analysis methods. The estimates of the median duration of CR, median DFS, and disease-free rate at each assessment visit were to be provided along with their 95% CIs. Subjects who do not show any evidence of disease at the end of study were to be censored at the date of last non-missing response assessment.

For Duration of CR, if

- Subjects died after 2 or more consecutive missing response assessments, subjects were to be censored at the date of last non-missing response assessment.
- Subjects who died for any cause, including unrelated to bladder cancer, were to be considered an event (ie, recurrence as it relates to analysis for the duration of CR).
- Subjects with new malignant lesions that were found only in the upper tract or prostatic urethra were not to be treated as having disease recurrence or progression and were to be censored at the date of last non-missing response assessment.
- Subjects who discontinued study treatment without disease recurrence and had 2 or more consecutive missing response assessments were to be censored at the date of last non-missing response assessment. Some subjects could have received certain concomitant medications or procedures (e.g., methotrexate, TURBT, fulguration) that potentially may impact duration of CR. The study medical team were to review all concomitant medications and procedures data and determine if subjects should be censored at the time of receiving these treatments.

The duration of CR analysis for Cohort A and C were to be performed only for patients who experience CR. The KM estimated survival curves were also to be produced.

The number and percentage of subjects who have achieved duration of CR ≥ 12 months (±14 days) were to be presented.

The secondary endpoints of CR rate at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months were to be calculated as the ratio of the number of patients who have CR at each assessment visit divided by the number of patients in the analysis population of Cohort A and C, respectively. The CR rates will be analyzed in a similar manner as the primary endpoint for Cohort A using a two-sided exact Clopper-Pearson 95% CI.

Analysis of Additional Secondary Efficacy Endpoints

Complete response was also to be assessed by Central Pathology Review (CPR) for all patients in Cohort A and Cohort C. The central pathologist was to evaluate the biopsy samples collected at screening, Week 12, and Month 6 (if applicable) for all patients in Cohort A. The CR rate at any time per CPR assessment results were to be calculated and analyzed using a two-sided exact (Clopper-Pearson) 95% CI. Differences between the CR rate evaluated by CPR and the CR rate evaluated by the local pathologist were to be tabulated. Overall concordance for all biopsies undergoing CPR (i.e., at screening, 3 months, and 6 months if applicable) vs. local pathology review were to be presented. Concordance of biopsy assessments were to be presented for screening and for responding and non-responding subjects.

Additional secondary efficacy endpoints of PFS, disease-specific PFS, OS, DSS, time to disease worsening, and time to cystectomy were assessed using KM analysis methods as appropriate.

For analysis populations, handling of missing data, sensitivity analyses and subgroup analyses see under Statistical methods for estimation and sensitivity analysis on primary estimand above.

5.3.2.1.4. Results

Participant flow and numbers analysed

Study Initiation Date: 31 July 2017 (first subject enrolled)

Date last subject completed: Study ongoing

Date of first data collection: 31 July 2017

Date of last data collection/Date of cut-off: 15 July 2024

This report includes the efficacy data from the BCG-unresponsive NMIBC subjects with carcinoma in situ (CIS) with or without Ta or T1 disease (Cohorts A and C).

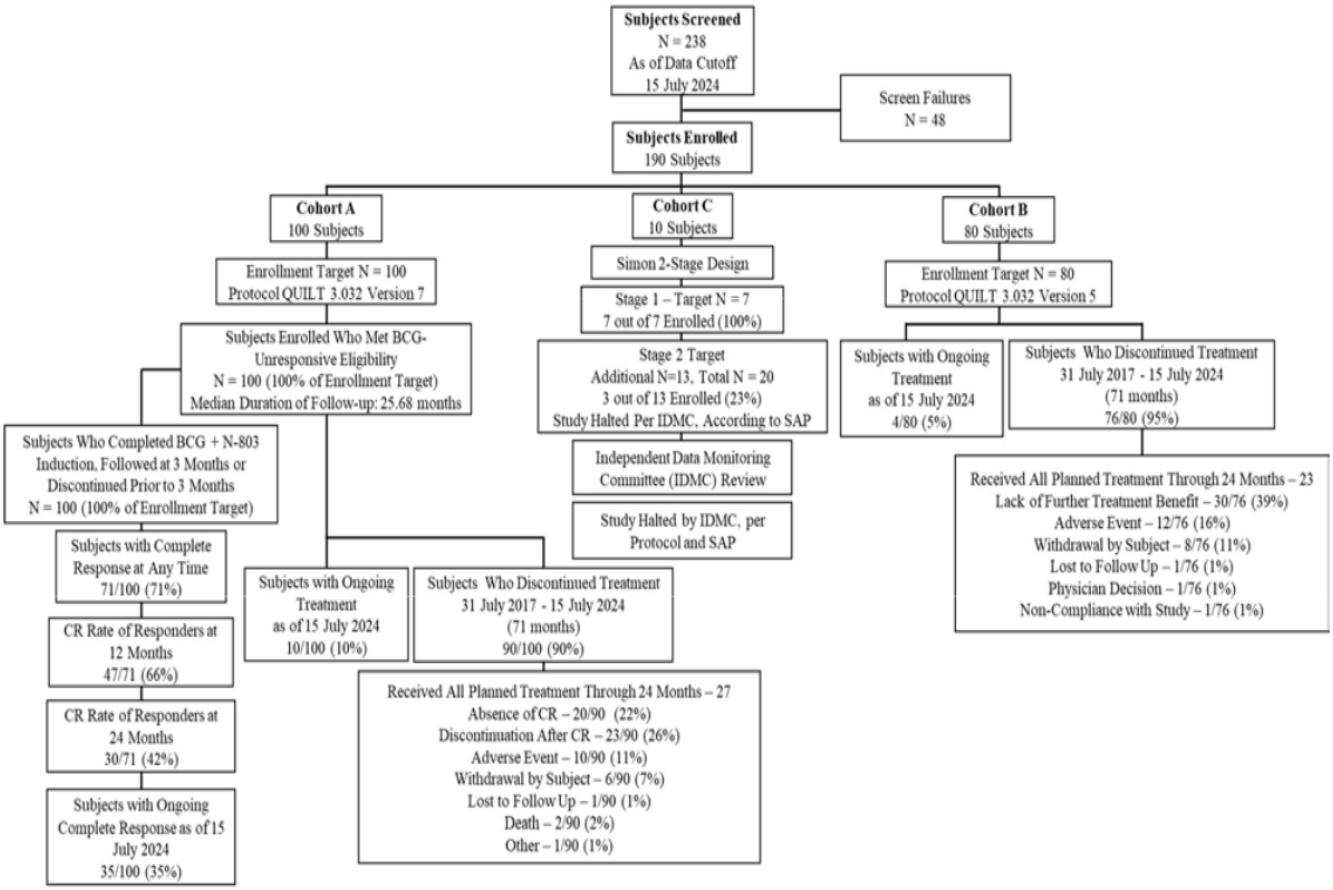
Subject Disposition:

As of the data cutoff date, a total of 190 subjects were enrolled in the study. Cohort A enrolled 100 subjects with histologically confirmed BCG-unresponsive and BCG-refractory or BCG-relapsed CIS (with or without Ta or T1 disease).

Cohort B enrolled 80 subjects with histologically confirmed BCG-unresponsive high-grade Ta or T1 disease.

Cohort C enrolled 10 subjects with histologically confirmed BCG-unresponsive CIS (with or without Ta or T1 disease).

Table 12 Participant flow



At the time of data cut-off, 90% of Cohort A, 95% of Cohort B, and 100% of Cohort C had received all planned drug treatments and/or were no longer on treatment. Treatment was ongoing for 10% of Cohort A, 5% of Cohort B, and 0% of Cohort C.

The most common reasons Cohort A subjects were no longer on treatment were received all planned treatment through 24 months (30%), discontinuation after CR (disease recurrence, progression, cystectomy or new anticancer therapy,26% of subjects), and absence of CR (22%).

In Cohort B, the most common reasons were lack of further treatment benefit (39%), received all planned treatment through 24 months (30%), and adverse event (AE;16%).

In Cohort C, the most common reasons were absence of CR (80%) and discontinuation after CR (20%).

Table 13 Subject Disposition in QUILT-3.032 (All Enrolled Subjects)

Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (High-Grade Papillary) (N = 80)	Cohorts A and B (N = 180)	Cohort C (CIS ± Ta/T1) (N = 10)	All Subjects (N = 190)
Subjects Enrolled	100	80	180	10	190
Safety Population[a]	100 (100%)	80 (100%)	180 (100%)	10 (100%)	190 (100%)
Treatment ongoing	10 (10%)	4 (5%)	14 (8%)	0	14 (7%)

Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (High-Grade Papillary) (N = 80)	Cohorts A and B (N = 180)	Cohort C (CIS ± Ta/T1) (N = 10)	All Subjects (N = 190)
Received All Planned Treatment and/or No Longer on Treatment	90 (90%)	76 (95%)	166 (92%)	10 (100%)	176 (93%)
Reason for No Longer on Treatment	90	76	166	10	176
Received All Planned Treatment Through 24 Months[b]	27 (30%)	23 (30%)	50 (30%)	0	50 (28%)
Absence of CR[c]	20 (22%)	NA	20 (12%)	8 (80%)	28 (16%)
Discontinuation after CR[c],[d]	23 (26%)	NA	23 (14%)	2 (20%)	25 (14%)
Lack of further treatment benefit	NA	30 (39%)	30 (18%)	NA	30 (17%)
Adverse event	10 (11%)	12 (16%)	22 (13%)	0	22 (13%)
Withdrawal by Subject	6 (7%)	8 (11%)	14 (8%)	0	14 (8%)
Death	2 (2%)	0	2 (1%)	0	2 (1%)
Lost to follow-Up	1 (1%)	1 (1%)	2 (1%)	0	2 (1%)
Non-Compliance with study drug	0	1 (1%)	1 (1%)	0	1 (1%)
Other	1 (1%)	0	1 (1%)	0	1 (1%)
Physician decision	0	1 (1%)	1 (1%)	0	1 (1%)

a Safety population includes all enrolled subjects who received at least one instillation of study drug.

b Received all planned treatment through 24 months refers specifically to subjects with study drug discontinuation and includes subjects with ongoing response (17 subjects in Cohort A and 19 subjects in Cohort B were still in response).

c CR is not an efficacy endpoint for Cohort B.

d Discontinuation after CR occurred due to disease recurrence (18 subjects in Cohort A and 2 subjects in Cohort C) or progression (2 subjects in Cohort A), cystectomy (1 subject in Cohort A), or initiation of new anticancer therapy (2 subjects in Cohort A).

The median duration of follow-up for subjects was 25.68 months in cohort A, 29.70 months in cohort B, and 35.78 months in cohort C.

Deviations from study plan

Changes in the planned conduct of the study

There were 10 amendments to the original protocol (dated 27 December 2016) resulting in 11 protocol versions.

Protocol Date
Version # 01 December 27, 2016
Version # 02 April 04, 2017
Version # 03 January 12, 2018
Version # 04 July 18, 2018
Version # 5.0 September 27, 2018
Version # 6.0 October 14, 2019
Version # 7.0 November 23, 2020
Version # 8.0 February 17, 2021
Version # 9.0 August 24, 2021
Version # 11 February 21, 2023

Version 11 of the protocol and Version 8 of the SAP were approved prior to the data cutoff date of 15 July 2024.

Up to 400 subjects were to be enrolled in this ongoing study. This includes an initial planned enrolment of 80 subjects in Cohort A for the analysis of the primary and key secondary efficacy endpoints. As requested by FDA, in order to evaluate the attribution of efficacy in combination therapy with N-803 plus BCG and to evaluate the efficacy of N-803 when administered as a monotherapy, the protocol was amended (Version 6 dated 19 October 2021) to include the addition of cohort C, in which subjects are treated with N-803 alone.

The data from cohort C and the published information on BCG monotherapy in this population is used to demonstrate the contribution of the effect for the combination of N-803 plus BCG.

In version 7 of the QUILT-3.032 protocol, enrolment in Cohort A was increased by 20 subjects, for a total of 100 subjects in Cohort A, in light of the expanded eligibility criteria accepted by the FDA to include subjects who are BCG-refractory or BCG-relapsed and to provide supportive data beyond that planned for the initial analysis of primary and key secondary endpoints.

A total of 80 subjects were to be enrolled in Cohort B, and up to 20 subjects in Cohort C (IDMC recommended closure at 10 subjects).

The IDMC meeting that took place on 11 November 2021 decided to close enrolment in Cohort C since the results of the first stage of the Simon's two-stage in cohort C showed < 3 subjects with a CR. After this date enrolment of the subjects with CIS continued only in Cohort A.

Table 14 Key Changes in Protocol Version 7

Protocol Version 7 23 November 2020	• Cohort A enrollment was expanded from 80 subjects to 100 subjects. • Cohort C enrollment was reduced from a maximum of 23 subjects to a maximum of 20 subjects. • All objectives for Cohort C were made exploratory objectives. • A PK objective was added for all cohorts: to evaluate systemic N-803 exposure after single and multiple intravesical instillations of 400 µg N-803. • The study duration was extended to 60 months (from 24 months), with response assessments taking place every 3 months through month 24, and then every 6 months through month 60. • For all cohorts, DoR rate endpoint collection was extended from 24 months to 60 months. For Cohort A, the final endpoint was extended from CR rate at 24 months to CR rate at 60 months. • A fourth treatment period was added: for subjects with no disease or low-grade Ta disease at months 24, 30, and 36, optional maintenance treatments were added at those time points, to be administered per PI discretion. • Protocol changed to specify enrollment was expanded to allow BCG-unresponsive and BCG-relapsed or BCG-refractory NMIBC (CIS ± Ta/T1) after 19 March 2020 FDA discussion indicating this change was acceptable and consistent with advice provided in December 2019 to investigators by the FDA for trials enrolling subjects with NMIBC. BCG-unresponsive was defined per FDA Guidelines and BCG-relapsed and BCG-refractory were defined based on the FICBT recommendations (Nieder 2005).

Major protocol deviations

A summary of major protocol deviations is presented in the table below.

Table 15 Summary of Major Protocol Deviations in QUILT-3.032 (Safety Population– All Cohorts)

	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (HG Papillary) (N = 80)	Cohorts A and B (N = 180)	Cohort C (CIS ± Ta/T1) (N = 10)	All Subjects (N = 190)
Subjects with Major Protocol Deviations[a]	10 (10%)	11 (14%)	21 (12%)	1 (10%)	22 (12%)
Subject Dosing	6 (6%)	3 (4%)	9 (5%)	0	9 (5%)
Concomitant Medication	2 (2%)	2 (3%)	4 (2%)	0	4 (2%)
Informed Consent	1 (1%)	3 (4%)	4 (2%)	0	4 (2%)
Visit/Assessment	2 (2%)	2 (3%)	4 (2%)	0	4 (2%)
Adverse Event	1 (1%)	1 (1%)	2 (1%)	0	2 (1%)
Inclusion/Exclusion Criteria	0	0	0	1 (10%)	1 (1%)

[a] Subjects may have had more than one type of major protocol deviation.

Baseline data

Demographics

Demographics were provided for all subjects receiving BCG plus N-803 across Study QUILT-3.032 and QUILT-2.005.

Table 16 Demographics and Baseline Characteristics in QUILT-3.032 (Safety Population – All Cohorts)

Variable Category/ Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (High-Grade Papillary) (N = 80)	Cohorts A and B (N = 180)	Cohort C (CIS ± Ta/T1) (N = 10)	All Subjects (N = 190)
Age (years)					
n	100	80	180	10	190
Mean	72.5	71.5	72.1 9	73.4	72.1
SD	9.05	10.03	9.48	4.95	9.30
Median	73.0	72.0	73.0	74.5	73.0
Min, Max	50, 91	46, 93	46, 93	67, 82	46, 93
Age group					
<65 years	16 (16%)	22 (28%)	38 (22%)	0	38 (20%)
≥65 years	84 (84%)	58 (73%)	142 (79%)	10 (100%)	152 (80%)
Gender					
Male	87 (87%)	59 (74%)	146 (81%)	6 (60%)	152 (80%)
Female	13 (13%)	21 (26%)	34 (19%)	4 (40%)	38 (20%)
Race					
American Indian or Alaska Native	1 (1%)	1 (1%)	2 (1%)	0	2 (1%)

Variable Category/ Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (High-Grade Papillary) (N = 80)	Cohorts A and B (N = 180)	Cohort C (CIS ± Ta/T1) (N = 10)	All Subjects (N = 190)
Asian	1 (1%)	2 (3%)	3 (2%)	0	3 (2%)
Black or African American	7 (7%)	2 (3%)	9 (5%)	1 (10%)	10 (5%)
Native Hawaiian or Other Pacific Islander	0	1 (1%)	1 (1%)	0	1 (1%)
White	90 (90%)	71 (89%)	161 (89%)	9 (90%)	170 (89%)
Other	0	1 (1%)	1 (1%)	0	1 (1%)
Not Reported	0	1 (1%)	1 (1%)	0	1 (1%)
Unknown	1 (1%)	1 (1%)	2 (1%)	0	2 (1%)
Ethnicity					
Hispanic or Latino	0	6 (8%)	6 (3%)	0	6 (3%)
Not Hispanic or Latino	97 (97%)	73 (91%)	170 (94%)	10 (100%)	180 (95%)
Not Reported	2 (2%)	0	2 (1%)	0	2 (1%)
Unknown	1 (1%)	1 (1%)	2 (1%)	0	2 (1%)
Baseline weight (kg)					
n	100	80	180	10	190
Mean	90.28	86.68	88.68	92.88	88.90
SD	19.046	23.303	21.059	25.390	21.251
Median	88.95	84.55	87.45	89.45	87.45
Min, Max	50.6, 132.0	41.7, 160.3	41.7, 160.3	57.2, 142.7	41.7, 160.3
Baseline ECOG Performance Status					
0	83 (83%)	61 (76%)	144 (80%)	6 (60%)	150 (79%)
1	17 (17%)	14 (18%)	31 (17%)	3 (30%)	34 (18%)
2	0	5 (6%)	5 (3%)	1 (10%)	6 (3%)
Baseline New York Heart Association (NYHA) class					
0	45 (45%)	43 (54%)	88 (49%)	6 (60%)	94 (49%)
I	47 (47%)	32 (40%)	79 (44%)	3 (30%)	82 (43%)
II	8 (8%)	5 (6%)	13 (7%)	1 (10%)	14 (7%)

Source: Table 14.1.2

Disease History

Table 17 Disease Characteristics in QUILT-3.032 (Safety Population – All Cohorts)

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (HG Papillary) (N = 80)	Cohort C (CIS ± Ta/T1) (N = 10)
Total Number of Prior BCG Doses			
n	100	80	10
Mean	16.7	12.2	14.9
SD	9.05	6.83	8.39

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (HG Papillary) (N = 80)	Cohort C (CIS ± Ta/T1) (N = 10)
Median	12.0	12.0	12.0
Min, Max	5, 48	5, 39	6, 36
Time from Last Dose of Prior BCG to Study Entry (months)			
n	100	80	10
Mean	7.57	5.97	6.87
SD	6.023	5.803	3.755
Median	5.73	4.90	5.62
Min, Max	0.3, 34.5	1.9, 53.0	2.7, 12.7
Time from Last Dose of Prior BCG to 1st Detected Recurrence[a] (months)			
n	99	79	10
Mean	3.50	3.56	5.34
SD	2.499	4.051	3.811
Median	2.56	3.12	3.11
Min, Max	0.7, 11.1	0.8, 36.4	1.4, 11.3
Time from 1st Detected Recurrence[a] to Study Entry (months)			
n	99	79	10
Mean	4.18	2.48	1.56
SD	5.215	2.280	0.827
Median	1.84	1.68	1.40
Min, Max	0.8, 32.9	0.6, 16.6	0.7, 3.8
Disease Type at 1st Detected Recurrence[a]			
CIS	70 (70%)	0	8 (80%)
CIS/Ta	21 (21%)	3 (4%)	2 (20%)
CIS/T1	8 (8%)	5 (6%)	0
High Ta	0	33 (41%)	0
T1	0	34 (43%)	0
Ta/T1	0	4 (5%)	0
Time from Last Disease-Positive Biopsy[b] to Study Entry (months)			
n	100	80	10
Mean	1.49	1.77	1.31
SD	0.891	0.956	0.307
Median	1.30	1.41	1.37
Min, Max	0.5, 6.7	0.6, 5.9	0.7, 1.8
Disease Type at Last Disease-Positive Biopsy[b]			
CIS	74 (74%)	1 (1%)	8 (80%)
CIS/Ta	17 (17%)	1 (1%)	2 (20%)
CIS/T1	8 (8%)	4 (5%)	0
CIS/Ta/T1	1 (1%)	0	0
High Ta	0	36 (45%)	0
T1	0	35 (44%)	0
Ta/T1	0	3 (4%)	0
Number of Prior TURBT			
n	87	78	10
Mean	4.1	3.8	3.2
SD	2.56	1.88	1.40
Median	4.0	3.0	2.5
Min, Max	1, 15	1, 11	2, 5
Time from Last Prior TURBT to Study Entry (months)			
n	87	78	10
Mean	10.30	1.77	9.45
SD	28.717	2.036	19.846

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)	Cohort B (HG Papillary) (N = 80)	Cohort C (CIS ± Ta/T1) (N = 10)
Median	1.45	1.33	1.40
Min, Max	0.3, 210.4	0.5, 17.2	0.7, 63.1

[a] For Cohorts A and C, the first detected recurrence refers to the first CIS positive biopsy performed after subject's last dose of prior BCG. For Cohort B, the first detected recurrence refers to the first papillary disease positive biopsy performed after subject's last dose of prior BCG.

[b] For Cohorts A and C, the last disease positive biopsy refers to the last CIS positive biopsy performed prior to study entry. For Cohort B, the last disease positive biopsy refers to the last disease positive biopsy (regardless of disease type) performed prior to study entry.

Outcomes and estimation

Primary Efficacy Endpoint – Cohort A

Complete Response at Any Time

Table 18 Complete Response Rate at Any Time in QUILT-3.032 (Overall Efficacy Population – Cohort A)

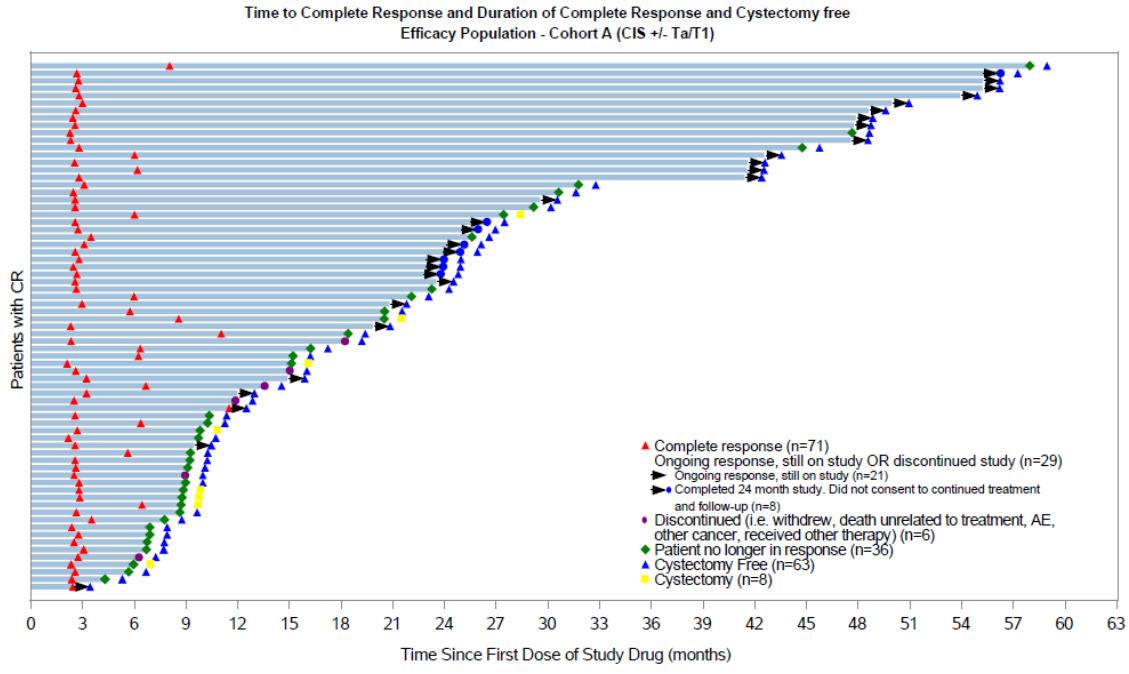
Variable	Cohort A (CIS ± Ta/T1) (N = 100)
Subjects with Complete Response (CR)[a]	71 (71%)
95% CI for CR Rate at Any Time[b]	61.1, 79.6

[a] Subject has been receiving 15mg oral methotrexate weekly during study

[b] The 95% Confidence Interval (CI) was calculated using exact binomial method.

The time to CR and duration of CR is provided for the 71 responders in figure below.

Figure 9 Time to Complete Response and Duration of Complete Response and Cystectomy Avoidance in Responders



Secondary endpoints-Cohort A

1. CR Rate at any Time Per Central Pathology Review

Table 19 Complete Response Rate at Any Time per Central Pathology Review in QUILT-3.032 (Efficacy Population – Cohort A)[a]

	Cohort A (CIS ± Ta/T1) (N = 94)
Subjects With CR	70 (74%)
95% CI for CR Rate at Any Time[b]	64.4, 82.9

[a] Includes subjects with central pathology review data available. One subject had a local response of CR at month 3 but random biopsy samples were not collected at month 3 and thus the subject was unevaluable for Central Pathology Review (CPR). Three subjects did not have CPR response assessment biopsies as it was not required in the protocol version to which they had been consented. Two subjects had biopsy samples collected, but the to which they are not available yet.

[b] The 95% Confidence Interval (CI) was calculated using exact binomial method.

The incidence of CR at any time was assessed by CPR from biopsy samples collected at week 12 (month 3) and month 6 (if applicable).

Table 20 Biopsy Concordance Between Local Pathology and Central Pathology Review for Complete Response at Any Time in QUILT-3.032 (Efficacy Population – Cohort A)[a]

	Local Pathology Review	Central Pathology Review	CPR Concordance With Local Pathology Review
Responder	67	70	66/67 (99%)
Non-Responder	27	24	23/27 (85%)
Total	94	94	89/94 (95%)

[a] Includes subjects with local and central pathology review data available. had a local response of CR at month 3 but random biopsy samples were not collected at month 3 and thus the subject was unevaluable for Central Pathology Review (CPR). Three subjects did not undergo CPR as response assessment biopsies did not require CPR under the protocol that they were consented. Two subjects had biopsy samples collected at month 3, but CPR results are not available yet.

Table 21 Overall Biopsy Sample Concordance between Local Pathology and Central Pathology Review in QUILT 3.032 (Efficacy Population – Cohort A)[a]

	Local Pathology Review	Central Pathology Review	CPR Concordance With Local Pathology Review
CIS With or Without Papillary	151	127	117/151 (77%)
High Grade Papillary Only	17	26	10/17 (59%)
Low Grade Only	2	10	1/2 (50%)
Negative for Malignancy	124	131	115/124 (93%)
Total	294	294	243/294 (83%)

[a] Concordance is provided for all biopsies undergoing local and central pathology review (i.e., at screening, 3 months, and 6 months if applicable).

Table 22 Discordance Rate Between Local & Central Review Per Literature

Title	Author	Year	Discordance Rate	N (specimens)
The influence of review pathology on study outcome of a randomized multicentre superficial bladder cancer trial	Witjes	1994	21% (T), 30% (Grade)	450
Impact of second opinion pathology in the definitive management of patients with bladder carcinoma	Coblentz	2001	18%	131
Second opinion of anatomical pathology: a complex issue not readily reduced to matters of right and wrong	Murphy	2001	21%	150
Second opinion pathology in tertiary care of patients with urologic malignancies	Wayment	2011	10%	833
The role of pathology review of transurethral bladder tumor resection specimens in the modern era	Lee	2010	29%	194
Pathology review impacts clinical management of patients with T1 – T2 bladder cancer	Traboulsi	2017	35%	98

Table 23 Baseline Biopsy Concordance between Local and Pathology and Center Pathology Review in QUILT-3.032 (Efficacy Population – Cohort A)[a]

	Local Pathology Review	Central Pathology Review	CPR Concordance With Local Pathology Review
CIS With or Without Papillary	94	72	72/94 (77%)
High Grade Papillary Only	0	9	0
Low Ta Only	0	4	0
Negative for Malignancy	0	9	0
Total	94	94	72/94 (77%)

CPR = Central pathology review

[a] Data shown here includes only subjects with both baseline local and central pathology review data available. Two subjects did not have CPR data as it was not required in the protocol version to which they had been consented. The baseline biopsy sample for one subject was not available for CPR.

For cohort A, there were 294 biopsies collected (including baseline and post-baseline biopsies) that were reviewed by both local and central pathologists (Table 24).

Table 24 Overall Concordance Between Local Pathology and Central Pathology (per Visit Level Analysis) Efficacy Population – Cohort A

	Central Pathology		
Local Pathology	**Positive for CIS**	**Negative for CIS**	**Total**
Positive for CIS	117/151 (77%)	34/151 (23%)	151
Negative for CIS	10/143 (7%)	133/143 (93%)	143
Total	127	167	250/294 (85%)

For cohort A, there were 305 cytopathology samples (including baseline and post- baseline cytopathology) that were reviewed by both local and central pathologists (Table 25).

Table 25 Overall Concordance Between Local Cytopathology and Central Cytopathology (per Visit Level Analysis) Efficacy Population – Cohort A

Local Cytopathology	Central Cytopathology		
	Positive for High-grade Urothelial Carcinoma	**Negative for High-grade Urothelial Carcinoma**	**Total**
Positive for high-grade urothelial carcinoma	9/29 (31%)	20/29 (69%)	29
Negative for high-grade urothelial carcinoma	24/276 (9%)	252/276 (91%)	276
Total	33	272	261/305 (86%)

[a] Overall concordance for all urine cytologies undergoing valid local and central cytopathology review

2. Duration of complete Response (DoR)

Table 26 Duration of Complete Response in QUILT-3.032 (Overall Efficacy Population – Cohort A)

Variable **Category/Statistic**	**Cohort A (CIS ± Ta/T1) (N = 100)**
Duration of Follow-up (months)[a]	
N	100
Mean	30.58
SD	15.411
Median	25.68
Q1, Q3	21.60, 42.56
Min, Max	3.2, 63.5
Subjects With CR[b]	71/100 (71%)
95% CI	(61.1, 79.6)
Subjects With Duration of CR ≥6 Months[c]	57/69 (83%)
95% CI	(71.6, 90.7)
Subjects With Duration of CR ≥12 Months[c]	40/67 (60%)
95% CI	(47.0, 71.5)
Subjects With Duration of CR ≥18 Months[c]	33/66 (50%)
95% CI	(37.4, 62.6)
Subjects With Duration of CR ≥24 Months[c]	21/63 (33%)
95% CI	(22.0, 46.3)
Subjects With Duration of CR ≥30 Months[c]	16/62 (26%)
95% CI	(15.5, 38.5)
Subjects With Duration of CR ≥36 Months[c]	15/61 (25%)
95% CI	(14.5, 37.3)
Subjects With Duration of CR ≥42 Months[c]	12/58 (21%)
95% CI	(11.2, 33.4)
Subjects With CR	71
Median Duration of CR (95% CI) (months)[d]	26.6 (13.0, 49.9)
Range of Duration of CR (months)	0.03 – 53.62
Subjects No Longer in Response Following Initial CR	36/71 (51%)
Disease recurrence	25/71 (35%)
New Anti-Cancer Therapy	6/71 (8%)
Death Unrelated to Bladder Cancer	2/71 (3%)
Disease progression	2/71 (3%)

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)
Cystectomy	1/71 (1%)
Subjects Censored for Duration of CR	35/71 (49%)
Treatment Discontinued Due to Adverse Event	1/71 (1%)
Withdrawal by Subject	2/71 (3%)
Died after 2 or More Consecutive Missing Response Assessments	2/71 (3%)
Subject Received Certain Concomitant Medications/Procedures	1/71 (1%)
Study Completed	8/71 (11%)
Study ongoing with follow-up (since 1st CR)	21/71 (30%)
≥12 months	17/71 (24%)
9-<12 months	1/71 (1%)
6-<9 months	1/71 (1%)
<3 months	2/71 (3%)
Percentage of Subjects (95% CI) With Duration of CR for[d]:	
≥3 months	97.1% (88.9, 99.3)
≥6 months	82.4% (71.1, 89.6)
≥9 months	67.1% (54.5, 77.0)
≥12 months	63.8% (51.0, 74.1)
≥15 months	60.4% (47.4, 71.1)
≥18 months	58.6% (45.6, 69.5)
≥24 months	52.3% (39.0, 64.1)
≥27 months	49.7% (36.1, 61.9)
≥30 months	44.2% (30.3, 57.2)
≥33 months	44.2% (30.3, 57.2)
≥36 months	44.2% (30.3, 57.2)
≥39 months	44.2% (30.3, 57.2)
≥42 months	40.5% (26.3, 54.3)
≥45 months	40.5% (26.3, 54.3)
≥48 months	36.0% (21.3, 50.9)
Duration of Follow-up for Subjects With CR (months)[a]	
N	71
Mean	31.99
SD	15.290
Median	26.74
Q1, Q3	23.52, 47.21
Min, Max	3.5, 63.5

NR = Kaplan-Meier statistic not reached.

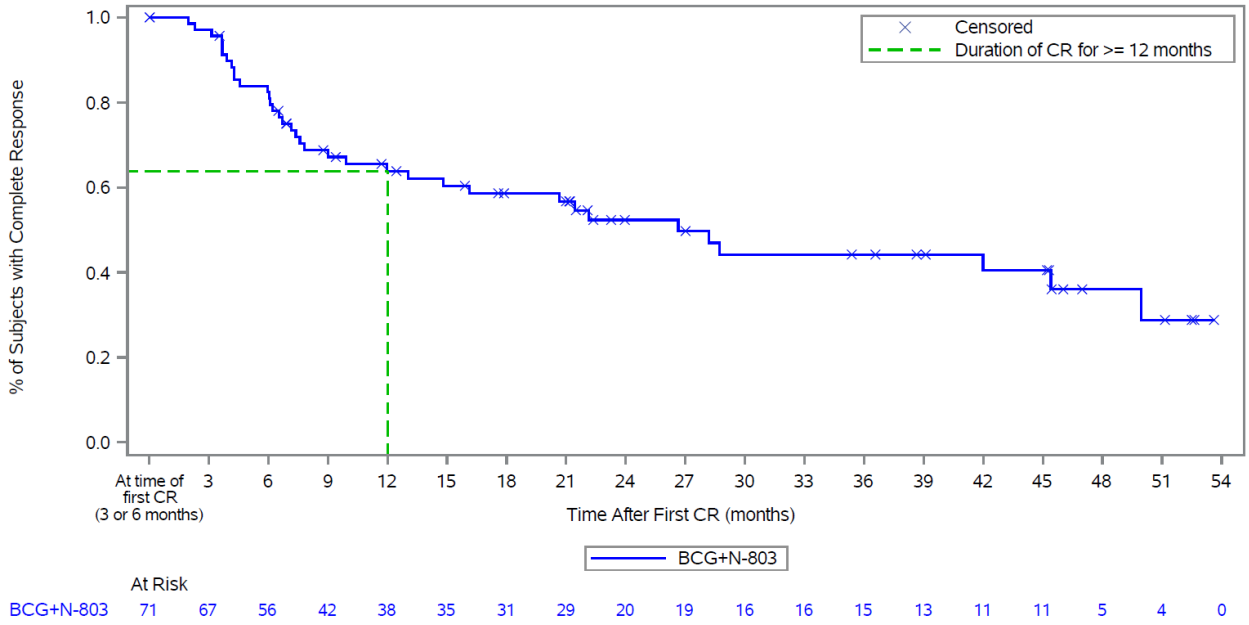
[a] Time from initial study drug administration to the date of last follow-up visit.

[b] One subject has been receiving 15mg weekly during study.

[c] Subjects with ongoing CR who have not reached the duration of CR interval are excluded.

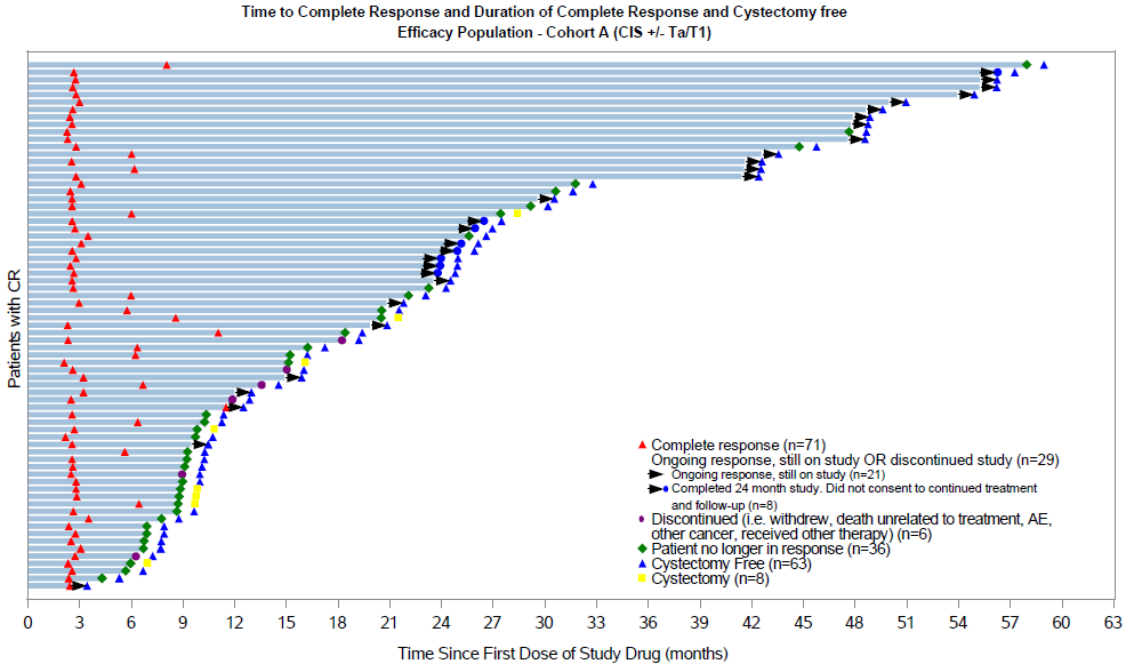
[d] Duration of CR was defined as the time from the date of first CR to the date of evidence that the subject no longer met the definition for CR. Responding subjects who were still in response at the end of study were censored at the last known date the subject was having CR. Median duration of CR and percentage of subjects with duration of CR by 3-month intervals were estimated using Kaplan-Meier analysis method from subjects who had CR.

Figure 10 Kaplan Meier Survival Curve for Duration of Complete Response in QUILT-3.032 (Efficacy Population – Cohort A)



Note: Duration of CR was defined as the time from the date of first CR to the date of evidence that the subject no longer met the definition for CR. Responding subjects who were still in response at the end of study were censored at the last known date the subject was having CR.

Figure 11 The time to CR and duration of CR is provided for the 71 responders in figure below



3. CR Rate by Assessment Visit

Table 27 Complete Response Rate by Visit in QUILT-3.032 (Overall Efficacy Population – Cohort A)

Visit	Cohort A (CIS ± Ta/T1) (N = 100)
Complete Response (CR)[a] Rate at:	
Any Time	
Subjects With CR	71 (71%)
95% CI for CR Rate[b]	61.1, 79.6
Month 3	
Subjects With CR	56 (56%)
95% CI for CR Rate[b]	45.7, 65.9
Month 6	
Subjects With CR	56 (56%)
95% CI for CR Rate[b]	45.7, 65.9
Month 9	
Subjects With CR	47 (47%)
95% CI for CR Rate[b]	36.9, 57.2
Month 12	
Subjects With CR	47 (47%)
95% CI for CR Rate[b]	36.9, 57.2
Month 15	
Subjects With CR	40 (40%)
95% CI for CR Rate[b]	30.3, 50.3
Month 18	
Subjects With CR	37 (37%)
95% CI for CR Rate[b]	27.6, 47.2
Month 21	
Subjects With CR	33 (33%)
95% CI for CR Rate[b]	23.9, 43.1
Month 24	
Subjects With CR	30 (30%)
95% CI for CR Rate[b]	21.2, 40.0
Month 27	
Subjects With CR	20 (20%)
95% CI for CR Rate[b]	12.7, 29.2
Month 30	
Subjects With CR	18 (18%)
95% CI for CR Rate[b]	11.0, 26.9
Month 33	
Subjects With CR	16 (16%)
95% CI for CR Rate[b]	9.4, 24.7

[a] One subject has been receiving 15mg weekly during study.

[b] The 95% Confidence Intervals (Cis) were calculated using exact binomial method. Visits were defined based on the elapsed calendar days since the first instillation of study drug. Refer to the Statistical Analysis Plan (SAP) for more details.

CR Rate by Visit: Subjects Who Did and Did Not Receive Re-Induction Therapy

Table 28 Complete Response Rate by Visit in Subjects Who Did and Did Not Receive Re-Induction Therapy in QUILT-3.032 (Efficacy Population – Cohort A)

Variable Visit	Subjects Not Re-inducted (N = 70)	Subjects Re-inducted (N = 30)	Cohort A (CIS ± Ta/T1) (N = 100)
Complete Response Rate[a] at:			
Any Time			
Subjects With CR	56 (80%)	15 (50%)	71 (71%)
95% CI for CR Rate[b]	68.7, 88.6	31.3, 68.7	61.1, 79.6
Month 3			
Subjects With CR	56 (80%)	0	56 (56%)
95% CI for CR Rate[b]	68.7, 88.6	0.0, 11.6	45.7, 65.9
Month 6			
Subjects With CR	45 (64%)	11 (37%)	56 (56%)
95% CI for CR Rate[b]	51.9, 75.4	19.9, 56.1	45.7, 65.9
Month 9			
Subjects With CR	37 (53%)	10 (33%)	47 (47%)
95% CI for CR Rate[b]	40.6, 64.9	17.3, 52.8	36.9, 57.2
Month 12			
Subjects With CR	35 (50%)	12 (40%)	47 (47%)
95% CI for CR Rate[b]	37.8, 62.2	22.7, 59.4	36.9, 57.2
Month 15			
Subjects With CR	32 (46%)	8 (27%)	40 (40%)
95% CI for CR Rate[b]	33.7, 58.1	12.3, 45.9	30.3, 50.3
Month 18			
Subjects With CR	30 (43%)	7 (23%)	37 (37%)
95% CI for CR Rate[b]	31.1, 55.3	9.9, 42.3	27.6, 47.2
Month 21			
Subjects With CR	29 (41%)	4 (13%)	33 (33%)
95% CI for CR Rate[b]	29.8, 53.8	3.8, 30.7	23.9, 43.1
Month 24			
Subjects With CR	26 (37%)	4 (13%)	30 (30%)
95% CI for CR Rate[b]	25.9, 49.5	3.8, 30.7	21.2, 40.0

[a] One subject has been receiving 15mg weekly during study.

[b] The 95% Confidence Intervals (CIs) were calculated using exact binomial method. Visits were defined based on the elapsed calendar days since the first instillation of study drug. Refer to the Statistical Analysis Plan (SAP) for more details.

4. Progression-Free Survival

Table 29 Progression Free Survival in QUILT-3.032 (Overall Efficacy Population – Cohort A)

Variable Category	Cohort A (CIS ± Ta/T1) (N = 100)
Subjects With Disease Progression or Death[a]	18 (18%)
Progression to T2 or Lymph Node/Distant Metastasis	10 (10%)
Death Unrelated to Bladder Cancer	8 (8%)
Median Progression-Free Survival (PFS) (months)[b]	NR
95% CI for the Median PFS	NR, NR
PFS Rate at[c]:	
Month 12	89.5% (81.4, 94.2)

Variable Category	Cohort A (CIS ± Ta/T1) (N = 100)
Month 15	88.3% (79.8, 93.4)
Month 18	87.0% (78.3, 92.4)
Month 21	87.0% (78.3, 92.4)
Month 24	85.7% (76.5, 91.5)
Time to Disease Progression or Death (months)[d]	
N	18
Mean	15.98
SD	13.224
Median	9.79
Min, Max	2.6, 47.8

Note: New malignant lesions that were found only in the upper tract or prostatic urethra were NOT counted as disease progression.

NR = Kaplan-Meier statistic not reached.

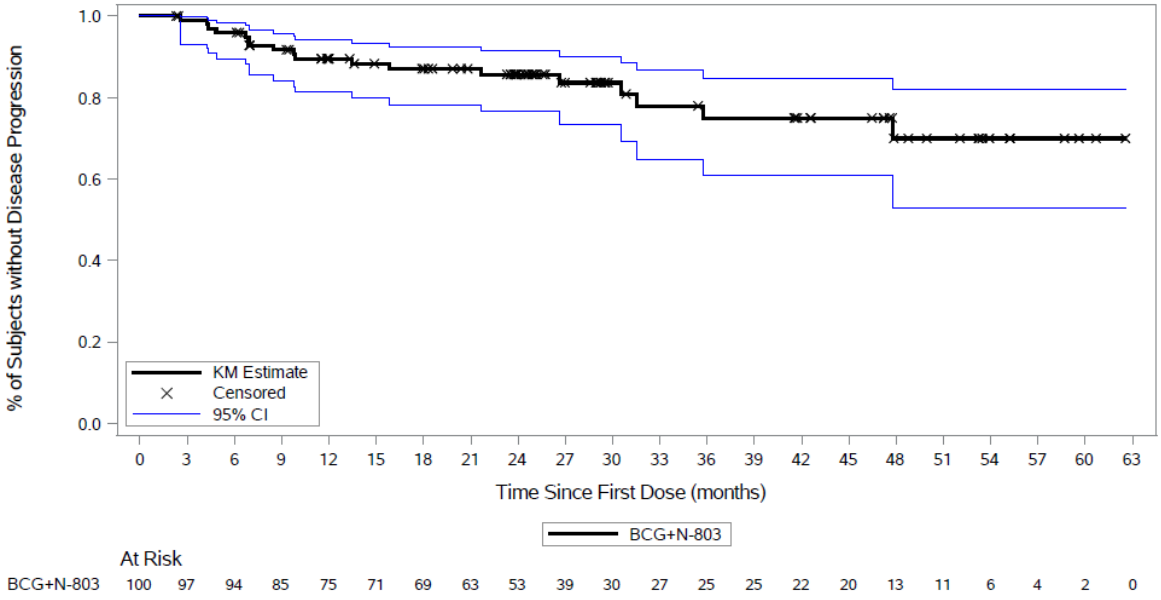
[a] Disease progression was defined as presence or development of any of the following:
- Muscle-invasive disease (stage ≥ T2);
- Lymph node (N+) or distant metastasis (M1).

[b] PFS was defined as the time from initial study drug administration to the date of disease progression or death (any cause), whichever occurred first. Subjects who didn't have disease progression or death at the end of study were censored at the last known date the subject was progression free.

[c] PFS rates were estimated using Kaplan-Meier analysis method.

[d] Time from initial study drug administration to the date of disease progression or death (any cause), whichever occurred first.

Table 30 Kaplan-Meier Survival Curve for Progression Free Survival in QUILT-3.032 (Overall Efficacy Population – Cohort A)



5. Disease-Specific Progression-Free Survival

DSPFS was defined as the time from study drug administration to disease progression (i.e., bladder cancer-specific disease progression).

Table 31 Disease specific progression-free survival in QUILT-3.0.32 (Overall efficacy population – Cohort A)

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)
Subjects With Disease Progression [a]	10 (10%)
Progression to T2 or Lymph Node/Distant Metastasis	10 (10%)
Median Disease-Specific Progression-Free Survival (PFS) (months)[b]	NR
95% CI for the Median DSPFS	NR, NR
DSPFS Rate at[c]**:**	
Month 12	93.6% (86.2, 97.1)
Month 15	92.3% (84.5, 96.3)
Month 18	91.0% (82.7, 95.4)
Month 21	91.0% (82.7, 95.4)
Month 24	91.0% (82.7, 95.4)
Time to Disease Progression (months) [d]	
n	10
Mean	13.05
SD	10.231
Median	9.10
Min, Max	2.6, 31.5

Note: New malignant lesions that were found only in the upper tract or prostatic urethra were NOT counted as disease progression.

NR = Kaplan-Meier statistic not reached.

[a] Disease progression was defined as presence or development of any of the following:
- Lymph node (N+) or distant metastasis (M1)
- Muscle-invasive disease (stage ≥T2)

[b] DSPFS was defined as the time from initial study drug administration to the date of disease progression. Subjects who didn't experience disease progression at the end of study were censored at the last known date the subject was disease progression free

[c] DSPFS rates were estimated using Kaplan-Meier analysis method.

[d] Time from initial study drug administration to the date of disease progression.

6. Cystectomy Rate and Time to Cystectomy

Time to cystectomy was measured as the probability of remaining cystectomy-free at each time point based on KM analysis.

Table 32 probability of remaining cystectomy-free at each time point based on KM analysis

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)
Subjects With Cystectomy	17 (17%)
Median Time to Cystectomy (months)[a]	NR
95% CI for the Median Time to Cystectomy	NR, NR
Cystectomy-Free Rate at[b]**:**	
Month 12	88.2% (79.7, 93.3)
Month 15	85.9% (76.9, 91.6)
Month 18	84.7% (75.5, 90.7)
Month 21	84.7% (75.5, 90.7)
Month 24	83.3% (73.7, 89.6)

Variable Category/Statistic	Cohort A (CIS ± Ta/T1) (N = 100)
Time to Cystectomy (months)	
n	17
Mean	12.63
SD	7.752
Median[c]	10.12
Min, Max	4.1, 31.5

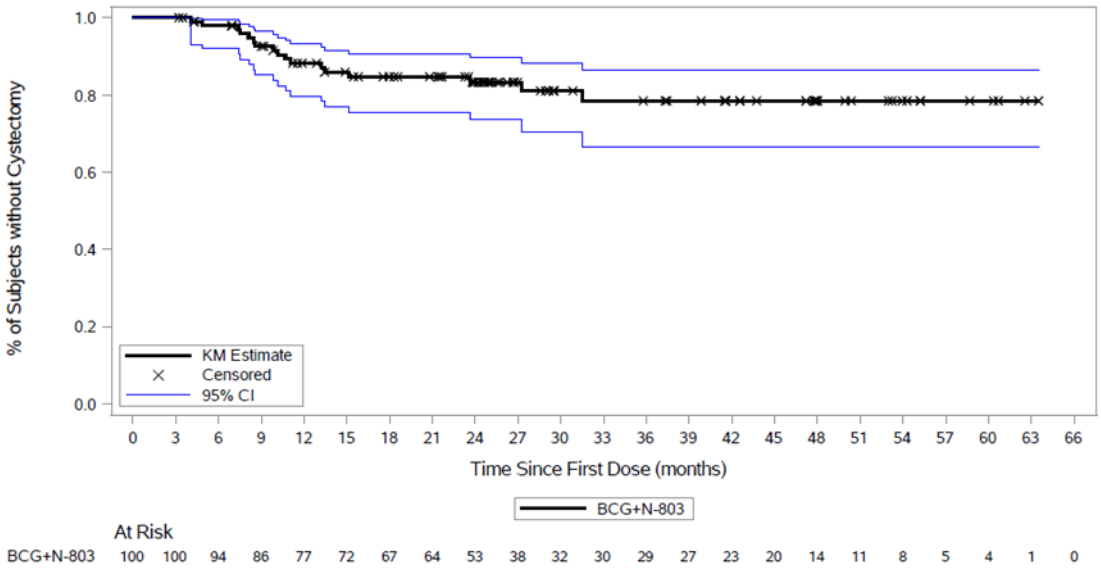
NR = Kaplan-Meier statistic not reached.

[a] Time to cystectomy was defined as the time from initial study drug administration to cystectomy using Kaplan-Meier analysis method. Subjects who didn't have documented cystectomy during the study were censored at the last date of follow-up visits.

[b] Cystectomy-free rates were estimated using Kaplan-Meier analysis method.

[c] Time to recurrence delayed cystectomy was calculated as the difference in median of time to cystectomy event between responding and non-responding subjects based on descriptive statistics.

Figure 12 Kaplan-Meier Survival Curve for Time to Cystectomy in QUILT-3.032 (Overall Efficacy Population – Cohort A)



Note: Time to cystectomy was defined as the time from initial study drug administration to cystectomy. Subjects who didn't have documented cystectomy during the study were censored at the last date of follow-up visits.

7. Overall Survival

Table 33 Overall Survival in QUILT-3.032 (Efficacy Population – Cohort A)

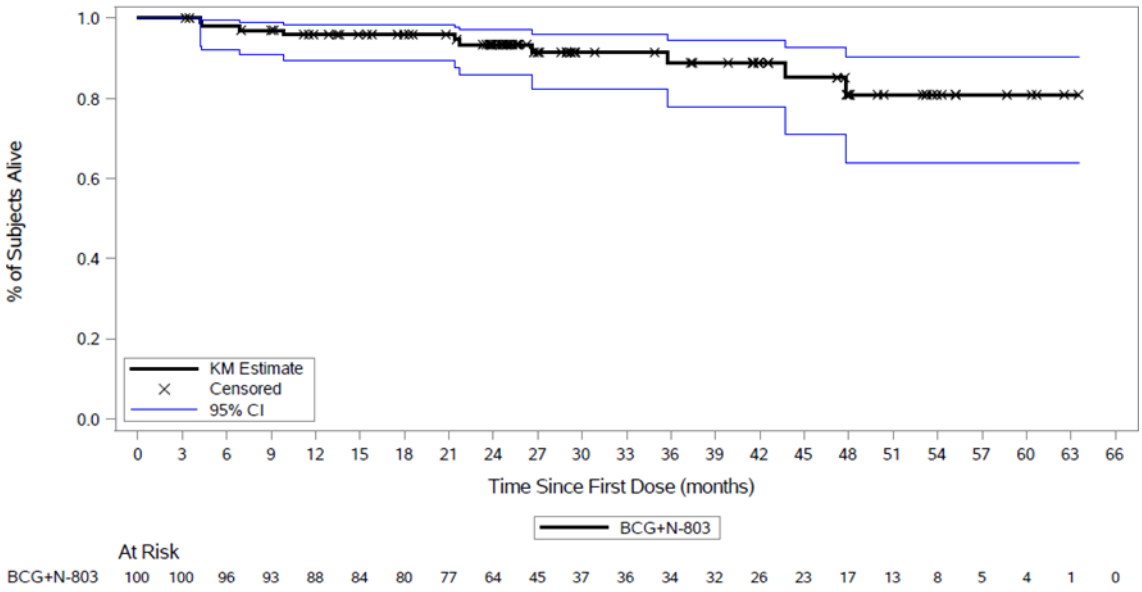
Variable Category	Responders (N = 71)	Non-Responders (N = 29)	Cohort A (CIS ± Ta/T1) (N = 100)
Number of Deaths	8 (11%)	2 (7%)	10 (10%)
Median Overall Survival (OS) (months)[a]	NR	NR	NR
95% CI for the Median OS	NR, NR	NR, NR	NR, NR
OS Rate at[b]:			
Month 12	95.7% (87.2, 98.6)	96.4% (77.2, 99.5)	95.9% (89.4, 98.4)
Month 15	95.7% (87.2, 98.6)	96.4% (77.2, 99.5)	95.9% (89.4, 98.4)
Month 18	95.7% (87.2, 98.6)	96.4% (77.2, 99.5)	95.9% (89.4, 98.4)
Month 21	95.7% (87.2, 98.6)	96.4% (77.2, 99.5)	95.9% (89.4, 98.4)
Month 24	92.3% (82.4, 96.7)	96.4% (77.2, 99.5)	93.4% (85.8, 97.0)

NR = Kaplan-Meier statistic not reached.

[a] OS was defined as the time from initial study drug administration to death resulting from any cause. Subjects who were alive at the end of study were censored at the last known date alive.

[b] OS rates were estimated using Kaplan-Meier analysis method.

Figure 13 Kaplan-Meier Survival Curve for Overall Survival in QUILT-3.032 (Overall Efficacy Population – Cohort A)



Note: OS was defined as the time from initial study drug administration to death resulting from any cause. Subjects who were alive at the end of study were censored at the last known date alive.

8. Disease-Specific Survival

Table 34 Disease-Specific Survival in QUILT-3.032 (Efficacy Population – Cohort A)

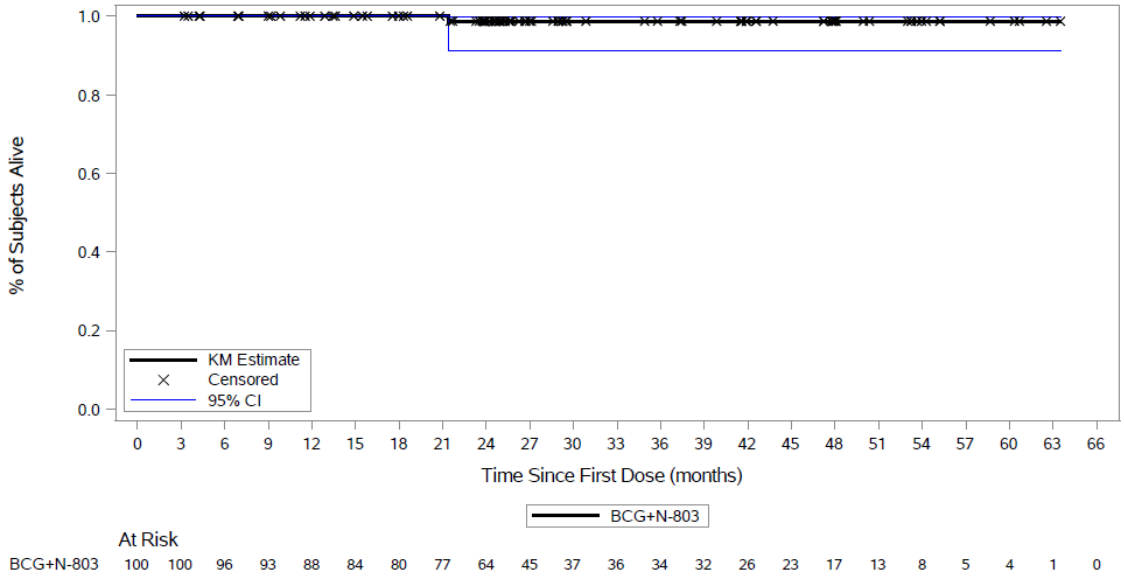
Variable Category	Responders (N = 71)	Non-Responders (N = 29)	Cohort A (CIS ± Ta/T1) (N = 100)
Number of Deaths Due to Bladder Cancer	1 (1%)	0	1 (1%)
Median Disease-Specific Survival (DSS) (Months)[a]	NR	NR	NR
95% CI for the Median DSS	NR, NR	NR, NR	NR, NR
DSS Rate at[b]:			
Month 12	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)
Month 15	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)
Month 18	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)
Month 21	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)
Month 24	98.2% (88.2, 99.8)	100.0% (100.0, 100.0)	98.7% (91.1, 99.8)

NR = Kaplan-Meier statistic not reached.

[a] DSS was defined as the time from initial study drug administration to death resulting from bladder cancer. Subjects who were alive or died due to other cause at the end of study were censored at the last known date that subjects were either alive or died due to other cause

[b] DSS rates were estimated using Kaplan-Meier analysis method.

Figure 14 Kaplan-Meier Survival Curve for Disease Specific Survival in QUILT-3.032 (Overall Efficacy Population – Cohort A)



Note: DSS was defined as the time from initial study drug administration to death resulting from bladder cancer. Subjects who were alive or died due to other cause at the end of study were censored at the last known date that subjects were either alive or died due to other cause.

9. Time to Disease Worsening

Time to disease worsening was defined as time from first instillation to a cystectomy, change in therapy (including systemic chemotherapy or radiation therapy), or death due to bladder cancer, whichever occurred first.

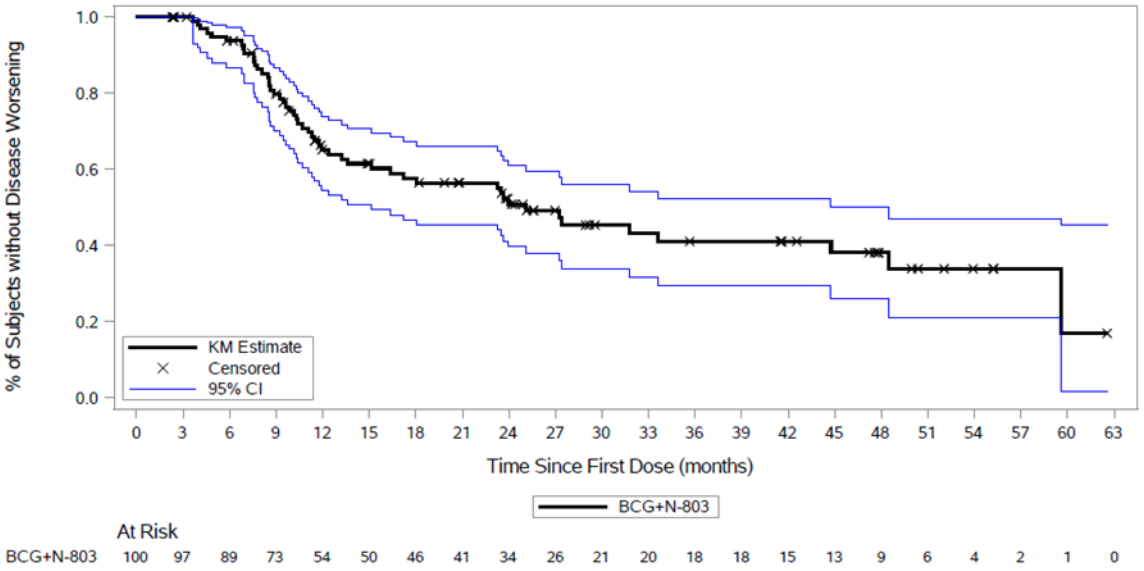
Table 35 Time to disease worsening in QUILT-3.032 (Efficacy Population – Cohort A)

Variable	Responders (N = 71)	Non-Responders (N = 29)	Cohort A (CIS ± Ta/T1) (N = 100)
Subjects With Disease Worsening	29 (41%)	22 (76%)	51 (51%)
Median Time to Disease Worsening (months)[a]	44.8	8.5	25.1
95% CI for the Median Time to Disease Worsening	27.2, NR	7.0, 9.8	15.1, 48.5

NR = Kaplan-Meier statistic not reached.

[a] Time to disease-worsening was defined as the time from initial study drug administration to cystectomy, change in therapy (including systemic chemotherapy or radiation therapy), or death due to bladder cancer, whichever occurred first. Subjects who didn't experience any documented disease worsening events during the study were censored at the last date of follow-up visits

Figure 15 Kaplan-Meier Survival Curve for Time to Disease Worsening in QUILT-3.032 (Overall Efficacy Population – Cohort A)



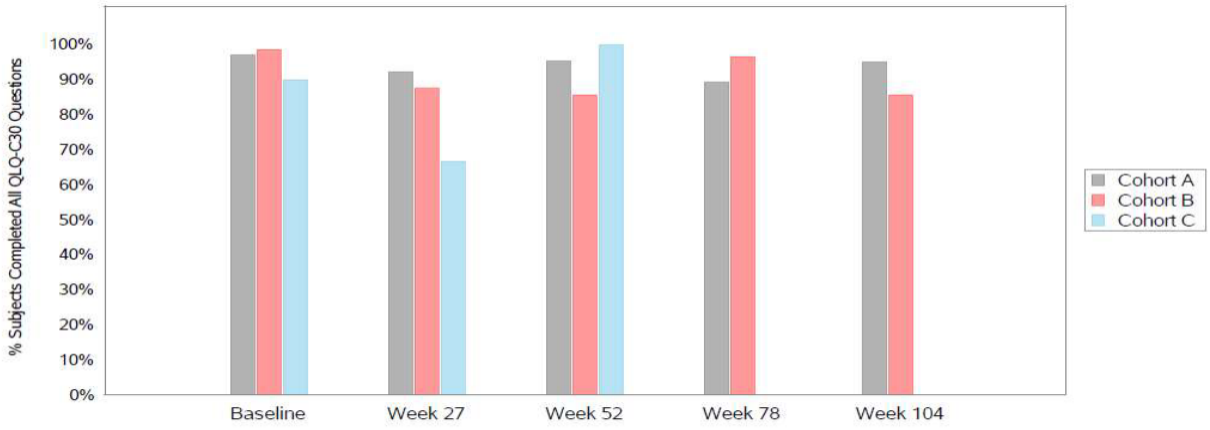
Note: Time to disease-worsening was defined as the time from initial study drug administration to cystectomy, change in therapy (including systemic chemotherapy or radiation therapy), or death due to bladder cancer, whichever occurred first. Subjects who didn't experience any documented disease worsening events during the study were censored at the last date of follow-up visits.

10. Quality of Life (QoL)

QoL was assessed by the EORTC questionnaires for subjects with cancer (QLQ-C30) and for subjects with NMIBC (QLQ-NMIBC24).

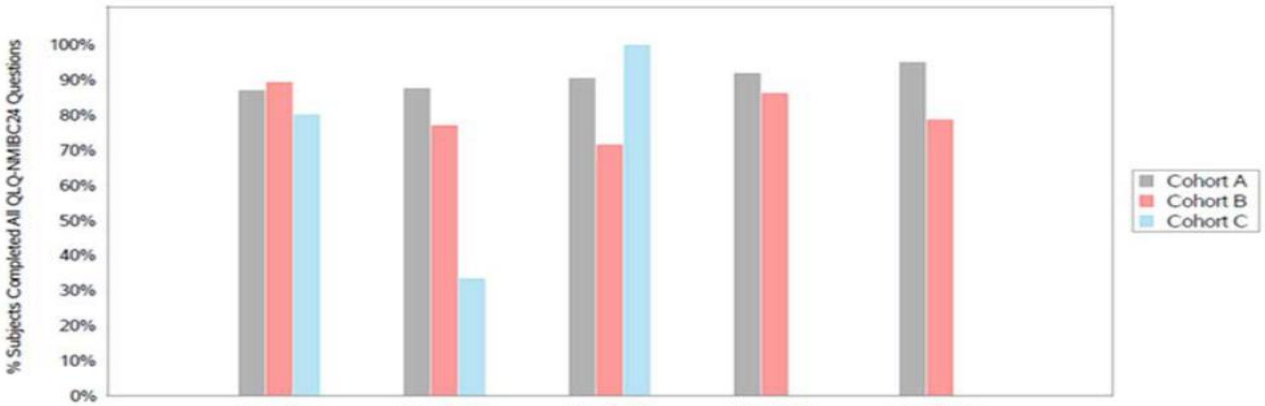
PRO assessments were completed for ongoing subjects by 185 subjects at baseline, 115 at Week 27, 78 subjects at Week 52, 66 at Week 78, and 34 at Week 104 across all cohorts.

Figure 16 Patient Reported Outcome (PRO) Completion Rate by Cohort for Subjects Who Are Expected to Have PRO Assessments and Have Completed All Questions: Efficacy Population; QLQ-C30 Questions



	Baseline	Week 27	Week 52	Week 78	Week 104
Cohort A	97 (97%)	59 (92%)	40 (95%)	33 (89%)	19 (95%)
Cohort B	74 (99%)	42 (88%)	30 (86%)	28 (97%)	12 (86%)
Cohort C	9 (90%)	2 (67%)	1 (100%)	0	0

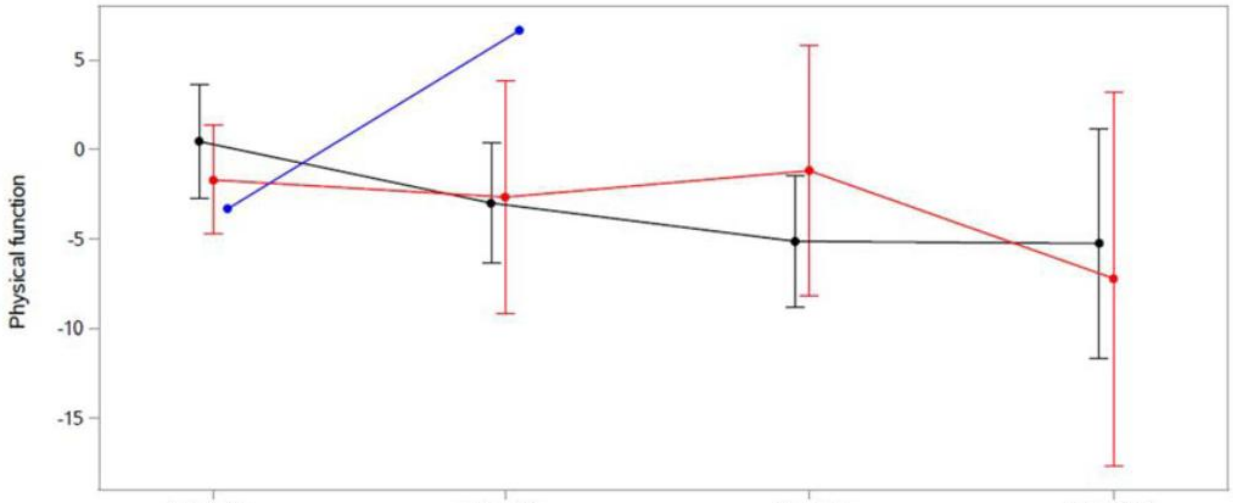
Figure 17 Patient Reported Outcome (PRO) Completion Rate by Cohort for Subject Who Are Expected to Have PRO Assessments and Have Completed All Questions: Efficacy Population; QLQ-NMIBC24 Questions



	Baseline	Week 27	Week 52	Week 78	Week 104
Cohort A	87 (87%)	56 (88%)	38 (90%)	34 (92%)	19 (95%)
Cohort B	67 (89%)	37 (77%)	25 (71%)	25 (86%)	11 (79%)
Cohort C	8 (80%)	1 (33%)	1 (100%)	0	0

Based on the 15 July 2024 data cut-off, in the QLQ C30, the median change in global health status from baseline to week 104 was 0.00 (no change).

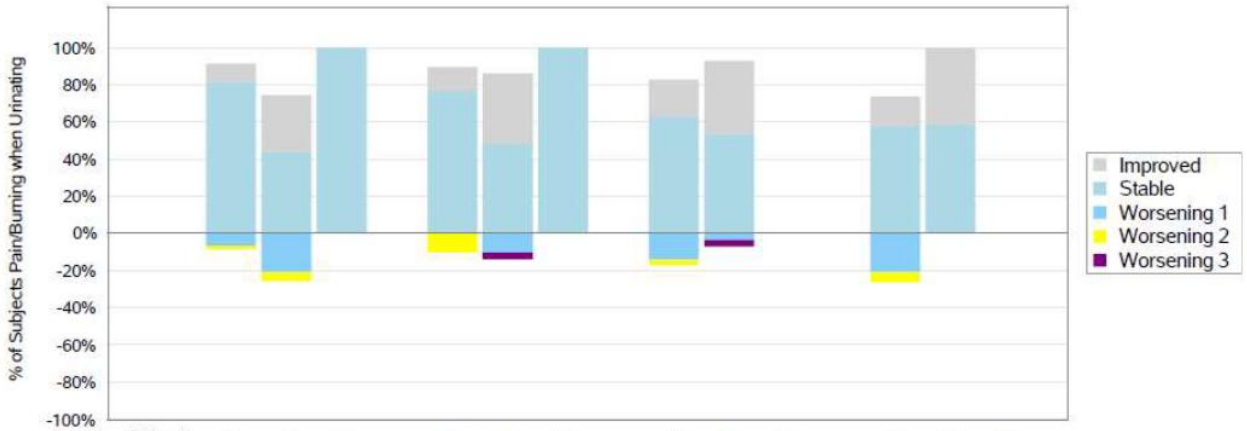
Figure 18 Mean of Change from Baseline (+/- 95% CI) in QLQ-C30 Physical Function Over Time by Cohort for Subjects Who Are Expected to Have Patient Reported Outcome (PRO) Assessments: Efficacy Population



Cohort A	59	40	35	19
Cohort B	43	30	28	12
Cohort C	2	1	0	0

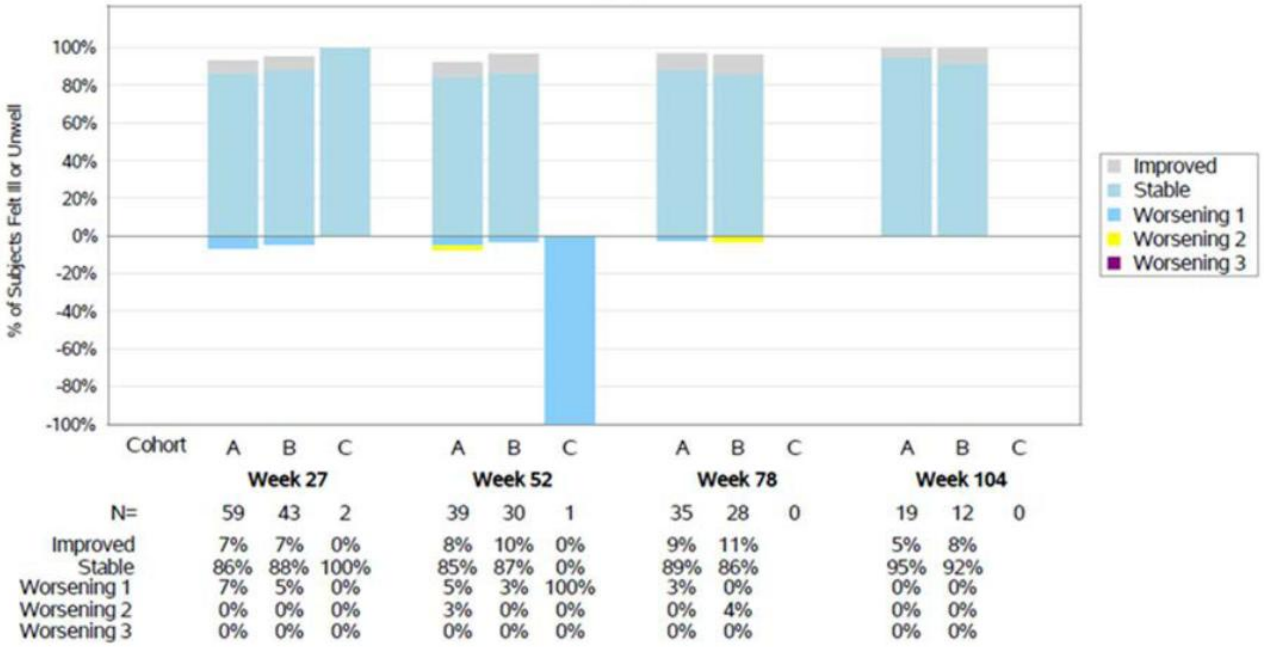
The majority of subjects in all cohorts reported improved or stable physical function within a year after treatment initiation.

Figure 19 Change in Responses from Baseline in Question 37 of QLQ-NMIBC24 by Cohort for Subjects Who Are Expected to Have Patient Reported Outcome (PRO) Assessments: Efficacy Population; % of Subjects Pain/Burning when Urinating



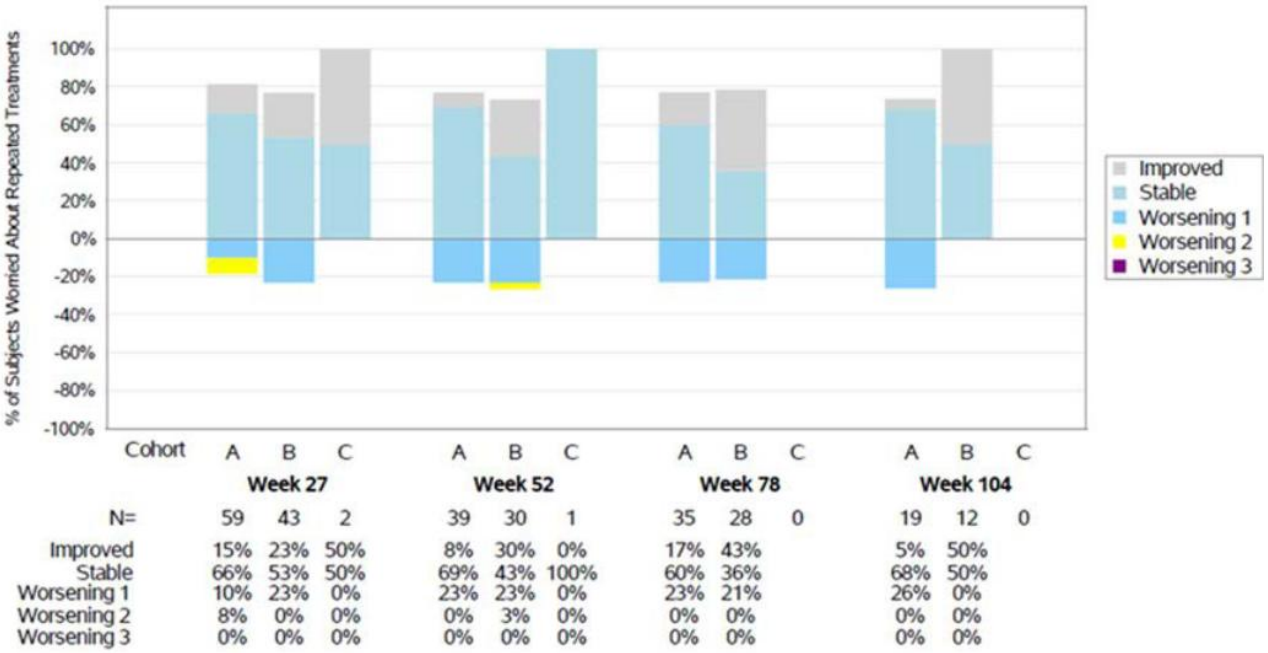
Cohort	A	B	C	A	B	C	A	B	C	A	B	C
	Week 27			**Week 52**			**Week 78**			**Week 104**		
N=	59	43	2	39	29	1	35	28	0	19	12	0
Improved	10%	30%	0%	13%	38%	0%	20%	39%		16%	42%	
Stable	81%	44%	100%	77%	48%	100%	63%	54%		58%	58%	
Worsening 1	7%	21%	0%	0%	10%	0%	14%	4%		21%	0%	
Worsening 2	2%	5%	0%	10%	0%	0%	3%	0%		5%	0%	
Worsening 3	0%	0%	0%	0%	3%	0%	0%	4%		0%	0%	

Figure 20 Change in Responses from Baseline in Question 39 of QLQ-NMIBC24 by Cohort for Subjects Who Are Expected to Have Patient Reported Outcome (PRO) Assessments: Efficacy Population; % of Subjects Felt Ill or Unwell



Cohort	A	B	C	A	B	C	A	B	C	A	B	C
	Week 27			Week 52			Week 78			Week 104		
N=	59	43	2	39	30	1	35	28	0	19	12	0
Improved	7%	7%	0%	8%	10%	0%	9%	11%		5%	8%	
Stable	86%	88%	100%	85%	87%	0%	89%	86%		95%	92%	
Worsening 1	7%	5%	0%	5%	3%	100%	3%	0%		0%	0%	
Worsening 2	0%	0%	0%	3%	0%	0%	0%	4%		0%	0%	
Worsening 3	0%	0%	0%	0%	0%	0%	0%	0%		0%	0%	

Figure 21 Change in Responses from Baseline in Question 41 of QLQ-NMIBC24 by Cohort for Subjects Who Are Expected to Have Patient Reported Outcome (PRO) Assessments: Efficacy Population; % of Subjects Worried About Repeated Treatments



Cohort	A	B	C	A	B	C	A	B	C	A	B	C
	Week 27			Week 52			Week 78			Week 104		
N=	59	43	2	39	30	1	35	28	0	19	12	0
Improved	15%	23%	50%	8%	30%	0%	17%	43%		5%	50%	
Stable	66%	53%	50%	69%	43%	100%	60%	36%		68%	50%	
Worsening 1	10%	23%	0%	23%	23%	0%	23%	21%		26%	0%	
Worsening 2	8%	0%	0%	0%	3%	0%	0%	0%		0%	0%	
Worsening 3	0%	0%	0%	0%	0%	0%	0%	0%		0%	0%	

Healthcare Utilization for Subjects Who Were on Treatment: Safety Population Months 0 Through 24 :

- Hospitalization rate ranges from 0 to 6% from Month 0 to Month 24 in all cohorts. The rate of opioid use is 6-28% from Month 0 to Month 14 and 4-16% from Month 14 to Month 24 in Cohort A and Cohort B; 0- 50% from Month 0 to Month 14 and 0% from Month 14 to Month

24 in Cohort C.

- The rate of opioid use related to bladder cancer is 1-17% from Month 0 to Month 14 and 0-8% from Month 14 to Month 24 in Cohort A and Cohort B; 0-11% from Month 0 to Month 14 and 0% from Month 14 to Month 24 in Cohort C.
- Only one subject in Cohort A received blood transfusion during Month 2-5. The rate of palliative procedures is 0-20% from Month 0 to Month 14 and 0-8% from Month 14 to Month 24 in Cohort A and Cohort B; 0- 100% in 1 subject from Month 0 to Month 14 and 0% from Month 14 to Month 24 in Cohort C.

Exploratory endpoints

1. Incidence of CR at Any Time - Cohort C

Enrolment for Cohort C followed a Simon's two-stage design, to minimize the sample size of cohort C if N-803 monotherapy had low activity. Assuming a clinically meaningful CR rate is 40%, the null hypothesis that the true CR rate was ≤ 40% was to be tested against a one-sided alternative. In the first stage of the Simon's two-stage design, 7 subjects were to be enrolled and evaluated for CR. If ≤ 3 of these subjects had a CR, the null hypothesis could not be rejected, and cohort C was to be closed. Otherwise, 13 subjects were to be enrolled additionally in the second stage.

Complete CR rate at any time for cohort C is presented in Table 36.

Table 36 Complete Response Rate at Any Time in QUILT-3.032 (Efficacy Population – Cohort C)

Variable	Simon's Two-Stage: Conditions to Proceed to Second Stage	Simon's Two-Stage First Stage (N = 7)	Cohort C (CIS ± Ta/T1) (N = 10)
Subjects With Complete Response	4/7 subjects in first stage needed to achieve CR	1 (14%)	2 (20%)

A single subject (1/7) in the first stage of the Simon's two-stage had a transient CR which relapsed by month 6. An IDMC evaluated cohort C results and, based on the protocol-defined stopping rules, recommended closing cohort C to further enrolment.

Thus, Cohort C was closed after enrolment of a total of 10 subjects. In accordance with the protocol, 3 subjects were enrolled (i.e., subjects 8-10) prior to response evaluation of the 7 subjects enrolled in the first stage of the Simon's two-stage based on the date of the IDMC of 18 November 2021. Of the total of 10 subjects enrolled, 2 subjects had a CR.

2. Incidence of CR at Any Time Per Central Pathology Review

Table 37 Complete Response at Any Time per Central Pathology Review in QUILT-3.032 (Efficacy Population – Cohort C)

Variable	Simon's Two-Stage First Stage (N = 7)	Cohort C (CIS +/- Ta/T1) (N = 10)
Subjects With CR	3 (43%)	4 (40%)

Table 38 Biopsy Concordance Between Local Pathology and Central Pathology Review for Complete Response at Any Time in QUILT-3.032 (Efficacy Population – Cohort C)

	Local Pathology Review	Central Pathology Review	CPR Concordance With Local Pathology Review
Responder	2	4	2/2 (100%)
Non-Responder	8	6	6/8 (75%)

Table 39 Overall Biopsy Sample Concordance between Local Pathology and Central Pathology Review in QUILT-3.032 (Efficacy Population – Cohort C)

	Local Pathology Review	Central Pathology Review	CPR Concordance With Local Pathology Review
CIS With or Without Papillary	23	21	21/23 (91%)
High Grade Papillary Only	5	5	4/5 (80%)
Low Grade Only	0	0	0
Negative for Malignancy	3	5	3/3 (100%)
Total	31	31	28/31 (90%)

3. Complete Response by Assessment Visit

A single subject in Cohort C had a CR at the 6-month assessment visit.

Table 40 Complete Response Rate by Visit in QUILT-3.032 (Efficacy Population – Cohort C)

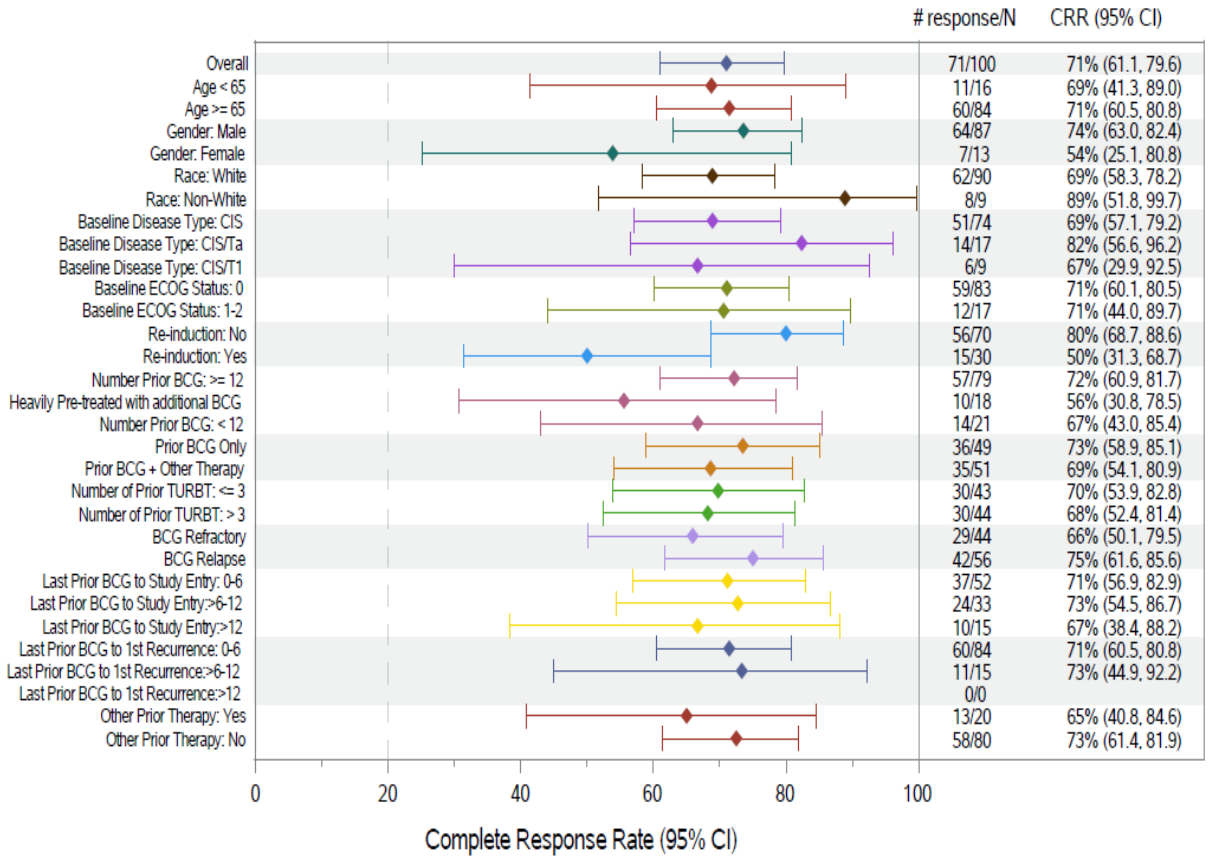
Visit	Simon's Two-Stage First Stage (N = 7)	Cohort C (CIS +/- Ta/T1) (N = 10)
Complete Response Rate at:		
Any Time		
Subjects With CR	1 (14%)	2 (20%)
Month 3		
Subjects With CR	1 (14%)	2 (20%)
Month 6		
Subjects With CR	0	1 (10%)

Pre-defined and post-hoc subgroup analyses

Subgroup Analyses by Predefined Subgroups

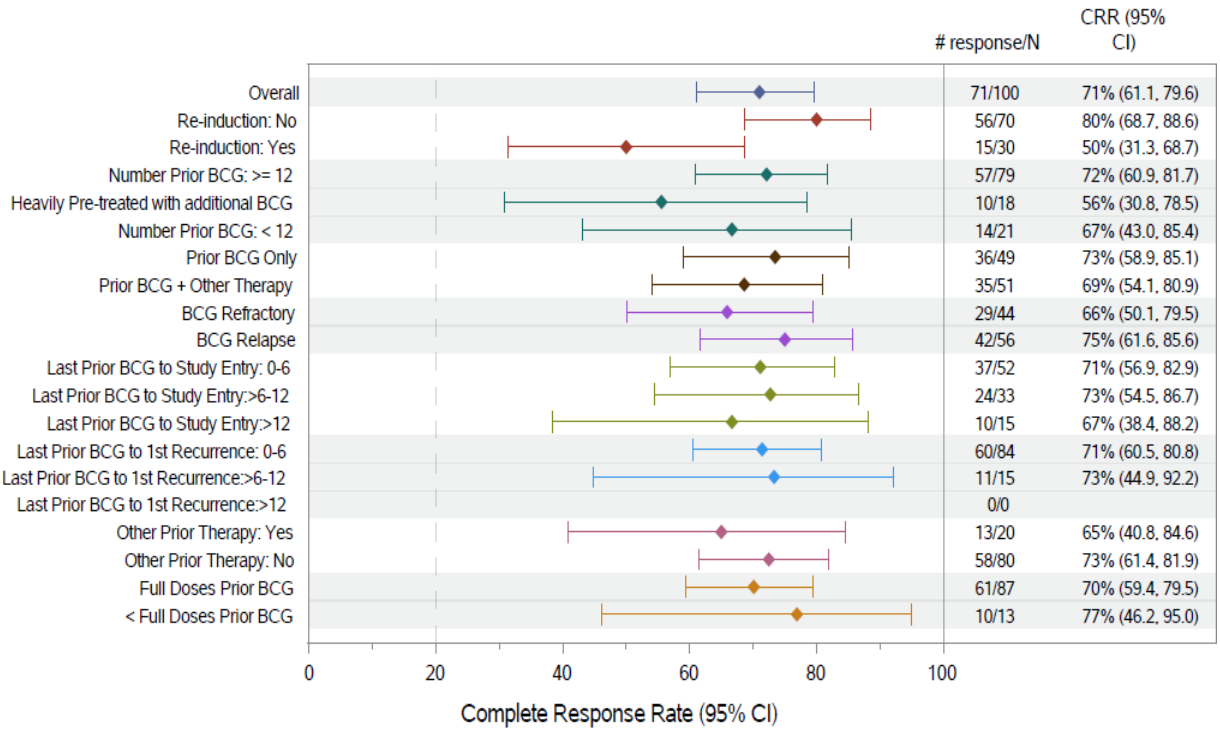
Complete Response Rate at Any Time by Subgroup Efficacy Population - Cohort A

Figure 22 Complete Response Rate at Any Time by Subgroup in QUILT-3.032 (Efficacy Population – Cohort A)



For the primary endpoint to be successful for Cohort A, the lower limit of the 95% CI must have been > 20%, indicated by the vertical dotted line.

Figure 23 Complete Response at Any Time by Subgroup in QUILT-3.032 With Respect to Prior BCG Therapy (Efficacy Population – Cohort A)



Note: Full dose prior BCG according to the AUA/SUO guideline 2016.
For the primary endpoint to be successful for Cohort A, the lower limit of the 95% CI must have been > 20%, indicated by the broken line.

Table 41 Duration of Complete Response by Subgroup Subjects with Complete Response (CR) - Cohort A

Subgroup Category	Subjects With CR	Cohort A (CIS ± Ta/T1) (N =71)
		Median Duration of CR in Months (95% CI)[a]
Overall	71	26.6 (13.0,49.9)
Age Group (yrs)		
<65	11	28.2 (13.0 , NR)
≥65	60	26.6 (9.0, 49.9)
Gender		
Male	64	26.6 (12.0, 45.4)
Female	7	49.9 (3.7, NR)
Race		
White	62	28.2 (13.0, NR)
Non-White	8	9.0 (3.9, NR)
Baseline Disease Type		
CIS	51	20.7 (7.8,45.4)
CIS/Ta	14	NR (7.6, NR)
CIS/T1	6	26.6 (3.9, NR)
Baseline ECOG Status		
0	59	22.1 (9.0, 45.4)
1-2	12	49.9 (4.3, NR)
Subjects With Re-induction?		
No	56	28.7 (20.7, NR)
Yes	15	12.0 (3.9, 21.5)

Subgroup Category	Subjects With CR	Cohort A (CIS ± Ta/T1) (N =71) Median Duration of CR in Months (95% CI)[a]
Number of Prior BCG Doses		
≥12	57	22.1 (12.0, 45.4)
Heavily Pretreated BCG-Unresponsive Subjects Treated with Additional BCG	10	9.9 (3.7, NR)
<12	14	NR (4.3, NR)
Prior Cancer Therapy		
BCG Only	36	42.0 (7.6, NR)
BCG + Other Therapy	35	22.1 (9.9, 49.9)
Number of Prior TURBT		
≤3	30	28.7 (16.1, NR)
>3	30	22.1(7.6, 49.9)
Subclassification of BCG Failure		
Refractory	29	22.1 (7.2, 49.9)
Relapse	42	28.2 (9.9, NR)
Time from Last Prior BCG to Study Entry (months)		
0-6	37	21.5 (7.8, NR)
>6-12	24	28.2 (7.4, NR)
>12	10	49.9 (2.3, NR)
Time from Last Prior BCG to First Recurrence of CIS Disease (months)		
0-6	60	28.2 (14.8, 49.9)
> 6-12	11	12.0 (2.3, NR)
> 12	0	-
Subjects With Other Intravesical or Systemic Therapies (excluding BCG) Between Last Prior BCG and Study Entry		
Yes	13	22.1 (6.0, NR)
No	58	28.7 (9.0, NR)

Note: Dashes indicates durations that had not been reached at the time of data cut-off.

NR = Kaplan-Meier statistic not reached.

[a] Duration of CR was defined as the time from the date of first CR to the date of evidence that the subject no longer met the definition for CR. Responding subjects who were still in response at the end of study were censored at the last known date the subject was having CR. Median duration of CR and the corresponding 95% Confidence Interval (CI) were estimated using Kaplan-Meier analysis method.

Table 42 Subgroup analyses of responses for BCG-Unresponsive/BCG-Refractory and BCG-Unresponsive/BCG-Relapsed Subjects

	Refractory (N = 44)	Relapsed (N = 56)	Cohort A (CIS ± Ta/T1) (N =100)
Complete Response (n)	44	56	100
CR Rate (95% CI)	66% (50.1, 79.5)	75% (61.6, 85.6)	71% (61.1, 79.6)
Median Duration of Follow Up	27.84	25.22	25.68
Range of Follow Up of All Subjects (months)	3.2-63.5	4.3-62.6	3.2-63.5
Median Duration of CR (months) (95% CI)	22.1 (7.2, 49.9)	28.2 (9.9, NR)	26.6 (13.0, 49.9)
Duration of CR[a] (95% CI)			
≥12 Months	65.9% (44.6, 80.7)	62.8% (46.0, 75.7)	63.8% (51.0, 74.1)
≥24 Months	49.8% (27.9, 68.4)	54.5% (37.7, 68.5)	52.3% (39.0, 64.1)

	Refractory (N = 44)	Relapsed (N = 56)	Cohort A (CIS ± Ta/T1) (N =100)
Progression-Free Survival[a] (95% CI)			
12 Months	90.3% (76.1, 96.2)	88.9% (77.0, 94.9)	89.5% (81.4, 94.2)
24 Months	81.3% (64.5, 90.7)	88.9% (77.0, 94.9)	85.7% (76.5, 91.5)
Disease-Specific Progression-Free Survival[a] (95% CI)			
12 Months	95.1% (81.8, 98.8)	92.3% (80.8, 97.0)	93.6% (86.2, 97.1)
24 Months	89.1% (73.3, 95.8)	92.3% (80.8, 97.0)	91. 0% (82.7, 95.4)
Disease-Specific Survival[a] (95% CI)			
12 Months	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)	100.0% (100.0, 100.0)
24 Months	97.1% (81.4, 99.6)	100.0% (100.0, 100.0)	98.7% (91.1, 99.8)
Overall Survival[a] (95% CI)			
12 Months	95.2% (82.1, 98.8)	96.4% (86.5, 99.1)	95. 9% (89.4, 98.4)
24 Months	89.7% (74.7, 96.0)	96. 4% (86.5, 99.1)	93.4% (85.8, 97.0)
Cystectomy-Free[a] (95% CI)			
12 Months	90.0% (75.4, 96.1)	86.9% (74.4, 93.5)	88.2% (79.7, 93.3)
24 Months	81.4% (64.7, 90.7)	84.7% (71.7, 92.1)	83.3% (73.7, 89.6)

NR = Kaplan-Meier statistic not reached.
[a] Based on KM analysis methods.

Table 43 Time to Cystectomy Event by subgroup Efficacy Population - Cohort A

Subgroup Category	Cystectomy n/N	Cohort A (CIS ± Ta/T1) (N =100) Median of Time to Cystectomy Event [a]
Overall	17/100	10.12
Age Group (yrs)		
< 65	1/16	15.11
≥65	16/84	9.97
Gender		
Male	14/87	10.86
Female	3/13	7.39
Race		
White	15/90	10.12
Non-White	2/9	9.04
Baseline Disease Type		
CIS	13/74	10.68
CIS/Ta	3/17	8.57
CIS/T1	1/9	8.44
Baseline ECOG Status		
0	15/83	10.12
1-2	2/17	20.67
Subjects With Re-induction?		
No	8/70	10.40
Yes	9/30	9.82
Number of Prior BCG Doses		
≥12	15/79	10.12
Heavily Pretreated BCG-Unresponsive Subjects Treated With Additional BCG	5/18	7.52
< 12	2/21	10.43

Subgroup Category	Cystectomy n/N	Cohort A (CIS ± Ta/T1) (N =100) Median of Time to Cystectomy Event [a]
Prior Cancer Therapy		
BCG Only	5/49	13.24
BCG + Other Therapy	12/51	9.20
Number of Prior TURBT		
≤3	6/43	10.43
>3	10/44	10.40
Subclassification of BCG Failure		
Refractory	8/44	11.96
Relapse	9/56	8.44
Time From Last Prior BCG to Study Entry (months)		
0-6	6/52	11.96
>6-12	5/33	8.44
>12	6/15	8.82
Time From Last Prior BCG to First Recurrence of CIS Disease (months)		
0-6	13/84	10.12
>6-12	4/15	15.59
>12	0	-
Subjects With Other Intravesical or Systemic Therapies (excluding BCG) Between Last Prior BCG and Study Entry		
Yes	6/20	7.98
No	11/80	10.68

Pre-defined and post-hoc sensitivity analyses

Sensitivity Analyses

Results of 3 sensitivity analyses of CR at any time in subjects in Cohort A, and comparison to the results for the efficacy population are presented in the table below.

Table 44 Sensitivity analyses (Cohort A)

	Overall Efficacy Population	Subjects With Upper Tract or Prostatic Urethra Disease Following Initial NMIBC Complete Response	Subjects Considered to Have Non-CR If They Had Persistent Malignant Cytology And Negative Bladder Biopsy But Absence of Documentation for Upper Tract Disease	Including Cohort B Subjects With Papillary and CIS Disease Who Were Determined Not to Have Met the Eligibility Requirement of Cohort A in Terms of BCG Dosage or Timing of Positive Biopsy	Change in Primary or Secondary Endpoint Outcome
Complete Response at Any Time					
CR rate at Any Time	71%	71%	67%	70%	Comparable
(95% CI)	(61.1, 79.6)	(61.1, 79.6)	(56.9, 76.1)	(59.8, 78.1)	
Subjects	71/100 subjects	71/100 subjects	67/100 subjects	73/105 subjects	
In-text results	Section 11.1.1.1	Section 11.3.1.1	Section 11.3.1.2	Section 11.3.1.3	
Reference	Table 14.2.1a	Table 14.2.1.1a	Table 14.2.1.2a	Table 14.2.1.3a	
Complete Response Rate by Assessment Visit					
CR Rate at Month 6	56%	55%	53%	55%	Comparable
(95% CI)	(45.7, 65.9)	(44.7, 65.0)	(42.8, 63.1)	(45.2, 65.0)	
Subjects	56/100 subjects	55/100 subjects	53/100 subjects	58/105 subjects	
CR Rate at Month 12	47%	46%	46%	45%	
(95% CI)	(36.9, 57.2)	(36.0, 56.3)	(36.0, 56.3)	(35.0, 54.8)	
Subjects	47/100 subjects	46/100 subjects	46/100 subjects	47/105 subjects	
CR Rate at Month 24	30%	30%	30%	29%	
(95% CI)	(21.2, 40.0)	(21.2, 40.0)	(21.2, 40.0)	(20.2, 38.2)	
Subjects	30/100 subjects	30/100 subjects	30/100 subjects	30/105 subjects	
CR Rate at Month 36	16%	-	-	-	
(95% CI)	(9.4, 24.7)	-	-	-	
Subjects	16/100 subjects	-	-	-	
Reference	Table 14.2.2.2a	Table 14.2.2.2.2a	Table 14.2.2.2.3a	Table 14.2.2.2.4a	
Duration of Complete Response[a]					
Duration of CR ≥6 Months (95% CI)	83% (71.6, 90.7)	-	-	-	Comparable
Duration of CR ≥12 Months (95% CI)	60% (47.0, 71.5)	58% (45.5, 70.2)	63% (50.4, 75.3)	58% (45.5, 69.8)	
Duration of CR ≥18 Months (95% CI)	50% (37.4, 62.6)	-	-	-	
Duration of CR ≥24 Months (95% CI)	33% (22.0, 46.3)	-	-	-	
Duration of CR ≥30 Months (95% CI)	26% (15.5, 38.5)	-	-	-	
Duration of CR ≥36 Months (95% CI)	25% (14.5, 37.3)	-	-	-	
Duration of CR ≥46 Months (95% CI)	21% (11.2, 33.4)	-	-	-	
Reference	Table 14.2.2.1a	Table 14.2.2.1.2a	Table 14.2.2.1.3a	Table 14.2.2.1.4a	
Progression-Free Survival					
PFS at Month 12	89.5%	NAP	NAP	*PFS for this sensitivity analysis was not assessed in Cohort B.*	Comparable
(95% CI)	(81.4, 94.2)				
PFS at Month 24	85.7%				
(95% CI)	(76.5, 91.5)				
Reference	Table 14.2.3.4a				

[a] Subjects with ongoing CR who have not reached the duration of CR interval are excluded.

[b] PFS is not impacted by this sensitivity analysis.

5.3.3. Clinical studies in special populations

No clinical studies in special populations were performed. In the pivotal study QUILT-3.032, the majority of the patients in Cohort A (84%) and all 10 patients in Cohort C were over 65 years of age and 40% were 75 years and older. Thus, the data in QUILT-3.032 represents mainly the results in elderly population. The subgroup analyses show consistent results for the primary endpoint CRR and secondary endpoint DoR across the two age subgroups, i.e., below and over 65 years of age.

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive study

QUILT-205

QUILT-205 is a long-term follow-up study of the subjects who participated in QUILT-2.005 Phase 1b.

QUILT-2.005 Phase 1b, was a dose finding study in NMIBC BCG-naïve subjects. The results of this study determined the N-803 dose for the subsequent NMIBC studies (N-803 at 400 µg intravesically). Since QUILT-2.005 Phase 1b was conducted in BCG-naïve subjects, the efficacy dose-response data from this study are only included in the evaluation of dose-response and dose selection in this summary. The data from its long-term follow-up study (QUILT-205) are included as supportive evidence of persistence of efficacy.

In QUILT-2.005 Phase 1b dose-expansion, totally 9 high-risk BCG-naïve NMIBC subjects were treated with 50 mg BCG plus 100 µg (n = 3), 200 µg (n = 3), or 400 µg (n = 3) N-803 administered via a urinary catheter into the bladder. In 9 out of 9 subjects (100%) a complete remission in CIS disease and lack of recurrence in papillary disease was observed by six months, response that was maintained through 24 months until the end of the study phase 1b part. Of these, six (6) subjects consented to be enrolled for further follow-up in QUILT-205 study.

Of the three patients not included in QUILT-205 study one (1) subject was lost to follow-up and two (2) subjects were deceased from causes other than bladder cancer at the time of the initiation of this follow-up study.

Of the six patients further enrolled. The cut-off for analysis for survival and bladder preservation at 15 July 2024 showed:

- At the last date of follow-up, 100% initial and prolonged complete remission in both CIS and papillary naïve NMIBC.
- A prolonged duration of complete remission and survival, with a range of 2.6 to 9.2 years to date and ongoing.
- The mean and median duration of survival is 9.1 years, and the median duration of survival is 9.0 years with subjects still ongoing remission to date up to 9.2 years.
- All 6/6 (100%) of subjects avoided cystectomy from initiation of treatment with N 803 plus BCG in the naïve setting for at least 8.6 years to date.
- One of the subjects with an ongoing 9.7-year survival had multiple other cancers occurring prior to the onset of bladder cancer including breast cancer and thyroid cancer.

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

Not applicable.

5.3.7. Patient’s organisations engagement

The CHMP engaged in early dialogue with patient organisations regarding the relevant aspects of the

acceptability of the current standard treatments, quality of life considerations, unmet medical needs and the level of benefit that would be expected for new medicines in relation to side-effects that would be considered acceptable.

The responses, which are summarised below, have been received from two patient's organisation:

Fighting Bladder Cancer

The current standard of care for patients who have not responded to BCG is usually radical cystectomy (RC), which comes with long-term quality of life implications and is not a viable option for those with comorbidities. For patients in this situation there is a large regional variation in bladder preserving procedures, consisting mostly in intravesical chemotherapies. This reflects the high unmet medical need.

While this sub-group of patients is desperate for more bladder preserving options, one key consideration is that a treatment that is an alternative to RC should have a high enough efficacy rate to balance the risk with opting to delay an RC and therefore the risk of further cancer spread.

World Bladder Cancer

Patients who do not proceed with RC face considerable variation in alternative therapeutic approaches, including repeated courses of BCG, alternative intravesical chemotherapy (e.g., hyperthermic mitomycin), or surveillance through regular cystoscopies, biopsies, and imaging. This inconsistency across treatment centres further highlights the unmet need for standardised, effective, and accessible bladder-sparing treatments. There is a lack of clinical trials for patients with CIS/BCG-unresponsive NMIBC in Europe.

Patients with BCG-unresponsive NMIBC urgently require effective bladder-sparing treatments with similar or better side-effect profile to existing alternatives to RC. Desired outcomes would include superior efficacy in preventing recurrence and progression compared to BCG therapy and on the other hand, manageable side effects allowing normal daily activities. Addressing these unmet needs would significantly enhance patient outcomes, adherence and maintain better quality of life.

5.3.8. Healthcare professional engagement

The CHMP engaged in early dialogue with healthcare professionals.

Key messages of the response received from the European Organisation for Research and Treatment of Cancer (EORTC) relating to Anktiva:

- RC remains the most effective treatment for BCG-unresponsive NMIBC, offering the highest oncological control. However, its invasive nature, associated morbidity, and significant impact on quality of life make it unsuitable for many patients, especially the elderly or those with comorbidities.
- Key objectives for novel treatments:
    1. Bladder-preserving alternatives are required for patients who cannot undergo or decline RC. These therapies must provide durable oncological control while improving quality of life and improve survival outcomes that are at least non-inferior to RC.
    2. Optimize safety, tolerability, and ease of administration to reduce patient burden.
    3. Integrate predictive biomarkers to personalize therapy and enhance treatment

effectiveness.

- Future directions: Advances in innovative intravesical agents, sustained-release therapies, and cost-effective, widely accessible options are essential. A patient-centred approach, balancing oncological outcomes with quality of life, will be important for transforming the treatment landscape of BCG-unresponsive NMIBC with CIS.

In conclusion, the EORTC highlighted that although the clinical standard of care for the BCG-unresponsive high-risk NMIBC is radical cystectomy, considering the subgroup of elderly patients, patients with comorbidities, or for the patients who decline the procedure there is an unmet medical need for effective, bladder-preserving alternatives that can provide durable oncological control while maintaining quality of life.

5.3.9. Overall discussion and conclusions on clinical efficacy

5.3.9.1. Discussion

The Applicant applied for the following indication: *Anktiva in combination with Bacillus Calmette-Guérin (BCG) is indicated for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.*

Design of the pivotal clinical study QUILT-3.032

Study QUILT-3.032 is a phase 2/3, open-label, single-arm, three-cohort, multicenter US-based study of intravesical N-803 plus BCG (cohort A and B) or N-803 monotherapy (cohort C) in subjects with BCG-unresponsive high-grade NMIBC. The trial is ongoing.

From 31 July 2017 (first subject enrolled) to 15 July 2024 (data cutoff), a total of 190 subjects were enrolled. The study was conducted in the US only, at 22 clinical sites.

For the current application the efficacy assessment is focused on the results from Cohort A and C of the study. This included patients with histologically confirmed presence of BCG-unresponsive NMIBC CIS (with or without Ta/T1 papillary disease). Cohort C was added during the conduct of the study to provide support for the assessment of the contribution of each component in the combination (N=10). These data are considered exploratory.

This study was designed and conducted in the US in interaction with the FDA, at a time when the FDA was developing the *Guidance for Industry: BCG-Unresponsive Non-muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment*. No EMA Scientific Advice has been given during the clinical development of N-803.

An additional part of the clinical development program is QUILT-2.005, an ongoing phase 2b, randomised open-label study comparing intravesical BCG in combination with N-803 versus BCG alone in BCG-naïve NMIBC patients. The efficacy data are blinded since both cohorts are ongoing and no results are presented in the dossier. Although conducted in a different patient population (i.e., BCG-naïve NMIBC patient), results from this trial are expected to further inform the contribution of N-803 to the overall efficacy of the combination. In addition, the randomised design is expected to further support a more robust assessment of efficacy while providing a larger and comparative safety dataset in a related disease setting. Data for the ongoing QUILT-2.005 Phase 2b study will be provided upon completion, estimated by June 2027. Preliminary data from this ongoing phase 2b trial has been provided during this procedure. Although the preliminary efficacy data seem promising for the combinational arm, no conclusions can currently be drawn. The Applicant has committed to provide the

final CSR of QUILT-2.005 as a Specific Obligation (**SOB**) in the context of a Conditional Marketing Authorization (CMA), with a due date of 30 June 2027.

Study population

The target population (Cohort A and C) consists, according to the eligibility criteria, of patients with high-risk BCG-unresponsive NMIBC CIS+/- papillary disease Ta/T1. BCG-unresponsive high-risk NMIBC CIS was defined as persistent or recurrent CIS alone or with Ta/T1 disease within 12 months of completion of adequate BCG therapy. This is adequately reflected in section 5.1 of the SmPC.

According to European Association of Urology (EAU) guidance, "BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure or develop CIS within 12 months of completion of adequate BCG exposure." Hence the definition of BCG-unresponsive NMIBC CIS+/- papillary disease Ta/T1 as per inclusion criteria in study QUILT-3.032 aligns with the EUA GL updated April 2024 criteria.

According to the EAU Guidelines, patients with BCG-unresponsive NMIBC are unlikely to respond to further BCG therapy and radical cystectomy (RC) is therefore the standard and preferred option. However, the invasive nature of RC, coupled with its significant morbidity and quality-of-life implications, makes this approach not feasible for many patients. This includes elderly patients, those with significant comorbidities, or those who decline the procedure due to personal preference. Consequently, there is a recognised unmet medical need for effective, bladder-preserving alternatives that can provide durable oncological control while maintaining quality of life. In the EU, there are currently no medicinal products authorised for use in patients with BCG-unresponsive NMIBC.

Inclusion of patients with BCG-unresponsive NMIBC was allowed without restrictions concerning fitness for cystectomy. All patients enrolled had an indication for RC. The study subjects were informed of the risks of delaying RC as part of the informed consent.

The applicant clarified that the reasons for participants not proceeding with RC were not systematically collected on QUILT-3.032.

Prior to treatment, all patients with Ta or T1 disease had undergone transurethral resection of bladder tumour (TURBT) to remove all resectable disease. Residual CIS not amenable to complete resection, fulguration, or cauterization was permitted. This has been adequately reflected in section 5.1 of the SmPC.

Due to the risk of systemic infections, BCG is contraindicated in patients who are immunocompromised, including those receiving immunosuppressive treatment or by immunosuppressive disease, as reflected in the EU SmPCs. Further, it is noted that patients receiving corticosteroid treatment were excluded from the clinical trials with N-803, due to potential, negative effects on the immunostimulating activity of N-803. This limitation is adequately reflected in section 5.1 of the SmPC. There was no signal of reduced efficacy in the limited number of patients exposed to corticosteroids during the study.

Study treatment

The dose of N-803 used in Study QUILT-3.302 was 400 µg N-803 per instillation in combination with BCG 50 mg administrated intravesical. The dose was selected in QUILT-2.005 phase 1b dose-escalation study.

The dosage and instillation regimen with N-803 400 µg and BCG 50 mg was used throughout the study cohorts A and C and is adequately described in the SmPC sections 4.2 and 5.1.

In study QUILT-3.032, TICE-BCG has been used as the only BCG product approved in the US, while in the EU multiple BCG strains are available. To support extrapolation, the applicant referred to the EUA

2024 guideline, a 2023 meta-analysis (Del Giudice 2023) and peer-reviewed analyses (Mangtani 2014) which did not identify clear efficacy differences between BCG strains. This justification is accepted.

The regimen consists of an induction therapy with N-803 administered intravesically with BCG once a week for 6 weeks. A second induction (re-induction) course was to be administered if CR was not achieved at month 3.

For patients with no or low-grade disease at the end of month 3, maintenance therapy was following induction therapy once a week for 3 weeks at months 4, 7, 10, 13 and 19 (for a total of 15 doses).

For patients with an ongoing complete response at month 25 and later, maintenance instillations could be administered once a week for 3 weeks at months 25, 31, and 37 for a maximum of 9 additional instillations. Per protocol the maintenance therapy from the month 7 and onwards could consist of N-803 plus BCG or N-803 monotherapy by investigator.

According to the protocol, maintenance therapy could consist of N-803 in combination with BCG or N-803 alone in cases of intolerance to BCG, as determined by the investigator.

The recommended treatment duration (maintenance) was amended twice from originally 12 months. Duration of maintenance therapy was extended to 18 months in protocol version 3 (2018). A fourth treatment period was added for subjects with no or low-grade disease at month 24, 30 and 36 (per PI discretion) as late as in 2020 (protocol version 7). Data on exposure to N-803 in study participants show that a small minority received study treatment for 36 months, and more than half of the participants with maintenance therapy received N-803 for 12 months or shorter.

The recommended duration of treatment is reflected in section 4.2 of the SmPC and is in accordance with the study protocol, e.g. until disease persistence after second induction (re-induction), disease recurrence or progression, unacceptable toxicity, or a maximum of 37 months.

Study assessment

Response assessments were completed every 3 months through month 24, and then every 6 months through month 60. Assessment for ongoing response beyond month 24 was per local community standards. After treatment discontinuation, subjects were to be followed for disease progression, post-treatment therapies, quality of life and survival through month 60. The total study duration was expanded from 2 years to 5 years through protocol amendment in 2020 (protocol version 7).

Biopsies collected at screening, week 12 and at 6 months were also sent for CPR, however the local pathology review forms the basis for the decisions at baseline and at response assessments. Pathology per CPR (including baseline diagnosis, CR and duration of CR) endpoints were added during study conduct (version 6, 2019).

It is stated in the Clinical Overview that "*Participants with (a) negative cystoscopy and negative (including atypical) urine cytology, also had random biopsies of 5 areas of the bladder (the trigone, dome, right and left lateral wall, and posterior wall) to confirm CR even when no visible disease was seen*. Random biopsies should be performed at 3 and/or 6 months (re-inducted). Random biopsies were not required to confirm CR later than 6 months on study.

Study objectives

The CR rate (defined as negative cystoscopy and negative urine cytology, including atypical urine cytology or positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology) is the recommended primary endpoint per FDA guidance for single-arm trials in patients with BCG-unresponsive NMIBC with CIS.

The algorithm to determine the CR rate was based on the combination of the results of the cystoscopy by the investigator, biopsy by the local pathology review and cytology by local pathology review and follows the FDA guidance for intravesical therapies. Per study protocol, besides the two core CR criteria (see above) two additional CR criteria recommended for the intravesical therapies according to the FDA guidance were added:

(a) CR considered when negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and mandatory templated bladder biopsies are negative, and (b) CR considered when at visit a negative cystoscopy with one or more consecutive missing, suspicious, or malignant urine cytologies were found and the subsequent urine cytology is negative or atypical with normal cystoscopy, or negative biopsy if cystoscopy is suspicious or abnormal. Addition of the last two criteria were justified in the FDA guidance by the limited systemic absorption of the intravesical therapies that does not deliver the investigational drug to the upper tract or prostatic urethra.

The CR definition is reflected in section 5.1 of the SmPC and is appropriately informative.

The criteria for discontinuing Anktiva/BCG and for switching to cystectomy as defined in the study protocol are highlighted in section 4.2 of the SmPC.

The study design and hypothesis are considered adequate to characterize the antitumoral activity of Anktiva given in combination with BCG in the BCG unresponsive nonmuscle invasive bladder cancer.

Estimands and Statistical Plan

The population for the estimand for the primary objective was all patients with BCG-unresponsive NMIBC. They were to be assigned treatment to N-803 in combination with BCG or N-803 alone and assessed as such regardless of discontinuation. The primary variable was CR of CIS at any time. Intercurrent events such as treatment discontinuation were to be handled by a treatment policy strategy.

The population for the estimand for the secondary objective was the subset of the BCG-unresponsive NMIBC patients who achieved a CR. They were to be assigned treatment to N-803 in combination with BCG or N-803 monotherapy and assessed as such regardless of discontinuation. The variable of interest was duration of complete response (DoR) which was to be analyzed by Kaplan-Meier methods and the median presented with a 95% confidence interval. Intercurrent events, including end of study, discontinuation of study treatment or death after two or more missing assessments, new upper tract or prostatic urethra lesions, and receipt of certain concomitant medications or procedures, were to be handled by a hypothetical strategy and patients censored at the last non-missing response assessment or when receiving concomitant medication or treatment.

Cohort C was added in an amendment in 2019 and the Simon two-stage design for Cohort C was introduced in another amendment in 2021.

The sample size for Cohort A was initially 80 but increased to 100 in an amendment in 2020. Interim results from the first 81 subjects in Cohort A and 6 subjects in Cohort C has been produced and published although no interim analysis was described in the protocol.

In an open label, single-arm trial, any changes to the design must be considered potentially data-driven and analysis based on the original statistical plan could be informative. In this case, an analysis conducted approximately at the originally planned sample size has already been provided, as this coincided with the unplanned interim analysis described above. Therefore, no further concerns are raised in this regard.

The data cutoff date for this application was 15 July 2024. The final analysis for each cohort was to be conducted once all enrolled patients in a cohort had completed the study. Cohorts A, B and C are

independent study cohorts and were evaluated separately for efficacy. The primary efficacy population and the safety population both included all enrolled subjects (n=100 in cohort A).

Subjects who died after 2 or more consecutive missing response assessments were censored at the date of last non-missing response assessment. There were only two such cases and a sensitivity analysis where those cases were considered an event showed consistent results with the primary analysis.

Furthermore, the study medical team were to review all concomitant medications and procedures data and determine if subjects should be censored at the time of receiving these treatments. The applicant provided a duration of CR sensitivity analysis where the potentially informative censoring of patients for treatment discontinuation (n=1), withdrawal by subject (n=2), death after two or more missing assessments (n=2), and subject received certain concomitant medication (n=1), were instead counted as events (loss of CR) at the time the patients are currently censored. The median duration of CR in this sensitivity analysis was 20.7 months, compared to 26.6 months in the original analysis. This is a "worst case" analysis and does not cause any concern.

Sensitivity analyses for CR rates, PFS and DoR were to include analyses testing different definitions of disease, baseline disease type, regardless of assigned cohort.

All analyses were conducted without adjustments for multiple testing. Hence, no type I error control has been implemented for secondary endpoints.

The conclusion on efficacy based on those statistical analyses relies heavily on two assumptions. First, that a CR as defined in this study is an indication of a treatment effect (and not an inaccurate ascertainment of a CR, i.e., a "false positive"), and secondly, that this treatment effect can be attributed to the Anktiva component of the combination treatment. Both of these aspects are discussed further below.

Change in the conduct of the study

Totally, 10 protocol amendments to the original protocol (dated 27 December 2016) were implemented throughout the course of the study resulting in 11 protocol versions. The last protocol version, Version 11, was approved prior to the data cutoff date of 15 July 2024. Protocol amendments (v2, v5, v6 and v7) that have resulted in changes in study size of the overall study were introduces following FDA recommendations. The most important protocol amendment that concerns the Cohort A was introduced with protocol version 7 (23 Nov 2020) in which the size of the target population (Cohort A) was increased to allow evaluation of the response, also following FDA recommendation. The Applicant explained that these changes were implemented based on a request by the FDA and were aimed to align the study objectives with the FDA's 2018 guidance. This is acknowledged.

The applicant clarified what data have been shared with the FDA during the study, the corresponding protocol versions in effect and the number of patients from whom data were available at the unplanned interim analysis presented to the FDA initially. The overview of the data shared and the reasons for the protocol amendments do not give rise to any concerns regarding the conduct of the study or data quality.

It is understood from the CSR and SAPs that protocol amendments and changes in the SAP were performed in consultation with the FDA. Corresponding meeting minutes are included in the dossier. The major protocol deviations were clearly defined and described. The major protocol deviations were handled appropriately and are not considered to impact the efficacy analyses.

The efficacy analysis was performed on the overall population of subjects with BCG-unresponsive CIS+/-Ta/T1 enrolled in Cohort A (n=100) and Cohort C (n=10). Until the time of data cut-off 15 July 2024, the treatment was completed for 90% of the Cohort A subjects and 100% of subjects in Cohort

C. The median duration of follow-up for subjects was 25.68 months in cohort A, and 35.78 months in cohort C.

Demographic characteristics were similar across cohort A and C and are considered representative for BCG-unresponsive NMIBC (CIS, CIS+/-Ta/T1) subjects.

Results

In Cohorts A, the diagnosis at study entry was CIS without Ta/T1 papillary disease (74%), CIS with Ta papillary disease (17%) or CIS with T1 +/- Ta papillary disease (9%). Baseline high-risk NMIBC disease status was 44% refractory and 56% relapsed.

The study population has relatively high comorbidity as expected based on age and the known cardiovascular risk associated with smoking. Smoking status in QUILT 3.032 was not collected. A statement has been included in section 5.1 of the SmPC: "Smoking status was not collected in QUILT-3.032.".

In Cohort C the diagnosis at study entry was CIS without Ta/T1 papillary disease (80%) and CIS with Ta papillary disease (20%). The median number of prior BCG doses received was 12 doses before study entry. For the subjects in Cohort A and C the median time after the last dose of BCG to study entry was of approximately 6 months.

The primary endpoint, CR rate at any time in Cohort A, was 71% (95% CI: 61.1, 79.6) which is considered sufficiently compelling to suggest that the combination of N-803 and BCG has antitumor activity in the context of BCG-unresponsive NMIBC. This CR rate exceeded the lower bound of the 95% CI of 20%, which was the prespecified success criterion. Given prior BCG-unresponsiveness and the results of Cohort C, the contribution of N-803 to the observed efficacy is not considered questionable.

The methodology for CR assessment established through the original protocol was redefined through protocol amendments under 2018 to ensure intra-patient comparability. Hence, besides the cystoscopy performed with the same method as for enrolment throughout the study curse for each patient, bladder biopsy was required to confirm CIS diagnosis for enrolment into Cohort A, as well to assess tumour response at Month 3 and at Month 6.

In addition, bladder biopsies were required in case of any suspicious lesion at cystoscopy, and in absence of this, random biopsies from 5 bladder regions (trigone, dome, right and left lateral wall, and posterior wall) as well as from prostatic urethra and upper tract evaluation in case of positive or suspicious urine cytology were to be performed.

However, reliability in the interpretation of cystoscopy, biopsy and cytopathology results and consequently in attribution of CR is considered uncertain. For the CR assessment, the pathology and cytology were assessed by the local reviewer and were further confirmed by an independent blinded central reviewer.

The concordance analyses between the local and central reviewer, partially answered the issue of CRR reliability, since the central pathology review (CPR) response assessment biopsies were not required in some of the protocol versions and thus the CPR was not available for all patients.

The results for CRR at any time in 94 evaluable patients for CPR were comparable to the CRR evaluated by local pathology reviewer, (74% vs 77%) with high concordance rate (95%). Overall, biopsy sample concordance between local pathology and CPR was 83% (243/294 biopsy samples), and the baseline biopsy concordance was 77% of subjects (72/94 subjects). The discordance rates were within range of what was reported in the literature (10-35%). For urine cytopathology the overall concordance rate between local pathology and central pathology was 86%.

Uncertainty regarding the sensitivity and specificity of the cystoscopy, biopsy and cytology for confirming true CR in the absence of cystectomy/cysto-urethrectomy/ cysto-prostatectomy as a reference standard limits the interpretability of the efficacy results. The variability of these diagnostic methods, influenced by local practice standards and individual urologist expertise, is well recognised in clinical practice and may lead to inaccurate ascertainment of CR ("false positive"). This uncertainty is intrinsically linked to the risk of progression to muscle-invasive or metastatic disease when cystectomy is delayed. Accordingly, this risk is reflected in section 4.4 of the SmPC with a warning highlighting the study data on this matter.

Of the 100 evaluable patients with BCG-unresponsive NMIBC with CIS, with or without papillary tumours, treated with Anktiva in combination with BCG in QUILT-3.032, 10% (n=10; 95% CI 4.9–17.6) progressed to muscle-invasive bladder cancer (T2 or greater), including two cases occurring during the treatment period. Among these 10 patients, 3 had achieved a CR before progression (treatment period 16.1–108.0 weeks), while 7 had not achieved a CR (treatment period 5.3–24.1 weeks). Four of these 7 patients without a CR received a second induction (re-induction), and 4 patients had progression determined at the time of cystectomy. The median time between determination of persistent or recurrent CIS and progression to muscle-invasive disease was 224 days (range 0–854). Among all participants in QUILT-3.032, with up to 63.5 months of follow-up, 5% developed metastatic disease by 24 months (none by 12 months). Progression to muscle-invasive or metastatic disease occurred in 5/70 (7%) patients who were not re-inducted and in 5/30 (17%) patients who underwent re-induction.

Notably, the CR rate in patients who underwent reinduction was lower [CR 50% (95% CI: 31.3, 68.7)] and showed a non-overlapping 95% CI compared with patients who did not require re-induction [CR 80% (95% CI: 68.7, 88.6)]. Thus, the subgroup that did not undergo re-induction drives the overall CR rate of 71% (95% CI: 61.1, 79.6) in the overall population. Among the 10 patients who progressed to muscle-invasive or metastatic disease, 5 had received re-induction, of which 3 subsequently underwent cystectomy.

Consequently, the section 4.4 of the SmPC was updated to highlight the risk of progression to muscle-invasive or metastatic disease when cystectomy is delayed with re-induction beyond week 12 in patients who have not achieved a CR. In addition, a recommendation that the cystectomy should be reconsidered as an alternative to re-induction was included.

The median DoR was 26.6 months (95% CI: 13.0, 49.9) in the efficacy population with CR from Cohort A (n=71). Totally 35/71 (49%) were censored of which majority were ongoing in study with follow-up (since 1st CR) 21/71 (30%) or completed the study 8/71 (11%). A small proportion were censored due to discontinuing the study due to AE, or death, withdrawal, or death after 2 or more consecutive missing response assessments. Arguably, the relatively long duration of complete response mitigates, to some extent, concerns about false-positive CR assessments. An updated analysis performed for a data cutoff (DCO) date of 15 January 2025, i.e., with 6 months of additional follow-up showed that the CR rate remains unchanged for the overall efficacy population at 71%, with a DOR of 26.6 months- the 95% CIs are stable. Overall, subgroup analyses remained nearly the same between the two DCO dates.

Among the 71 patients with a CR at any time, a total of 36/71 (51%) patients were no longer in response following CR under the study interval for which the following reasons were reported: Disease recurrence 25/71 (35%), New Anti-Cancer Therapy 6/71 (8%), Death Unrelated to Bladder Cancer 2/71 (3%), Disease progression 2/71 (3%), Cystectomy 1/71 (1%).

The prespecified sensitivity analyses showed similar results with the primary analysis in terms of primary and secondary endpoints (i.e. CR rate by assessment visit and DoR).

Progression-Free Survival and Disease-Specific Progression-Free Survival (DSPFS)

As of the data cut-off (15 July 2024) in Cohort A ITT population (n=100 subjects) 10% of subjects progressed to muscle-invasive disease (stage ≥T2), or lymph node/distant metastases. The median PFS and Disease-Specific Progression-Free Survival (DSPFS) were not reached.

Cystectomy Rate and Time to cystectomy

The cystectomy rate was 17% and the time to cystectomy for the 17 subjects estimated based on KM method was 10.12 (4.1, 31.5) months. According to the subgroup analysis for responders/non-responders, the median time to cystectomy event was 14.18 months for responders who had a cystectomy and 8.11 months for non-responders who had a cystectomy.

Cystectomy was reported for the 11% (8/71) of the responders vs 31% (9/29) of the non-responders. Notably, in terms of cystectomy postponing or avoidance, cystectomy avoidance rate in the overall population was 83% (83/100 subjects). The cystectomy avoidance rate was 89% in responders and 69% in non-responders.

The probability of being cystectomy-free at 12 months was 95.5% for responders and 69.3% for non-responsive subjects based on KM analysis. The probability of being cystectomy-free at 24 months was 90.3% and 64.7%, respectively.

Among responders and non-responders, a total of seven subjects had progression to muscle-invasive or metastatic disease; five in the bladder, one subject had muscle-invasive bladder cancer in the ureter, and one subject had lymph node progression only. In addition, three of the subjects with T2/T3-tumour had progression to lymph nodes.

Pathological staging per cystectomy in the subgroup of responders shows that one participant had muscle invasive cancer (T2) and one had spread to lymph nodes (TaN2). The remaining 6 subjects with initial CR and cystectomy had CIS or Ta/Cis. The time delay between last study treatment and cystectomy ranged from 67 days to 488 days. The time delay was not greater for those subjects who had developed T2/N2 tumour (67 days and 203 days, respectively). Uncertainty remains regarding the time lapse between the CR and the assessment leading up to cystectomy and the numbers of patients with development of muscle-invasive bladder cancer who were under study treatment.

Subjects who underwent re-induction had a higher cystectomy rate (30%=9/30) than those who were not re-inducted (11%=8/70). This is in line with the subgroup analysis of the primary efficacy endpoint, in which the CR at any time was lower (50%) in re-induced participants. In addition, duration of CR was shorter in this subgroup (median 12 months).

Overall Survival

As of the data cut-off for Cohort A (15 July 2024) 10% of the subjects in the ITT population (n=100) had died. The median OS was not reached. At the time of database cutoff, 8 deaths had occurred in responders (11%, 8/71) and 2 in non-responders (7%, 2/29). One death related to bladder cancer was reported. The patient discontinued treatment due to disease recurrence following an initial CR. The biopsy confirmed disease progression to muscle invasive disease (stage ≥ T2). The patient progressed further to metastatic disease, received 3 lines of therapies for advanced/metastatic disease and died of metastatic progressive disease 538 days from the last dose of N-803 plus BCG.

Quality of Life

QoL was assessed using EORTC questionnaires for subjects with cancer (QLQ-C30) and for subjects with NMIBC (QLQ-NMIBC24).

The absence of a comparative arm hamper interpretation of PRO data. Similar aspects are concerning PROs evaluated with disease-specific QLQ-NMIBC24 questionnaire.

Subgroups

In Cohort A, the prespecified subgroup analyses of the primary and main secondary endpoints by the prior therapies, timing to the start of study treatment, as well by the patient- and disease relevant characteristics were comparable between them and with the results in the primary efficacy population which is also the ITT population.

Contribution of the components

Cohort C, including subjects with BCG-unresponsive NMIBC with CIS +/ -Ta/T1 treated with N-803 monotherapy, was introduced in SAP v6 dated 14 Oct 2019, to support the evaluation of the contribution of the components of the combination N-803 + BCG, following FDA recommendations.

Efficacy in Cohort C was limited to two patients achieving CR (20% 2/10 subjects), with only 1/10 (10%) subject maintaining CR at 6 months. Hence the Cohort C was closed after the analysis of efficacy results of the first stage of the Simon's two-stage in cohort C, when only 10 of the 20 planned subjects were included.

The limited activity of N-803 in terms of CR rate at any time of 20% in this clinical setting contrasts the CR rate of 71% observed in Cohort A subjects treated with combination N-803+BCG and supports contribution of the N-803 to the effect of the combination.

Moreover, additional BCG prior to enrolment in QUILT-3.032 in 19 subjects in Cohort A resulted in a transient CR in only 3 (16%) subjects. Eighteen (18) subjects remained for evaluation of the synergistic effect of adding N-803 to BCG. Ten (10) out of 18 (56%) subjects achieved complete response to the combination.

With regard to the BCG component, further treatment with BCG in patients with BCG-unresponsive NMIBC is not justified, as these patients are unlikely to benefit from further therapy with BCG. This is supported by the international guidelines (NCCN Guidelines, AUA/SUO Joint Guidelines, European Association of Urology Guidelines), literature, as well as the data indicating treatment failure in 19 patients with BCG-unresponsive NMIBC exposed to additional BCG treatment prior enrolment in QUILT-3.032 study.

In conclusion, altogether, the data provided so far in the context of a single-arm trial suggest that the antitumor activity of the N-803+BCG combination relay on the synergistic activity of the components.

Comprehensiveness of the data

Due to the limitations in the pivotal study design, including the absence of a randomised comparator arm as well as a limited sample size, the available data are not considered comprehensive to support a full marketing authorisation (see section 1489.6.3.1. . As outlined above, these uncertainties include the risk of inaccurate ascertainment of CR ("false positives"), the challenge in quantifying the potential risk of progression to muscle-invasive or metastatic disease when cystectomy is delayed in eligible patients and the limited follow-up which is not considered sufficient to fully characterise long-term outcomes.

Follow-up measures

Final results from the ongoing QUILT-3.032 study, including five-year follow-up data for all patients, will be submitted as part of a Specific Obligation (SOB) to confirm long-term efficacy and safety. Study completion and submission of final results is expected by 31 December 2029.

5.3.9.2. Conclusions on the clinical efficacy

The available efficacy data, including a CR rate at any time of 71% and a median duration of complete response (DoR) of 26 months, are considered to support a clinically relevant benefit of adding N-803 to BCG in patients with BCG-unresponsive high risk NMIBC. The studied population is at high risk for disease progression to muscle-invasive bladder cancer. In the EU, there are currently no medicinal products authorised for this specific indication, and treatment options are limited for patients who are medically unfit for or unwilling to undergo radical cystectomy, which remains the standard of care.

The antitumor activity of Anktiva in combination with BCG has been demonstrated. However, due to limitations in the pivotal study design, including the absence of a randomised comparator arm as well as the limited sample size, the available data are not considered comprehensive within the meaning of the CMA legislation (see section 9.6.3.1.). These limitations include the risk of inaccurate ascertainment of CR ("false positive"), the challenge in quantifying the potential increased risk of progression to incurable disease by delaying cystectomy in eligible patients and the limited follow-up which is not considered sufficient to fully characterise long-term outcomes.

5.4. Clinical safety

5.4.1. Safety data collection

Safety was assessed by the incidence and severity of treatment emergent AEs (TEAEs), Adverse Events of Special Interest (AESIs,) clinical laboratory tests, changes in vital signs, treatment exposure, concomitant medications, immunogenicity, and physical examinations for all subjects who received at least 1 dose of intravesical study treatment.

In QUILT-3.032 and QUILT-2.005-P1b/2b, all AEs are or were recorded by the investigator from the time the subject received their first dose to 30 days after the last dose of study drug or until the last study treatment visit, whichever was longer.

In QUILT-3.032, samples for haematology and blood chemistry were collected at screening, baseline (i.e., study day 1 prior to treatment), weekly through week 6 of the induction period, week 12 and week 15 of the second treatment period, weeks 27, 40, 52, and 78 of the third treatment period, and weeks 104, 130, and 156 of optional fourth treatment period, if applicable.

In QUILT-2.005-P2b, samples for haematology and blood chemistry were collected at screening, baseline, weekly through week 6 of the induction period, week 12 of the second treatment period, and weeks 27, 52, and 78 of the third treatment period.

5.4.2. Patient exposure

The exposure in the studies (QUILT-3.032 and QUILT-2.005) primarily contributing to the safety dataset in the proposed indication, is described in Table 45 and Table 46.

In addition, data are available for 10 NMIBC subjects receiving intravesical N-803 monotherapy in Study QUILT-3.032.

There is also one study in 20 healthy volunteers (QUILT-1.004), with subcutaneous administration of two consecutive doses of N-803 (10 µg/kg and 20 µg/kg, respectively).

All studies are open-label.

Studies QUILT-3.032 and 2.005-P2b were ongoing at time of the MAA. The data cut-off date is 15 July 2024.

Table 45 Subject Disposition: Safety Population – Study QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

Category	BCG Unresponsive (QUILT-3.032)[b]	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
Safety population, n	**180**	**106**	**98**	**286**
Treatment ongoing, n(%)	14 (8%)	5 (5%)	7 (7%)	19 (7%)
Received all planned treatment and/or no longer on treatment	166 (92%)	101 (95%)	91 (93%)	267 (93%)
Reason for no longer receiving treatment	**166**	**101**	**91**	**267**
AE	22 (13%)	12 (12%)	14 (15%)	34 (13%)
Non-AE[a]	144 (87%)	89 (88%)	77 (85%)	233 (87%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

AE, adverse event; BCG, Bacillus Calmette-Guérin.

[a] "Non-AE" include absence of complete response (CR), discontinuation after CR, lack of further treatment benefit, COVID19-related, death, lack of efficacy, lost to follow-up, non-compliance with study drug, non-compliance with study schedule, physician decision, progressive disease, received all planned treatment through 24 months, study terminated by investigator, withdrawal by subject, and other.

[b] For safety population only subjects were considered receiving N-803 and BCG (Cohort A and Cohort B of QUILT-3.032).

Data cut-off 15 July 2024

Table 46 Treatment Exposure and Percentage of Protocol Dose Overall: Safety Population – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

Variable Category/Statistic	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
Time from first to last dose (months)				
Median	9.94	13.44	13.26	12.09
Min, max	0.8, 39.6	0.9, 22.1	0.0, 23.2	0.8, 39.6
Number of doses administered				
Median	15.0	15.0	15.0	15.0
Min, max	4, 33	4, 24	1, 24	4, 33
Number of doses administered category, n (%)				
<6	2 (1%)	2 (2%)	7 (7%)	4 (1%)
6 – 9	50 (28%)	18 (17%)	16 (16%)	68 (24%)

Variable Category/Statistic	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
10 – 12	30 (17%)	22 (21%)	13 (13%)	52 (18%)
13 – 15	17 (9%)	17 (16%)	18 (18%)	34 (12%)
16 – 18	8 (4%)	39 (37%)	40 (41%)	47 (16%)
19 – 21	39 (22%)	6 (6%)	3 (3%)	45 (16%)
>21	34 (19%)	2 (2%)	1 (1%)	36 (13%)
Subjects with at least 1 dose skipped, n (%)	14 (8%)	6 (6%)	6 (6%)	20 (7%)
1 dose skipped	7 (4%)	5 (5%)	3 (3%)	12 (4%)
2 doses skipped	3 (2%)	0	3 (3%)	3 (1%)
3 doses skipped	2 (1%)	0	0	2 (1%)
4 doses skipped	1 (1%)	1 (1%)	0	2 (1%)
13 doses skipped	1 (1%)	0	0	1 (<1%)
Percentage of protocol dose (%)[a]				
Median	100.0	100.0	100.0	100.0
Min, max	66.7, 105.6	66.7, 122.2	16.7, 150.0	66.7, 122.2
Percentage of protocol dose category, n (%)				
≥90%	171 (95%)	100 (94%)	87 (89%)	271 (95%)
80% to <90%	5 (3%)	4 (4%)	5 (5%)	9 (3%)
70% to <80%	2 (1%)	1 (1%)	2 (2%)	3 (1%)
<70%	2 (1%)	1 (1%)	4 (4%)	3 (1%)

BCG, Bacillus Calmette-Guérin; Max, Maximum; Min, Minimum.

[a] The percentage of protocol dose was calculated as the number of doses administrated divided by the number of protocol doses × 100% during each study period.

Data cut-off 15 July 2024

5.4.3. Adverse events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

The severity of AEs was graded using National cancer institute (NCI) Common terminology criteria for adverse events (CTCAE) v4.03.

If multiple episodes of an event occurred in a subject, the event with the maximum severity or strongest relationship to study medication was used for analysis.

Treatment-emergent AEs (TEAEs) were defined as any AE that begins or worsens in grade after the start of study drug (N-803 or BCG) until 30 days after the last dose of study drug.

An overview of TEAEs reported for the NMIBC combined analysis population receiving N-803 plus BCG or BCG alone is presented in Table 47.

Table 47 Summary of Treatment-Emergent Adverse Events: Safety Population – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

Category	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005 P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
Subjects with ≥1 of the following:				
Any AE, n (%)	159 (88%)	102 (96%)	90 (92%)	261 (91%)
Treatment-related TEAE	109 (61%)	82 (77%)	76 (78%)	191 (67%)
Grade ≥3 AE	36 (20%)	25 (24%)	23 (23%)	61 (21%)
Treatment-related grade ≥3 TEAE	6 (3%)	8 (8%)	3 (3%)	14 (5%)
SAE	27 (15%)	11 (10%)	10 (10%)	38 (13%)
Treatment-related SAE	2 (1%)	3 (3%)	2 (2%)	5 (2%)
AE with action of study drug permanently discontinued	18 (10%)	7 (7%)	12 (12%)	25 (9%)
Treatment-related TEAE with action of study drug permanently discontinued	10 (6%)	5 (5%)	7 (7%)	15 (5%)
AE with action of study drug interruption	56 (31%)	42 (40%)	28 (29%)	98 (34%)
Treatment-related TEAE with action of study drug interruption	27 (15%)	25 (24%)	20 (20%)	52 (18%)
AE with outcome of death	2 (1%)	0	0	2 (1%)
AE with treatment-related outcome of death	0	0	0	0

(data cutoff 15 July 2024)

5.4.3.1. Common adverse events

TEAEs occurring with >5% incidence for all subjects receiving BCG plus N-803 or BCG only by treatment and NMIBC diagnosis are summarised in Table 48.

Table 48 Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term Occurring in >5% of All Subjects Receiving BCG plus N-803 or BCG Only: Safety Population by Treatment and NMIBC Diagnosis – QUILT-3.032 and QUILT-2.005 Phase P1b/P2b

System Organ Class Preferred Term	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
Any TEAE, n (%)	159 (88%)	102 (96%)	90 (92%)	261 (91%)
Renal and urinary disorders	120 (67%)	85 (80%)	76 (78%)	205 (72%)
Dysuria	63 (35%)	43 (41%)	34 (35%)	106 (37%)
Haematuria	53 (29%)	43 (41%)	45 (46%)	96 (34%)
Pollakiuria	57 (32%)	35 (33%)	39 (40%)	92 (32%)
Micturition urgency	39 (22%)	25 (24%)	34 (35%)	62 (22%)
Bladder spasm	15 (8%)	15 (14%)	9 (9%)	30 (10%)

System Organ Class Preferred Term	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	BCG + N-803 (N = 286)
Urinary tract pain	6 (3%)	15 (14%)	12 (12%)	21 (7%)
Cystitis noninfective	11 (6%)	6 (6%)	3 (3%)	17 (6%)
Nocturia	9 (5%)	6 (6%)	12 (12%)	15 (5%)
Urinary incontinence	7 (4%)	8 (8%)	12 (12%)	15 (5%)
Urinary retention	8 (4%)	6 (6%)	5 (5%)	14 (5%)
Proteinuria	2 (1%)	6 (6%)	3 (3%)	8 (3%)
General disorders and administration site conditions	68 (38%)	61 (58%)	58 (59%)	129 (45%)
Fatigue	36 (20%)	39 (37%)	35 (36%)	75 (26%)
Chills	24 (13%)	17 (16%)	18 (18%)	41 (14%)
Pyrexia	18 (10%)	17 (16%)	15 (15%)	35 (12%)
Influenza-like illness	7 (4%)	15 (14%)	16 (16%)	22 (8%)
Oedema peripheral	1 (1%)	6 (6%)	4 (4%)	7 (2%)
Infections and infestations	70 (39%)	49 (46%)	42 (43%)	119 (42%)
Urinary tract infection	39 (22%)	31 (29%)	21 (21%)	70 (24%)
COVID-19	10 (6%)	4 (4%)	3 (3%)	14 (5%)
Cystitis	5 (3%)	7 (7%)	5 (5%)	12 (4%)
Upper respiratory tract infection	3 (2%)	8 (8%)	2 (2%)	11 (4%)
Gastrointestinal disorders	48 (27%)	42 (40%)	40 (41%)	90 (31%)
Nausea	14 (8%)	18 (17%)	14 (14%)	32 (11%)
Diarrhoea	16 (9%)	9 (8%)	9 (9%)	25 (9%)
Abdominal pain	10 (6%)	7 (7%)	7 (7%)	17 (6%)
Constipation	5 (3%)	9 (8%)	13 (13%)	14 (5%)
Vomiting	4 (2%)	7 (7%)	6 (6%)	11 (4%)
Musculoskeletal and connective tissue disorders	35 (19%)	36 (34%)	32 (33%)	71 (25%)
Arthralgia	10 (6%)	14 (13%)	9 (9%)	24 (8%)
Back pain	10 (6%)	10 (9%)	7 (7%)	20 (7%)
Myalgia	4 (2%)	7 (7%)	7 (7%)	11 (4%)
Flank pain	5 (3%)	2 (2%)	6 (6%)	7 (2%)
Nervous system disorders	33 (18%)	27 (25%)	21 (21%)	60 (21%)
Headache	11 (6%)	13 (12%)	14 (14%)	24 (8%)
Dizziness	9 (5%)	7 (7%)	5 (5%)	16 (6%)
Respiratory, thoracic, and mediastinal disorders	21 (12%)	33 (31%)	22 (22%)	54 (19%)

System Organ Class Preferred Term	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	BCG + N-803 (N = 286)
Cough	6 (3%)	14 (13%)	10 (10%)	20 (7%)
Dyspnoea	5 (3%)	11 (10%)	3 (3%)	16 (6%)
Oropharyngeal pain	0	6 (6%)	4 (4%)	6 (2%)
Vascular disorders	18 (10%)	28 (26%)	23 (23%)	46 (16%)
Hypertension	9 (5%)	22 (21%)	15 (15%)	31 (11%)
Metabolism and nutrition disorders	16 (9%)	12 (11%)	15 (15%)	28 (10%)
Decreased appetite	3 (2%)	3 (3%)	9 (9%)	6 (2%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

BCG, Bacillus Calmette-Guérin; TEAE, Treatment-emergent adverse event.

(data cutoff 15 July 2024)

Grade 3 (according to NCI CTCAE) or higher TEAEs occurring in >1 subject for all subjects receiving BCG plus N-803 or BCG only are presented in Table 49.

Table 49 Incidence of Treatment-Emergent Grade 3 or Higher Adverse Events by MedDRA System Organ Class and Preferred Term Occurring in >1 of All Subjects Receiving BCG plus N-803 or BCG Only: Safety Population by NMIBC Diagnosis and Treatment – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

System Organ Class Preferred Term	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
Any grade ≥3 TEAE, n (%)	36 (20%)	25 (24%)	23 (23%)	61 (21%)
Vascular disorders	5 (3%)	13 (12%)	14 (14%)	18 (6%)
Hypertension	5 (3%)	12 (11%)	12 (12%)	17 (6%)
Renal and urinary disorders	8 (4%)	3 (3%)	3 (3%)	11 (4%)
Haematuria	4 (2%)	1 (1%)	1 (1%)	5 (2%)
Infections and infestations	8 (4%)	4 (4%)	4 (4%)	12 (4%)
Urinary tract infection	3 (2%)	0	0	3 (1%)
Pneumonia	1 (1%)	1 (1%)	1 (1%)	2 (1%)
Sepsis	1 (1%)	1 (1%)	1 (1%)	2 (1%)
Metabolism and nutrition disorders	4 (2%)	0	0	4 (1%)
Hyperkalaemia	2 (1%)	0	0	2 (1%)
Musculoskeletal and connective tissue disorders	3 (2%)	2 (2%)	0	5 (2%)
Back pain	1 (1%)	1 (1%)	0	2 (1%)
Myalgia	2 (1%)	0	0	2 (1%)
Nervous system disorders	2 (1%)	3 (3%)	0	5 (2%)
Syncope	0	2 (2%)	0	2 (1%)
Respiratory, thoracic and mediastinal disorders	2 (1%)	3 (3%)	1 (1%)	5 (2%)
Acute respiratory failure	1 (1%)	1 (1%)	0	2 (1%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

BCG, Bacillus Calmette-Guérin; TEAE, Treatment-emergent adverse event.

AEs were graded according to NCI CTCAE v 4.03

(data cutoff 15 July 2024)

5.4.3.2. Adverse drug reactions

The Applicant applied the same methodology to determine ADRs as was used for determining relationship of AEs to study drug in Study QUILT-3.032, which is provided below:

> *The Investigator must determine the relationship between the administration of the study drug and the occurrence of an AE/SAE as "not suspected" or "suspected," as defined below:*

- *Not suspected: The temporal relationship of the AE or SAE to the study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.*
- *Suspected: The temporal relationship of the AE or SAE to the study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.*

If an event is assessed as suspected of being related to a comparator, ancillary, or additional study drug that has not been manufactured or provided by Altor BioScience, please provide the name of the manufacturer when reporting the event.

The frequency of the ADRs presented in the SmPC were based on all-cause AEs, in accordance with the EMA oncology guidance. The applicant suggests that the ADR table should contain the PTs which are clinically meaningful or occurred at > 1% rate to guide shared decision making between the patient and physician.

The ADRs includedin section 4.8 of the SmPC are listed in Table 50 Table 55.

Table 50 Summary of ADRs included in section 4.8 of the SmPC

System organ class	Frequency category	Adverse reaction	Number of events in QUILT-3.032 (Cohort A+B), n=180
Infections and infestations	Very common	Urinary tract infections	43 (24%)
	Common	Cystitis, Bacteriuria[a], Bacteraemia, Sepsis	6 (3%), 6 (3%), 3 (2%), 2 (1%)
Blood and lymphatic system disorders	Common	Anaemia[b], Leukocytosis, Lymphadenopathy	6 (3%), 2 (1%), 2 (1%)
Metabolism and nutrition disorders	Common	Decreased appetite, Dehydration	3 (2%), 2 (1%)
Nervous system disorders	Common	Dizziness, Headache	9 (5%), 11 (6%)
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea	7 (4%)
Gastrointestinal disorders	Common	Diarrhoea, Nausea, Abdominal pain[c], Constipation, Vomiting	16 (9%), 15 (8%), 16 (9%), 5 (3%), 4 (2%)
Skin and subcutaneous tissue disorders	Common	Night sweats, Pruritus, Rash	4 (2%), 3 (2%), 7 (4%)
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[d]	19 (11%)
	Common	Myalgia[e], Arthralgia, Muscular weakness	8 (4%), 11 (6%), 4 (2%)
	Uncommon	Arthritis	1 (1%)
Renal and urinary disorders	Very Common	Haematuria[f], Dysuria, Pollakiuria, Micturition urgency	63 (35%), 63 (35%), 58 (32%), 39 (22%)
	Common	Bladder spasm, Cystitis noninfective, Nocturia, Urinary incontinence, Urinary tract pain[g], Urinary retention,	16 (9%), 11 (6%), 11 (6%), 7 (4%), 8 (4%), 10 (6%),

		Bladder pain[h],	8 (4%),
		Urge incontinence,	2 (1%),
		Lower urinary tract symptoms,	2 (1%),
		Urinary hesitation,	2 (1%),
		Urine flow decreased,	2 (1%),
		Leukocyturia[i]	8 (4%),
	Uncommon	Urine abnormality,	1 (1%)
		Polyuria,	1 (1%)
		Glomerular filtration rate decreased,	1 (1%)
		Blood urea increased	1 (1%)
			1 (1%)
Reproductive system and breast disorders	Common	Genital pain[j],	9 (5%),
		Prostatitis,	3 (2%),
		Benign prostatic hyperplasia	3 (2%)
	Uncommon	Penile discharge	
General disorders and administration site conditions	Very common	Fatigue,	36 (20%),
		Chills,	24 (13%),
		Pyrexia	18 (10%)
	Common	Influenza like illness,	7 (4%),
		Chest pain	6 (3%)
	Uncommon	Installation site pain	1 (1%)
Investigations	Common	Blood creatinine increased,	5 (3%)
		Cancer cells urine present	2 (1%)

[a] includes bacteriuria, asymptomatic bacteriuria and bacterial test positive
[b] includes anaemia and anaemia macrocytic
[c] includes abdominal pain, abdominal pain lower and suprapubic pain
[d] includes musculoskeletal pain, back pain, flank pain and pain in extremity
[e] includes myalgia and pain
[f] includes haematuria, cystitis haemorrhagic and blood urine present
[g] includes urinary tract pain and urinary tract discomfort
[h] includes bladder pain, bladder discomfort and bladder irritation
[i] includes leukocyturia and white blood cells in urine
[j] includes penile pain, penile burning sensation, vulvovaginal burning sensation

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest (AESIs)

The incidences of treatment-emergent AESI occurring with >5% incidence for all subjects receiving BCG plus N-803 by NMIBC diagnosis and treatment are summarised in Table 51.

Table 51 Incidence of Treatment-Emergent Adverse Event of Special Interest by MedDRA Preferred Term in >5% of All Subjects Receiving BCG plus N-803 or BCG Only: Safety Population

AESI Term Preferred Term[a]	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
At least 1 treatment-emergent AESI, n (%)	147 (82%)	101 (95%)	87 (89%)	248 (87%)
Renal, urinary, and bladder disorders	120 (67%)	85 (80%)	76 (78%)	205 (72%)
Dysuria	63 (35%)	43 (41%)	34 (35%)	106 (37%)
Haematuria	53 (29%)	43 (41%)	45 (46%)	96 (34%)
Pollakiuria	57 (32%)	35 (33%)	39 (40%)	92 (32%)
Micturition urgency	39 (22%)	25 (24%)	34 (35%)	64 (22%)
Bladder spasm	15 (8%)	15 (14%)	9 (9%)	30 (10%)
Urinary tract pain	6 (3%)	15 (14%)	12 (12%)	21 (7%)
Cystitis noninfective	11 (6%)	6 (6%)	3 (3%)	17 (6%)
Urinary incontinence	7 (4%)	8 (8%)	12 (12%)	15 (5%)
Nocturia	9 (5%)	6 (6%)	12 (12%)	15 (5%)
Infections	70 (39%)	49 (46%)	42 (43%)	119 (42%)
Urinary tract infection	39 (22%)	31 (29%)	21 (21%)	70 (24%)
Fatigue	36 (20%)	39 (37%)	35 (36%)	75 (26%)
Chills	24 (13%)	17 (16%)	18 (18%)	41 (14%)
Nausea and vomiting symptoms	15 (8%)	21 (20%)	16 (16%)	36 (13%)
Nausea	14 (8%)	18 (17%)	14 (14%)	32 (11%)
Vomiting	4 (2%)	7 (7%)	6 (6%)	11 (4%)
Pyrexia	18 (10%)	17 (16%)	15 (15%)	35 (12%)
Hypertension	11 (6%)	22 (21%)	15 (15%)	33 (12%)
Diarrhoea	16 (9%)	9 (8%)	9 (9%)	25 (9%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT 2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3). Same adverse event can be classified in more than one special interest term.
AESI, Adverse event of special interest; BCG, Bacillus Calmette-Guérin.
a Some AESI can be classified in more than one AESI term.

(data cutoff 15 July 2024)

A summary of grade ≥3 AESI reported in >1 of all subjects receiving BCG plus N-803 or BCG by NMIBC diagnosis and treatment is displayed in Table 52.

Table 52 Incidence of Treatment-Emergent Grade 3 or Higher Adverse Events of Special Interest by MedDRA Preferred Term Occurring >1 Subject: Safety Population by NMIBC Diagnosis and Treatment – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

AESI term Preferred term[a]	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106)	BCG (N = 98)	
At least 1 grade ≥3 treatment-emergent AESI, n (%)	19 (11%)	18 (17%)	17 (17%)	37 (13%)
Hypertension	6 (3%)	12 (11%)	12 (12%)	18 (6%)
Renal, urinary, and bladder disorders	8 (4%)	4 (4%)	3 (3%)	12 (4%)
Haematuria	4 (2%)	1 (1%)	1 (1%)	5 (2%)
Infections	8 (4%)	4 (4%)	4 (4%)	12 (4%)
Urinary tract infections	3 (2%)	0	0	3 (1%)
Pneumonia	1 (1%)	1 (1%)	1 (1%)	2 (2%)
Sepsis	1 (1%)	1 (1%)	1 (1%)	2 (2%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3). Same adverse event can be classified in more than one special interest term.

AE, Adverse event; AESI, Adverse event of special interest; BCG, Bacillus Calmette-Guérin.

[a] Some AEs can be classified in more than one AESI term.

(data cutoff 15 July 2024)

Serious adverse events (SAEs)

Thirty-eight (38) subjects (13%) of all subjects receiving N-803 in combination with BCG in studies QUILT-3.032 and QUILT-2.005 and 10 (10%) subjects receiving BCG monotherapy in QUILT-2.005 had at least one treatment-emergent SAE. The incidences of treatment-emergent SAEs occurring in more than 1 subject are summarised in Table 53. Nearly all treatment-emergent SAEs were reported as recovered or resolved.

SAEs that were considered treatment-related by the investigator occurred in 2% of subjects, and generally occurred in single instances. These events included:

BCG + N-803

- Grade 3 haematuria (one subject)
- Grade 3 cystitis noninfective (one subject)
- Grade 3 syncope (one subject)
- Grade 4 sepsis (one subject)

- Grade 2 urinary tract infection (one subject)
- In addition there was one case of Grade 3 disseminated BCG infection, considered related to BCG but not to N-803. The case was reported as resolved.
- Grade 3 neurosarcoidosis (one subject; non-treatment emergent)

BCG monotherapy

- Grade 3 bladder spasm, Grade 2 urinary retention, and Grade 3 kidney infection (one subject)
- Grade 4 sepsis (one subject)

Table 53 Incidence of Treatment-Emergent Serious Adverse Events Occurring in >1 Subject Receiving BCG plus N-803 or BCG Only: Safety Population by NMIBC Diagnosis and Treatment - QUILT-3.032 and QUILT-2.005 Phase

System Organ Class Preferred Term	**BCG Unresponsive (QUILT-3.032)**	**BCG Naïve (QUILT-2.005-P1b/P2b)**		**All Subjects Receiving BCG + N-803 (N = 286)**
	BCG + N-803 (N = 180)	**BCG + N-803 (N = 106**	**BCG (N = 98)**	
At least 1 treatment-emergent SAE, n (%)	27 (15%)	11 (10%)	10 (10%)	38 (13%)
Infections and infestations	9 (5%)	4 (4%)	2 (2%)	13 (5%)
Urinary tract infection	2 (1%)	1 (1%)	0	3 (1%)
Bacteraemia	2 (1%)	0	0	2 (1%)
Sepsis	1 (1%)	1 (1%)	1 (1%)	2 (1%)
Renal and urinary disorders	8 (4%)	0	3 (3%)	8 (3%)
Haematuria	3 (2%)	0	1 (1%)	3 (1%)
Nervous system disorders	3 (2%)	3 (3%)	0	6 (2%)
Syncope	0	2 (2%)	0	2 (1%)
Respiratory, thoracic and mediastinal disorders	2 (1%)	1 (1%)	1 (1%)	3 (1%)
Acute respiratory failure	1 (1%)	1 (1%)	0	2 (1%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

BCG, Bacillus Calmette-Guérin; SAE, serious adverse event.

(data cutoff 15 July 2024)

Deaths

A total of 26 deaths were reported in studies QUILT-3.032 and QUILT-2.005 P1b/2b. The most commonly reported causes of death were disease progression or other events related to malignant disease (n=10), including one case) with cause of death reported as unknown but with disease progression as contributing diagnosis.

Altogether, in the two studies, five cases of death were reported as due to an AE. Two cases were due to treatment-emergent AEs (cardiac arrest and cholangitis, respectively), occurring 26 and 3 days after last study treatment, respectively. Three events (cerebrovascular accident, unknown cause of death, and pneumonia, respectively) were non-treatment-emergent, occurring 81, 72 and 153 days after the last study treatment, respectively. None of the AEs leading to death was, by the investigator, considered related to study treatment.

Immune-related AEs

Listings of potential immune-related adverse events (irAE)s in patients with BGC-unresponsive NMIBC (QUILT-3.032) and BCG-naïve patients (QUILT-2.005) are provided in Table 54 and Table 55, respectively.

Table 54 Listing of Subjects With Potential Immune-Related Adverse Events, QUILT- 3.032: BCG Plus N-803

Immune-Related AE	Grade	Outcome	Relationship to Study Drug(s)[a]	Age (y)	Gender	Treatment Duration (days)
Infections and infestations						
Conjunctivitis	1	Resolved	Unrelated	71	F	1152
Conjunctivitis	2	Resolved	Unrelated			
Skin and subcutaneous disorders						
Alopecia	1	Resolved	Unrelated	77	M	99
Psoriasis	2	Resolving	Unlikely	80	M	547
Musculoskeletal and connective tissue disorders						
Rheumatoid arthritis	1	Resolved	Possible	72	F	505
Respiratory, thoracic, and mediastinal disorders						
Idiopathic pulmonary fibrosis	1	Not resolved	Unrelated	79	M	1114
Gastrointestinal disorders						
Pancreatitis acute	3	Resolved	Unrelated	65	F	751
Immune system disorders						
Drug hypersensitivity	3	Resolved	Unrelated	73	M	568
Drug hypersensitivity	1	Not Resolved	Unrelated	79	M	756
Drug hypersensitivity	1	Resolved	Unrelated	79	M	756
General disorders and administration site conditions						
Systemic inflammatory response syndrome	3	Resolved with sequelae	Unrelated	73	M	568

[a] AE relatedness reflects the Investigator assessment.

(data cutoff 15 July 2024)

Table 55 Listing of Subjects with Potential Immune-Related Adverse Events, QUILT- 2.005-P2b (BCG + N-803 or BCG only)

Immune-Related AE	Grade	Outcome	Relationship to Study Drug(s)[a]	Age	Gender	Treatment Group	Treatment Duration (days)
Eye disorders							
Conjunctivitis allergic	1	Resolved	Unlikely	74	M	Cohort B: BCG	232
Gastrointestinal disorders							
Colitis	2	Resolved	Unrelated	74	F	Cohort A: BCG + N-803	517
Stomatitis	1	Resolved	Unrelated	61	F	Cohort A: BCG	653
Stomatitis	1	Resolved	Probable	62	M	Cohort A: BCG + N-803	191
Stomatitis	1	Resolved	Not related	67	M	Cohort A: BCG + N-803	206
Colitis	2	Unresolved	Unrelated	71	M	Cohort A BCG +N-803	368
Infections and infestations							
Conjunctivitis	2	Resolved	Unrelated	53	F	Cohort B: BCG	372
Conjunctivitis	1	Not Resolved	Probable	67	M	Cohort B: BCG + N-803	456
Conjunctivitis	1	Resolved	Unrelated	55	M	Cohort B: BCG + N-803	393
Musculoskeletal and connective tissue disorders							
Arthritis reactive	1	Resolved	Probable	60	M	Cohort A: BCG + N-803	253
	2	Resolved	Probable			Cohort A: BCG + N-803	253
	1	Resolved	Probable			Cohort A: BCG + N-803	253
Skin and subcutaneous disorders							
Psoriasis	2	Not resolved	Possible	57	M	Cohort B: BCG + N-803	583
Alopecia	1	Unresolved	Unrelated	79	M	Cohort A: BCG	557

[a] AE relatedness reflects the Investigator assessment.

(data cutoff 15 July 2024)

No subject receiving BCG monotherapy had an immune-related AE with a relationship of probable or possibly related to treatment.

No immune-related AEs were reported for the 10 subjects who received N-803 alone.

Irritable bladder syndrome

BCG-unresponsive subjects (QUILT.3.032)

- A total of 21 subjects had at least 1 grade ≥2 irritable bladder symptom
- One subject in QUILT-3.032 reported grade 3 increased urinary frequency and the subject had reported urinary frequency and urinary urgency at baseline. This was the only grade ≥3 irritable bladder symptom reported across the 2 studies.

- A total of 19 subjects were reported to have grade ≥2 urinary frequency.
- A total of three subjects were reported to have urinary incontinence.
- A total of nine subjects were reported to have urinary urgency.

BCG-naïve subjects (QUILT-2.005)

- A total of 16 subjects had at least 1 grade ≥2 irritable bladder symptom, and all 17 subjects received BCG plus N-803. No subjects who received BCG alone had an irritable bladder symptom.
- All irritable bladder symptoms in QUILT-2.005 were grade 2.
- A total of 11 subjects were reported to have urinary frequency.
- One subject was reported to have urinary frequency and urgency.
- A total of two subjects were reported to have urinary incontinence.
- A total of eight subjects were reported to have urinary urgency.

Adverse Events Resulting in Compromised Bladder Mucosa

Two subjects were reported to have a TEAE resulting in compromised bladder mucosa in QUILT-3.032 (Table 56).

Table 56 Listing of Subjects With Adverse Events Resulting in Compromised Bladder Mucosa, QUILT-3.032: BCG + N-803

AE	Grade	Relationship to Study Drug(s)[a]	Subject Number	Age	Gender	Treatment Duration (days)
Bladder perforation	2	Unrelated		67	F	593
Cystitis ulcerative	1	Unrelated		≥ 80	M	583

[a] AE relatedness reflects the Investigator assessment.

(data cutoff 15 July 2024)

The event of bladder perforation occurred in a subject who had received 18 doses of BCG + N-803, 54 days after the last dose of N-803 plus BCG. The event was considered attributed to a complication following a recent bladder biopsy.

The event of ulcerative cystitis occurred in a subject who had received 18 doses of BCG + N-803. The event was reported 4.5 months after the last dose, when a cystoscopy was performed. The event was considered likely attributed to the patient's treatment with apixaban and not to the previous treatment with BCG + N-803.

5.4.5. Discontinuation due to adverse events

For all subjects receiving BCG plus N-803, TEAEs that led to study drug discontinuation occurred in 9% of subjects in studies QUILT-3.032 and QUILT-2.005 (Table 57). Those events occurring in >1 subject are summarised in Table 57.

TEAEs reported as treatment-related and leading to study drug discontinuation, in all subjects receiving BCG plus N-803, occurred in 5% of subjects. The only treatment-related AEs assessed as related to treatment and reported in more than 1 subject were cystitis and dysuria.

Table 57. Incidence of Treatment-Emergent Adverse Events With Action of Discontinuation of Study Drug Occurring in >1 Subject Receiving BCG plus N-803 or BCG Only: Safety Population

System Organ Class Preferred Term	BCG Unresponsive (QUILT-3.032)	BCG Naïve (QUILT-2.005-P1b/P2b)		All Subjects Receiving BCG + N-803 (N = 286)
	BCG + N-803 (N = 180)	BCG + N-803 (N = 106	BCG (N = 98)	
At least 1 TEAE with action of study drug discontinuation, n (%)	18 (10%)	7 (7%)	12 (12%)	25 (9%)
Infections and infestations	4 (2%)	3 (3%)	5 (5%)	7 (2%)
Cystitis	2 (1%)	2 (2%)	0	4 (1%)
Renal and urinary disorders	8 (4%)	3 (3%)	6 (6%)	11 (4%)
Bladder spasm	2 (1%)	2 (2%)	0	4 (1%)
Cystitis noninfective	2 (1%)	0	0	2 (1%)
Dysuria	2 (1%)	0	2 (2%)	2 (1%)
Hematuria	2 (1%)	0	0	2 (1%)
Pollakiuria	1 (1%)	1 (1%)	1 (1%)	2 (1%)
Gastrointestinal disorders	1 (1%)	1 (1%)	0	2 (1%)
Abdominal pain	1 (1%)	1 (1%)	0	2 (1%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

BCG, Bacillus Calmette-Guérin; TEAE, Treatment-emergent adverse event.

(data cutoff 15 July 2024)

5.4.6. Safety in special populations

Age

Of all subjects treated with BCG + N-803, the majority were ≥65 years of age.

For all subjects treated with BCG + N-803 (QUILT-3.032 and QUILT-2.005), there were no relevant differences between the age groups in rate of TEAEs or Grade ≥3 TEAEs (Table 58 Summary of Treatment-Emergent Adverse Events by Age Group, NMIBC Disease: Safety Population (QUILT-3.032 and QUILT-2.005 P1b/2b)). Incidences of AESI, treatment-related AESI, AESI grade ≥3, and treatment-related AESI grade ≥3 were generally similar to those presented for TEAEs.

In BCG-unresponsive subjects (QUILT-3.032), the only TEAE that occurred more commonly (with >10% more frequency) in subjects ≥65 was fatigue (8% versus 23%). More common to subjects <65 was pyrexia (21% versus 7%). Grade 3 or higher TEAEs occurred less frequently in subjects <65 (13%) compared to subjects ≥65 (22%). Treatment-related grade ≥3 TEAEs were comparable between age groups (5% vs 3%).

Table 58 Summary of Treatment-Emergent Adverse Events by Age Group, NMIBC Disease: Safety Population (QUILT-3.032 and QUILT-2.005 P1b/2b)

	All Subjects Receiving BCG plus N-803					
	Cohort A (CIS ± Ta/T1) (N = 161)		Cohort B (HG Papillary) (N = 125)		All Subjects (N = 286)	
Category	Age <65 (N = 38)	Age ≥65 (N = 123)	Age <65 (N = 38)	Age ≥65 (N = 87)	Age <65 (N = 76)	Age ≥65 (N = 210)
Any TEAE, n (%)	37 (97%)	117 (95%)	33 (87%)	74 (85%)	70 (92%)	191 (91%)
Treatment-related	28 (74%)	79 (64%)	25 (66%)	59(68%)	53 (70%)	138 (66%)
Grade ≥ 3 TEAE	5 (13%)	29 (24%)	7 (18%)	20 (23%)	12 (16%)	49 (23%)
Treatment-related	1 (3%)	7 (6%)	3 (8%)	3 (3%)	4 (5%)	10 (5%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3),at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

BCG, Bacillus Calmette-Guérin; CIS, Carcinoma in situ; HG, High grade; TEAE, Treatment-emergent adverse event.

(data cutoff 15 July 2024)

Gender

Comparisons of TEAEs by gender should consider the 4.7-fold difference between the number of male subjects (n = 235) and female subjects (n = 51) treated with BCG plus N-803 overall. This difference roughly approximates the real-world scenario in which bladder cancer is 4 times more common in men than women.

A summary of TEAEs by gender NMIBC disease, and treatment for all subjects receiving BCG plus N-803 is provided in Table 59.

For all subjects receiving BCG plus N-803, incidences were generally comparable between males and females for TEAEs and treatment-related TEAEs overall. Treatment-related AESI grade ≥3 also occurred with comparable incidence.

Table 59 Summary of Treatment-Emergent Adverse Events by Gender, NMIBC Disease, and Treatment: Safety Population – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

	All Subjects Receiving BCG plus N-803					
	Cohort A (CIS ± Ta/T1) (N = 161)		Cohort B (HG Papillary) (N = 125)		All Subjects (N = 286)	
Category	Male (N = 136)	Female (N = 25)	Male (N = 99)	Female (N = 26)	Male (N = 235)	Female (N = 51)
Any TEAE, n (%)	130 (96%)	24 (96%)	85 (86%)	22 (85%)	215 (91%)	46 (90%)
Treatment-related	90 (66%)	17 (68%)	67 (68%)	17 (65%)	157 (67%)	34 (67%)
Grade ≥3 TEAE	25 (18%)	9 (36%)	23 (23%)	4 (15%)	48 (20%)	13 (25%)
Treatment-related	6 (4%)	2 (8%)	6 (6%)	0	12 (5%)	2 (4%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3),at 200 µg/instillation (N = 3), and at 100 µg/instillation(N = 3).

BCG, Bacillus Calmette-Guérin; CIS, Carcinoma in situ; HG, High grade; TEAE, Treatment-emergent adverse event.

(data cutoff 15 July 2024)

Race and Ethnicity

Comparisons of TEAEs between race should consider that a majority of the subjects receiving BCG plus N-803 were White (86%), 5% of subjects were Black or African American and 4% were Asian. Due to the small sample size and for the purpose of the following analyses, a dichotomous comparison was performed with 'White' as one population and 'Other' (i.e., subjects of other races) as the comparator.

A summary of TEAEs by race for all subjects receiving BCG plus N-803 is provided in Table 60. For all subjects receiving BCG plus N-803, the incidence of TEAEs and treatment-related TEAEs were generally comparable between the groups analysed.

Table 60 Summary of Treatment-Emergent Adverse Events by Race, NMIBC Disease, and Treatment, Safety Population – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

	All Subjects Receiving BCG + N-803[a]					
	Cohort A (CIS ± Ta/T1) (N = 158)		Cohort B (HG Papillary) (N = 123)		All Subjects (N = 281)	
Category	White (N = 140)	Other (N = 18)	White (N = 106)	Other (N = 17)	White (N = 246)	Other (N = 35)
Any TEAE, n (%)	133 (95%)	18 (100%)	92 (87%)	14 (82%)	225 (91%)	32 (91%)
Treatment-related	95 (68%)	10 (56%)	70 (66%)	13 (76%)	165 (67%)	23 (66%)
Grade ≥3 TEAE	29 (21%)	5 (28%)	22 (21%)	5 (29%)	51 (21%)	10 (29%)
Treatment-related	7 (5%)	1 (6%)	6 (6%)	0	13 (5%)	1 (3%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3),at 200 µg/instillation (N = 3), and at 100 µg/instillation(N = 3).

[a] Subjects whose race was unknown or not reported were excluded from analysis (n = 5).

BCG, Bacillus Calmette-Guérin; CIS, Carcinoma in situ; HG, High grade; TEAE, Treatment-emergent adverse event.

(data cutoff 15 July 2024)

NMIBC Disease Type

Amongst all subjects receiving BCG plus N-803, there were 43.6% of subjects with HG papillary, 31.9% with CIS only, and 24.5% with CIS with papillary disease. TEAEs by NMIBC disease and treatment are summarised in Table 61.

Table 61 Summary of Treatment-Emergent Adverse Events by NMIBC Disease Type and Treatment: Safety Population – QUILT-3.032 and QUILT-2.005 Phase 1b and 2b

Category	All Subjects Receiving BCG + N-803								
	Cohort A (CIS ± Ta/T1) (N = 161)			Cohort B (HG Papillary) (N = 125)			All Subjects (N = 286)		
	CIS only (N = 96)	HG Pap only (N = 0)	CIS w/HG Pap (N = 65)	CIS only (N = 1)	HG Pap only (N = 119)	CIS w/HG Pap (N = 5)	CIS only (N = 97)	HG Pap only (N = 119)	CIS w/HG Pap (N = 70)
Any TEAE, n (%)	89 (93%)	0	65 (100%)	0	104 (87%)	3 (60%)	89 (92%)	104 (87%)	68 (97%)
Treatment-related	57 (59%)	0	50 (77%)	0	82 (69%)	2 (40%)	57 (59%)	82 (69%)	52 (74%)
Grade ≥3 TEAE	20 (21%)	0	14 (22%)	0	27 (23%)	0	20 (21%)	27 (23%)	14 (20%)
Treatment-related	3 (3%)	0	5 (8%)	0	6 (5%)	0	3 (3%)	6 (5%)	5 (7%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3).

BCG, Bacillus Calmette-Guérin; CIS, Carcinoma in situ; CIS w/HG Pap, CIS with HG papillary; HG Pap, high grade papillary; TEAE, Treatment-emergent adverse event.

(data cutoff 15 July 2024)

Incidence of TEAEs overall was similar between all 3 disease type groups. Among the most common TEAEs, those occurring with a >10% difference in incidence between disease groups included pollakiuria (CIS only, 29% versus HG papillary 37% versus CIS with HG papillary 29%), bladder spasm (5% versus 10% versus 19%), fatigue (21% versus 33% versus 23%), chills (11% versus 12% versus 23%), pyrexia (13% versus 6% versus 21%), urinary tract infection (24% versus 20% versus 33%), nausea (12% versus 6% versus 19%), and hypertension (7% versus 16% versus 7%). The only *treatment-related* TEAE with a >10% difference in incidence between disease groups was bladder spasm (4% versus 8% versus 16%).

5.4.7. Immunological events

Change in ADA status from baseline to post-baseline is summarised for all subjects receiving BCG plus N-803 in Table 62.

The incidence of potential irAEs was examined for all subjects who were negative for ADAs at baseline and positive at any post-baseline assessment. No potential irAEs occurred in any of these subjects (n = 8). Thus, the change in ADA status did not appear to have an impact on subject safety.

Anti-N-803 antibodies were reported in 7% of the subjects who received N-803 plus BCG. None of the subjects who were reported to have anti-N-803 antibodies were reported to have an immune-related adverse event. Except for three subjects, antibodies were not detected until after at least 1 year of treatment.

Table 62 Change in Antidrug Antibody Status From Baseline to Post-Baseline: Safety Population by NMIBC Disease and Treatment (Subjects Receiving BCG Plus N-803) - QUILT-3.032 and QUILT-2.005-Phase 1b and 2b

Variable Category	BCG Unresponsive (QUILT-3.032) (N = 180)	BCG Naïve (QUILT-2.005-P1b/P2b) (N = 106)	All Subjects Receiving BCG + N-803 (N = 286)
Baseline			
Positive	7/156 (4%)	3/91 (3%)	10/247 (4%)
Negative	149/156 (96%)	88/91 (97%)	237/247 (96%)
Post-baseline			
Subjects with Baseline Negative and Changed to Positive at Any Post-baseline Assessments	4/148 (3%)	4/85 (5%)	8/233 (3%)

Note: Summary of confirmatory results for Antidrug Antibodies, if performed. Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400µg/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400µg/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400µg/instillation (N = 3), at 200 µg/instillation (N = 3), and at 100 µg/instillation (N = 3). Changes in ADA status were summarised for subjects who had baseline ADA and at least one post-baseline ADA assessment.

ADA, Antidrug antibody; BCG, Bacillus Calmette-Guérin.

(data cutoff 15 July 2024)

5.4.8. Safety related to drug-drug interactions and other interactions

Co-administered medications that compromise the function of Fc receptors can affect therapeutic proteins (TP) that interact with Fc receptors. However, because there is no systemic exposure to N-803 when administered intravesically, the potential for N-803 to be a victim of co-administered medications that compromise the function of Fc receptors is low.

As the mechanism of action for N-803 depends on immune cell activation, drugs that suppress the immune system theoretically could have an indirect impact on the efficacy and immunogenicity of N-803. Ongoing chronic systemic steroid therapy (>10 mg oral prednisone daily or equivalent) is not allowed in QUILT-3.032 or QUILT-2.005.

In nonclinical and clinical studies, intravesical dosing of N-803 or N-803 in combination with BCG resulted in altered cytokine levels in urine and serum. However, there is no evidence of cytokine release syndrome from nonclinical or clinical studies. The potential for N-803 to affect CYP450 enzymes via elevation of cytokines is discussed in the Pharmacokinetic assessment.

No evaluation of AEs by concomitant therapy subgroups was performed in these studies.

5.4.9. Vital signs and laboratory findings

The most common (>5% of subjects) hematologic abnormalities for all subjects receiving BCG plus N-803 overall were grade 1 low haemoglobin (35%), grade 1 low lymphocytes (13%), grade 1 low platelets (11%), and grade 1 low leukocytes (7%). Abnormalities grade ≥3 were uncommon. These included grade 3 low haemoglobin (1%), grade 3 low neutrophils (1%), and grade 4 low lymphocytes (<1%).

Worsening of NCI CTCAE Grade from Baseline for haematology Parameters Grade 3 - 4 was reported in 1% of all subjects who received N-803 plus BCG for decreased haemoglobin, <1% for decreased lymphocytes, and 1% for decreased neutrophils, while none were reported in the small cohort that received intravesical N-803 alone.

The only haematology parameter of any grade that worsened in grade from baseline in ≥15% of subjects receiving BCG plus N-803 in cohort A of QUILT-3.032 was decreased haemoglobin (16%). There were no subjects with grade 3–4 decreased haemoglobin that worsened in grade from baseline in this cohort.

The only haematology parameter of any grade that worsened in grade from baseline in ≥15% of subjects receiving N-803 in cohort C of QUILT-3.032 was decreased leukocytes (20%). All of these events were grade 1.

Worsening of NCI CTCAE Grade from Baseline for chemistry Parameters Grade 3 -4 was reported in 1% or less or not reported for of all subjects who received N-803 plus BCG except for increased glucose (5%), and increased glucose was reported for 10% in the small cohort that received N-803 alone. The protocol did not specify if glucose values were drawn in the fasted state.

The most common (occurring in ≥15% of subjects) chemistry parameters of any grade that worsened in grade from baseline for all subjects receiving BCG plus N-803 (Safety Population), subjects receiving BCG plus N-803 in cohort A of QUILT-3.032, and subjects receiving N-803 only (cohort C of QUILT-3.032) were increased creatinine (74%, 69%, and 60%, respectively).

For subjects receiving BCG plus N-803 in cohort A of QUILT-3.032, grade 3 – 4 increased creatinine and increased potassium worsened in grade from baseline in 0% and 2% of subjects, respectively.

Grade 3 – 4 chemistry parameters that worsened in grade from baseline were uncommon in the Safety Population as well as in subjects in cohort A and cohort C of QUILT-3.032. Increased glucose was the only grade 3 – 4 chemistry parameter that worsened in grade from baseline in >1% of all 3 populations (5%, 4%, and 10%, respectively). The majority of chemistry parameters that worsened in grade from baseline were grade 1 or 2.

5.4.10. Post marketing experience

Anktiva was approved by the FDA in the US on 22 April 2024. A total of 63 doses of Anktiva have been distributed in the market since May 2024. No adverse events have been reported to the Sponsor (data cutoff 15 July 2024).

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

Safety database

The safety assessment of intravesical administration of N-803 in combination with BCG is primarily based on data from two studies:

- study QUILT-3.032 in BCG-unresponsive subjects with NMIBC, which is the pivotal efficacy study for this application, including a small cohort treated with N-803 only
- study QUILT-2.005 Phase 2b (P2b) in BCG-naïve subjects with NMIBC, including a comparator arm with BCG only.

In both studies, the same dose as reflected in the SmPC was used, i.e. an induction phase of 400 µg N-803 + BCG once weekly for 6 weeks, which based on response assessment was followed by either maintenance treatment (3 weekly instillations at 3-month intervals) or a re-induction course. The data from these studies are therefore supportive of the proposed dosage.

A total of 98 subjects received BCG alone in the comparator arm in study QUILT-2.005 Phase 2b, allowing assessment of the added toxicity associated with the combination of BCG and N-803.

The total number of patients exposed to BCG + N-803 in the two main studies is 277. An additional 9 patients were treated with N-803 + BCG at different N-803 doses (100 µg, 200 µg and 400 µg, n=3 per dose group) in the dose-finding study QUILT-2.005 Phase 1b (P1b). Thus, a total of 286 patients (referred to as 'Safety population' below) have been treated with intravesical BCG in combination with N-803.

The primary safety database, forming the basis for section 4.8 of the SmPC, consists of cohorts A and B from Study QUILT-3.032 (n=180). The Applicant did not include safety data from study QUILT-2.005 Phase 2b in the primary safety database due to the differences in treatment experience and disease characteristics (BCG naive vs. BCG-unresponsive) between the subjects in the two studies. This is accepted. However, the assessment has taken into account data from QUILT-2.005 Phase 2b as supportive when determining which ADRs should be listed in the SmPC (see below).

Overall, the safety database for patients in the sought indication (BCG-unresponsive CIS ± Ta/T1; N=100) or generally BCG-unresponsive NMIBC patients (N=180) is limited. As a result, the identification of ADRs is restricted to the most common ADRs only. The single-arm design of QUILT-3.032 further limits the assessment of the causality of AEs and, thus, the individual safety profile of N-803. Although, safety data from cohort C in QUILT-3.032 and data from study QUILT-2.005 Phase 2b provide additional information on the contribution of N-803 to the safety profile of the BCG + N-803 combination, the available safety data are considered insufficient to meet the principles for the extent of population exposure to assess clinical safety, as laid out in the guideline ICH Topic E1 Step 5 (CPMP/ICH/375/95).

In the two main studies, a median of 15 doses of BCG + N-803 (range: 4 – 33 doses) have been administered at the cut-off date for this application (15 July, 2024; 7% of patients had treatment still ongoing). For comparison, the maximum number of doses recommended in the SmPC is six (6) or 12 induction doses + 15 maintenance doses (3 weekly doses every 3rd month) + an additional 9 doses (3 weekly doses every 6th month) in patients with an ongoing complete response. Altogether, 45 patients in the studies were treated with 19-21 doses, corresponding to one induction phase and the first 15 maintenance doses recommended in the SmPC, and 36 patients have been treated with > 21 doses.

In study QUILT-3.032, the median duration of safety follow-up (defined as the period until 30 days after the last dose of study treatment) was 10.92 months (range: 1.8, 42.3) in Cohort A plus B, and 5.70 months in Cohort C (range: 2.2, 10.7). The median duration of study follow-up (from the first dose to the last follow-up visit) was 25.7 months in cohort A, 29.7 months in cohort B and 35.8 months in cohort C in QUILT-3.032.

In study QUILT-2.005 Phase 2b, the median duration of safety follow-up was 15.0 months in Cohort A and 18.1 months in Cohort B. The median duration until the last follow-up visit was 23.7 months in Cohort A and 24.2 months in Cohort B.

Data for N-803 monotherapy is sparse. In QUILT-3.032, a cohort of 10 patients were treated with intravesical N-803 monotherapy. In addition, data from subcutaneous administration of N-803 is available from 20 healthy volunteers in study QUILT-1.004.

Safety data collection and analysis

In both QUILT-3.032 and QUILT-2.005 Phase 1b/2b, adverse events including their severity grade, seriousness, duration, action taken and outcome were recorded by investigators from the time the subject received their first dose until 30 days after the last dose of the study drug or until the last study treatment visit, whichever occurred later.

Beyond the 30-day period following the last study dose, procedure, or discontinuation date, only SAEs deemed related to treatment were to be recorded in QUILT-3.032, while no AEs, including SAEs, were to be collected in QUILT-2.005 Phase 1b/2b.

Adverse events

N-803 monotherapy

Following *subcutaneous* administration of two consecutive doses of N-803 (10 µg/kg and 20 µg/kg, separated by 15 days) to 20 healthy volunteers in QUILT-1.004, a large portion of subjects (≥75%) reported chills and pyrexia. The rate of pyrexia increased with dose. Lymphadenopathy was reported in 30% of subjects. An approximately 50% decrease in lymphocyte count was observed in 50% of subjects at the lower dose and 100% of subjects at the higher dose. This effect was reversible within 96 hours after dosing. Flow cytometry indicated that the decrease in lymphocyte count was followed by a selective and persistent increase in NK cell number.

A publication of the study (Rubinstein at al., 2022) suggests that these changes may reflect redistribution of lymphocyte levels between blood and tissue, rather than acute changes in total cell levels. Further, N-803 induced elevated serum levels of IL-6, IL-10, and IFN-γ. Altogether, these data are in line with the immune-stimulating mechanism of action of N-803. The AE data for systemic administration of N-803 may be considered less relevant for the current safety evaluation, as PK analysis showed no evidence of N-803 in systemic circulation following intravesical instillation.

BCG + N-803 combination

Common adverse events

After intravesical administration of BCG + N-803, the most commonly reported TEAEs were within the SOC Renal and urinary disorders, reported in 72% of all patients in the Safety population. In BCG-naïve patients, there were generally no clinically relevant differences in the frequency of TEAEs in this SOC between BCG + N-803 and BCG monotherapy. Many of the reported reactions may be attributed to the instillation procedure or the intended immunologic response, rather than representing adverse reactions to BCG or N-803. Grade ≥3 AEs and SAEs within this SOC were few (reported in 4% and 3% of Safety population, respectively) and the only PT within this SOC reported as Grade ≥3 AE and/or SAE in more than one patient was haematuria (reported at similar frequency [1%] after BCG + N-803 and after BCG only in study QUILT-2.005).

A total of 45% of the Safety population reported TEAEs within the SOC General disorders and administration site conditions. The most commonly reported systemic reactions were likely a consequence of the intended immune-response to treatment and included fatigue, chills, pyrexia and influenza-like illness, with no relevant differences in frequency or severity between treatment groups (BCG + N-803 vs. BCG monotherapy).

TEAEs were also commonly reported within the SOC Infections and infestations (42% of the Safety population). The most common infection was Urinary tract infection (UTI), which was reported in 70/286 patients (24%). In study QUILT-2.005, UTI was slightly more common in the BCG + N-803 group (29%) than in the BCG only group (21%). The investigators assessed the UTI as treatment-related in 31/286 patients (11%). Other infections were reported at lower rates and most cases included infections that were considered not related to treatment. In 3 patents (1%), all in study QUILT-3.032 (BCG-unresponsive), a Grade ≥3 UTI was reported. These 3 events were also SAEs.

Gastrointestinal disorders, most commonly nausea and diarrhoea, were reported in a total of 31% of the Safety population with no relevant differences between treatment groups in study QUILT-2.005. Most events were Grade 1-2. Four subjects had a Grade ≥3 gastrointestinal event, but these events were not considered treatment-related by the investigator, an assessment that is agreed.

Other commonly reported TEAEs (≥10% of subjects in any treatment group) included arthralgia, headache, cough, dyspnoea and hypertension. Of these, only headache was assessed as treatment-related by the investigator. There were no relevant differences between treatment groups (BCG + N-803 or BCG monotherapy) in the frequencies of these TEAEs.

In addition, 10 subjects (4%) in the Safety population reported related non-treatment emergent AEs including AEs of dyspnoea and confusional state as well as grade 3 AEs of bacteraemia, encephalopathy and sepsis.

Longer median AE durations were reported in subjects treated with BCG + N-803 compared with BCG monotherapy for bladder spasm, urinary tract pain and micturition urgency, potentially indicating a slight effect of the combination treatment on the duration of the AEs. Other AEs dysuria, haematuria, pollakiuria, fatigue, chills and pyrexia: 2-5 days and urinary tract infection: 11 days) had generally similar duration (short to median) in all study arms.

Some changes in haematology parameters were observed, the most commonly reported was low haemoglobin, low lymphocytes, low leukocytes, and low platelets. Most effects were Grade 1. For haemoglobin, 14% of the Safety population reported worsening in grade from baseline (16% in QUILT-3.032). In BCG-naïve patients in QUILT-2.005, there were generally no relevant differences between patients treated with BCG + N-803 or BCG monotherapy in terms of haematology parameters.

The most common change in clinical chemistry was increased creatinine (reported in 80% of the Safety population, no ≥Grade 3 reactions), which in study QUILT-2.005 was observed at similar rates in patients treated with BCG + N-803 or BCG monotherapy. Increased blood creatinine is appropriately listed as an ADR in section 4.8 of the SmPC. The largest difference between treatment groups in clinical chemistry parameters was seen for high ALP, which was reported in 20% of subjects treated with BCG + N-803 and 10% of patients treated with BCG monotherapy.

Grade 3 or higher TEAEs occurred in 21% of all subjects receiving BCG plus N-803, most of which were Grade 3. The most commonly reported Grade ≥3 TEAE was hypertension, which was reported in 6% of the Safety population overall. There were no relevant differences between treatment groups in Study QUILT-2.005 in terms of Grade ≥3 TEAEs.

Grade 4 TEAEs were reported in altogether 9 subjects receiving BCG + N-803, and none of these events were assessed by the investigator as treatment-related, which is agreed.

Serious adverse events and deaths

SAEs were reported in 38/286 patients (13%) treated with BCG + N-803. Five of these reactions were considered related to N-803, and included haematuria, cystitis, UTI, sepsis and syncope. In study QUILT-2.005 (BCG-naïve patients), there was one SAE of disseminated BCG infection, which is an identified risk with BCG treatment. The patient had received BCG in combination with N-803. This case was assessed by the investigator as related to BCG and not to N-803. In the EU SmPC for BCG [BCG Medac] disseminated BCG infection is reported as an uncommon ADR of BCG treatment (≥ 1/1 000, < 1/100), with information on potential flare-ups of latent BCG infection with delayed onset included in section 4.4 of the SmPC. One case in a safety population of 286 patients might therefore not be unexpected. There is currently no immediate concern that addition of N-803 to BCG would increase the risk for disseminated BCG infection.

Section 4.4 of the SmPC for Anktiva includes a warning stating that the risk of severe systemic BCG-infection, potentially requiring anti-tuberculosis therapy, should be considered before starting BCG therapy, with a reference to the SmPC of the specific BCG product used.

Several cases of bacteraemia and sepsis (8 AEs in 6 subjects) have been reported in subjects treated with BCG in combination with N-803, including 3 AEs considered related to the study treatment. Sepsis and bacteraemia have been included in the list of ADRs in section 4.8 of the SmPC.

Overall, few SAEs were reported, and the pattern of SAEs is not unexpected/concerning in this patient population. All ongoing SAEs were followed up after the end of study participation until resolution or stabilisation of the SAE. Ongoing non-serious Grade 3 or 4 were not followed beyond the 30-day period after the last treatment dose.

For a majority of subjects receiving BCG plus N-803, TEAEs, including SAEs, were reported as recovered/resolved or recovering/resolving while on study.

Among a total of 26 deaths in studies QUILT-3.032 and QUILT-2.005 P1b/2b, five (5) were reported as due to AEs and only two (2) were due to a TEAE, i.e. occurring within 30 days after the last treatment. No deaths were assessed by the investigator as treatment-related, which is agreed. The most commonly reported causes of death were related to malignant disease (n=10).

Comparison of BCG-naïve and BCG-unresponsive subjects shows a low incidence of treatment-related grade ≥3 TEAEs and treatment-related SAEs, and no treatment-related deaths in either population. Overall, safety profiles were similar between the two groups. In both studies, renal and urinary disorders predominated, and included dysuria, pollakiuria, and micturition urgency, which occurred with comparable incidence.

Other significant adverse events

Adverse events of special interest (AESIs)

With the exception of "atrial fibrillation" (2 unrelated AEs in 2 subjects treated with BCG + N-803), terms or search queries defined as AESIs by the Applicant are mostly well-known and listed adverse reactions of intravesical BCG treatment. Consequently, AESIs occurred in 87% of subjects in the Safety population with 65% of subjects reporting treatment-related AESIs. As such, the value of the AESI analysis is limited.

In studies QUILT-3.032 and QUILT-2005 Phase 2b, the frequency of discontinuations due to AEs were similar in the N-803 + BCG and the BCG monotherapy groups (13-15%), indicating that addition of N-803 to BCG does not decrease tolerability to treatment. TEAEs reported as treatment-related and leading to study drug discontinuation, occurred in 5% of subjects receiving BCG plus N-803. The only treatment-related AEs assessed as related to the treatment and reported in more than 1 subject were cystitis and dysuria.

Although systemic exposure to N-803 is negligible following intravesical instillation, the use of a novel immuno-stimulating agent raises some concern regarding immune-related adverse reactions (irAEs) including the potential triggering of autoimmune disease. The number of irAEs in the two main safety studies was low and occurred in both treatment groups in study QUILT-2.005 Phase 2b, although treatment-related irAEs (as assessed by the investigator) were only reported in the BCG + N-803 group. Thus, currently available data may not indicate a risk for irAEs following N-803 treatment. Given a small safety database, the lack of long-term safety data and the novel and not well-characterised immunomodulatory mechanism of N-803, including on memory T-cell generation, however, the potential occurrence of late-onset irAEs is considered a potential risk that need further surveillance post-marketing. Immunological adverse reactions are therefore included in the list of

safety concerns in the RMP, as an important potential risk. Long-term safety is included as missing information in the RMP.

Special populations

The majority of subjects in QUILT-3.032 and QUILT-2.005 were ≥65 years of age (210 of 286 in the Safety population). There were no relevant differences in TEAEs between age groups. The only TEAE that occurred more commonly (with >10% higher frequency) in subjects ≥65 was fatigue. Grade ≥3 events were more commonly reported in elderly subjects, but there was no difference in Grade ≥3 TEAEs that were assessed as treatment-related.

Immunogenicity

The bioanalysis of anti N-803 antibodies (ADAs) and neutralising antibodies (nAb:s) is discussed under Clinical Pharmacology above. ADAs were reported in 7% of the subjects who received N-803 plus BCG. None of the subjects who were positive for anti-N-803 antibodies were reported to have an immune-related adverse event.

5.4.11.1.1. Overall assessment of available safety data

Addition of N-803 to BCG for the treatment of patient with BCG-unresponsive NMIBC with CIS, with or without papillary tumours, does not seem to add any major safety risks to the already known risks with intravesical instillation of BCG monotherapy. Most of the commonly reported AEs were consequences of the intended local inflammatory reaction or attributed to the instillation procedure. The safety profile of BCG in combination with N-803 appears to be consistent with what is anticipated for this treatment modality, and the treatment was overall well tolerated with low occurrence of Grade ≥ 3 adverse reactions and serious AEs as well as AEs leading to discontinuation. However, the safety database is limited, and does not allow for the identification of uncommon or rare ADRs. The available safety data is therefore not considered comprehensive within the meaning of a CMA (see section 9.6.3.1.). Additional safety data will be provided as part of the agreed SOBs under the CMA which will further support the evaluation of the safety profile.

5.4.11.1.2. Adverse drug reactions in the SmPC

The ADRs agreed for inclusion in section 4.8 of the SmPC are described in section 5.4.3.2. above.

5.4.11.2. Conclusions on clinical safety

No new safety concerns have been identified for N-803 in combination with BCG compared with BCG monotherapy. However, the available safety data is considered non-comprehensive to support a full marketing authorisation due to the limitations and uncertainties in the safety database. Additional safety data will be provided as part of the agreed SOBs under the CMA, which will further support the evaluation of the safety profile.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 63 Summary of safety concerns in proposed RMP

Important Identified Risk	None
Important Potential Risk	Immunological adverse reactions
Missing information	Long-term safety

6.1.2. Discussion on proposed safety specification

Severe systemic BCG infection, an important identified risk for BCG, is not considered a direct risk with N-803, and the current evidence for an increased risk when combined with N-803 is weak. Therefore, currently, this risk does need not to be included in the RMP for Anktiva at this stage, unless a new signal arises, e.g. from the randomised controlled trial QUILT-2.005 Phase 2b, which has been proposed as a SOB in the context of a CMA.

Although the currently available data on irAEs do not give raise to specific concern, N-803 is an immune-stimulating agent with a new target, and the safety database is still relatively limited. The lack of systemic exposure to N-803 is not considered as sufficient reassurance that the local immunologic reaction might not trigger a systemic reaction. Thus, there is some uncertainty regarding the potential risk for irAEs, and irAEs has been added as an important potential risk in the list of safety concerns.

Considering the short safety follow-up after treatment completion or discontinuation, long-term safety data appear limited, and the long-term safety profile of N-803 remains unclear. "Long-term safety" has been added as an item of missing information in the safety specification of the RMP. Long-term safety will be further characterised through extended 5-year follow-up in the ongoing study QUILT-3.032 agreed as part of the SOB (see Table 67).

Regarding the potential risk of anaphylactic reactions, it is a common risk for biologics. However, as there is no systemic exposure to N-803 after intravesical administration, and as anaphylactic reactions have so far not been observed after intravesical (or subcutaneous) administration of N-803, it does not seem relevant to list this risk as a safety concern, unless a new signal arises.

Also, the potential for medication errors is a general risk. In line with PhV guidance, this risk should be reviewed in PSURs for any product and does not need to be listed as a safety concern.

The proposed list of safety concerns is acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The applicant considers that routine pharmacovigilance activities are sufficient to monitor the safety profile of the product. No specific adverse reaction follow-up questionnaires or other forms are proposed.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

The PRAC rapporteur agrees that routine pharmacovigilance is considered sufficient.

6.2.2.2. Additional pharmacovigilance activities

There are currently no planned additional pharmacovigilance activities, although the applicant explains that the potential risks will continue to be closely monitored in clinical trials.

6.3. *Plans for post-authorisation efficacy studies*

Table 64 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study; Status	Summary of objective	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
QUILT-3.032; Ongoing	To examine the complete response rate, and duration of response for all patients enrolled in Cohort 1 (NMIBC CIS)	Long term efficacy	Interim reports	To be submitted with annual re-assessment*
			Final report	31/12/2029
QUILT-2.005 Ongoing	To assess the efficacy in BCG naïve patients with high-grade NMIBC by determining the complete response rate in Cohort A (NMIBC CIS), and disease-free survival in Cohort B (high-grade papillary disease Ta/T1 only)	Long term efficacy	Interim analysis#	30/06/2026
			Final CSR	30/06/2027
CIS, carcinoma *in situ*; IDMC, Independent data monitoring committee; NMIBC, non-muscle invasive bladder cancer. *Submission of annual reports until all patients have either experienced recurrence of high-grade non-muscle invasive bladder cancer, progression, death, or been lost to follow-up, for up to 4 years (trial completion 05/2029). #An interim analysis by an IDMC is expected by Q1 2026, with the possibility of sample size adjustment. Full enrolment is expected to be completed by Q2 2026 with the cutoff for the analysis of the primary endpoint (i.e. CR rate at 6 months) for the interim CSR by Q4 2026.				

6.4. *Risk minimisation measures*

6.4.1. Proposed risk minimisation measures

Table 65 Planned routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Immunological adverse reactions	Routine risk communication: • SmPC section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None
Long-term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

It is agreed that routine risk minimization measures are considered sufficient to mitigate risks of the products and no additional risk minimization measures are warranted at this stage.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation activities are proposed by the applicant, which is endorsed.

6.5. *RMP Summary and RMP Annexes overall conclusion*

The RMP Part VI and the RMP Annexes are acceptable.

In addition, the following minor revisions are recommended to be considered with the next RMP update: The audience of RMP summaries is very broad. At the next update the applicant should ensure that the summary is focused on essential information and uses a plain-language approach.

6.6. Overall conclusion on the Risk Management Plan

The CHMP considers that the risk management plan version 0.4 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP 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 submission requirements

The active substance is not included in the Union reference dates (EURD) list, and a new entry will be required. The new list of EURD list entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. However, the applicant did request an alignment of the PSUR cycle with the UK birth date of 04 July 2025. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the Product Information.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

Refer to the annotated SmPC.

8.1.1. SmPC section 4.1 justification

The approved indication is supported by the results of the pivotal clinical study submitted in the dossier, study QUILT-3.032, which evaluated Anktiva in combination with BCG in adult patients with BCG-unresponsive NMIBC with CIS, with or without papillary tumours. The target population in the indication is fully aligned with the population studied in the pivotal trial, including disease characteristics, prior BCG exposure and BCG-unresponsiveness, and restriction to adult patient population. No additional restrictions with respect to age, weight, or other patient-related factors were considered necessary.

8.2. Package Leaflet (PL)

Refer to the annotated PL.

8.3. Labelling text

See the attached labelling text.

8.4. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The language used for the purpose of user testing the PL was English. Assessment of the User Testing is attached in Appendices.

8.5. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Anktiva (Nogapendekin alfa inbakicept) is included in the additional monitoring list as it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

The agreed indication is: *Anktiva in combination with Bacillus Calmette-Guérin (BCG) is indicated for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.*

Anktiva is proposed to be administered intravesically at a recommended dose of 400 micrograms in combination with BCG, at a dose of 50 mL once a week for 6 weeks until disease persistence after the last induction cycle (initial, or, if administered, second induction (re-induction)), disease recurrence or progression, unacceptable toxicity, or a maximum of 37 months. Following the initial assessment of the response at month 3, a maintenance phase is recommended in case of complete response (lack of disease or low-grade Ta), or a second induction course (re-induction) may be given if residual CIS and/or high-grade Ta is observed at week-12 assessment.

The aim of the therapy with Anktiva is to avoid or postpone cystectomy.

9.1.2. Available therapies and unmet medical need

Current clinical guidelines for patients with intermediate or high-risk NMIBC, including CIS, recommend transurethral resection of bladder tumour (TURBT), followed by BCG as first-line therapy (Daniels 2020, Chang 2016, Gontero 2015). A high rate of tumours persists or recur despite treatment with BCG (Kamat 2017).

Several categories of BCG failures, broadly defined as any high-grade disease occurring during or after BCG therapy, have been proposed. BCG-unresponsive is one subgroup of patients where additional

BCG is unlikely to provide benefit and are regarded high-risk NMIBC patients because of their overall poor prognosis. In such cases, radical cystectomy (RC) is usually performed.

The European Association of Urology (EAU) guidelines for NMIBC (EAU NMIBC Guidelines, April 2024) recommend RC as the first option in case of treatment failure of intravesical BCG. Alternatively, enrolment in clinical trials investigating new treatment strategies, or bladder preserving approaches may be considered in patients who are unsuitable or who refuse cystectomy. However, for the BCG-unresponsive NMIBC, no intravesical or systemic therapy has been approved in the EU to date.

9.2. *Main clinical studies*

The evidence for the currently sought indication emerges from QUILT-3.032, a phase 2 open-label, single-arm, three-cohort, multicenter, US-based study in patients with BCG-unresponsive high-risk NMIBC with CIS, with or without Ta/T1 papillary disease, treated with intravesical N-803 in combination with BCG (cohort A and B) or N-803 alone (cohort C). Pivotal efficacy results pertain to Cohort A. Cohort B is not included in the efficacy evaluation, since this cohort does not fall within the scope of the indication sought in this procedure.

The primary endpoint was complete response (CR) rate at any time, as defined by cytology and cystoscopy/biopsy findings in the patient population randomised into Cohort A. The key secondary endpoint was duration of complete response (DoR), defined as time to loss of CR. PFS and disease specific survival are other key endpoints.

In total, 190 subjects were enrolled in the study of which 100 were enrolled in Cohort A and 10 in Cohort C. Until the time of data cut-off 15 July 2024, the treatment was completed for 90% of the Cohort A subjects and 100% of subjects in Cohort C. Cohort C was added to investigate the contribution of N-803 to the overall efficacy of the combination. However, this cohort was closed by the IDMC due to limited efficacy of N-803 alone.

Demographic and disease characteristics were similar across cohorts A and C and considered representative for BCG-unresponsive NMIBC subjects.

The treatment regimen consisted of an induction phase with N-803 in combination with BCG administered weekly over 6 weeks, with assessment of the response at month 3, followed by a maintenance phase if complete response (lack of disease or low-grade Ta) had been achieved, or a course (re-induction) if residual CIS and/or high-grade Ta were observed at month 3. The duration of treatment was until disease persistence after second induction (re-induction), disease recurrence or progression (new CIS and/or any T1 disease or greater), unacceptable toxicity, or a maximum of 37 months.

Until the data cut-off (15 July 2024), the median duration of follow-up for subjects was 25.68 months in cohort A, and 35.78 months in cohort C.

9.3. *Favourable effects*

- The primary endpoint was met: CR rate at any time in Cohort A (ITT population, n=100) was 71% (95% CI: 61.1, 79.6), which exceeded the lower bound of the 95% CI of 20%, which was the prespecified success criteria.
- Median DoR was 26.6 months (95% CI: 13.0, 49.9).

In Cohort A, the prespecified subgroup analyses of the primary and main secondary endpoints were consistent with the results in the primary efficacy population, which is also the ITT population.

9.3.1. Uncertainties and limitations about favourable effects,

- The single-arm trial design, with the absence of a control arm, limits the contextualization of the efficacy results. Furthermore, assessment of CR rate in NMIBC carries a risk of inaccurate ascertainment of CR ("false positive"), due to the known variability in the interpretation of cystoscopy and cytological evaluations. However, this concern is mitigated to some extent by pre-specified assessment procedures, high concordance between local and central cytology readings, as well as the observed duration of response, which together support the robustness of the efficacy findings. In addition, data from the ongoing study QUILT-2.005 Phase 2b will be submitted as a SOB (due date 30/06/2027), to further support the characterisation of the efficacy contribution of Anktiva to the combination and help address the uncertainty regarding the observed treatment effect.
- Approximately 10% of patients progressed to muscle-invasive or metastatic disease during the study. Due to the limited sample size (N=100) there is uncertainty around the precision of this estimate and the generalisability of the findings. In addition, 5 of 30 patients who did not respond to the first induction, and received a second induction (re-induction), progressed, raising uncertainty about the benefit of re-induction in non-responders. To mitigate this risk, a warning has been included in section 4.4 of the SmPC regarding the risk of progression to muscle-invasive or metastatic disease with delayed cystectomy, specifically in the context of re-induction. Longer follow-up of patients in the ongoing study QUILT-3.032 will be submitted as a SOB (due date 31/12/2029), which is expected to provide additional information on risk of progression, particularly in the subgroup of non-responders to initial induction.
- At the data cut-off (15 July 2024), the median duration of follow-up in cohort A was 25.68 months (range 3.2-63.5 months). In a population of NMIBC where durable CR is the treatment goal and radical cystectomy represents a curative treatment option, the available follow-up is not considered sufficient to fully characterise long-term outcomes, including duration of complete response and progression to muscle-invasive disease. This uncertainty will be addressed through the SOB to submit the final results of the ongoing QUILT-3.032 study with 5 years follow-up for all patients in the ITT population. The planned due date is 31/12/2029.

9.4. Unfavourable effects

The safety assessment is largely based on the pooled Safety population, which consists of 286 subjects with NMIBC who received intravesical instillations of BCG in combination with N-803 in the pivotal study QUILT-3.032 (BCG-unresponsive subjects, n=180, uncontrolled) or in the supportive study QUILT 2.005 (BCG naïve subjects, n=106, controlled). In QUILT-2.005 Phase 2b, a comparator arm was included, with 98 subjects treated with intravesical BCG only. The TEAE frequencies below are presented for the pooled Safety population, while due to differences in study populations between the two studies in terms of treatment experience and disease characteristics, the safety information in the SmPC is based only on Study 3.032.

The most commonly reported TEAEs were within the SOC Renal and urinary disorders, reported in 72% of all patients in the Safety population. Other commonly reported events were within the SOCs Infections and infestations (42%), General disorders and administration site conditions (45%), Gastrointestinal disorders (31%) and Musculoskeletal and connective tissue disorders (25%).

The most commonly reported Renal and urinary disorders included dysuria (37%), haematuria (34%), pollakiuria (32%) and micturition urgency (22%). Non-infective cystitis was reported in 6% of

subjects. Events of severity Grade ≥3 (NCI CTCAE criteria) within this SOC was reported in 4% of subjects, the most common Grade ≥3 event being haematuria (see below).

The most commonly reported PTs within SOC General disorders and administration site conditions included fatigue (26%), chills (14%) and pyrexia (12%). All these events were of severity grade <3.

Among infections and infestations, the most commonly reported PT was urinary tract infection (24%). There were three cases of UTI reported as SAEs. Other SAEs within this SOC were bacteraemia (2 cases), sepsis (2 cases) and one case of Grade 3 disseminated BCG infection.

Among gastrointestinal disorders, the most commonly reported PTs included nausea (11%) and diarrhoea (9%). All events of nausea or diarrhoea were of severity grade <3.

The most commonly reported PTs within SOC Musculoskeletal and connective tissue disorders included arthralgia (8%) and back pain (7%).

Grade ≥3 events were reported in 21% of subjects treated with BCG in combination with N-803. Grade ≥3 events reported in 2 or more subjects included hypertension (6%), haematuria (2%), pneumonia (1%), sepsis (1%), urinary tract infection (1%), hyperkalaemia (1%), syncope (1%), acute respiratory failure (1%), hyperkalaemia (1%), myalgia (1%) and back pain (1%).

There were two treatment-emergent Grade 5 AEs in subjects treated with BCG + N-803; reported causes of death were cardiac arrest and cholangitis, respectively. None of these events were considered related to treatment.

SAEs were reported in 13% of subjects treated with BCG in combination with N-803. SAEs that were considered related to N-803 by the investigator occurred in 2% of subjects and included haematuria, non-infective cystitis, syncope, sepsis and urinary tract infection. Treatment discontinuation due to a TEAE was reported in 9% of all subjects treated with BCG in combination with N-803. Discontinuation due to AEs that were considered treatment-related were reported in 5%. AEs leading to discontinuation that were assessed as related to treatment and reported in more than 1 subject were cystitis and dysuria. In study QUILT-2.005, treatment discontinuation due to a TEAE was reported in 7% of subjects treated with BCG in combination with N-803 and in 12% treated with BCG only.

A majority of the subjects in the Safety population (210/286) were ≥65 years of age. There were no clear differences in safety profile between younger or older subjects.

9.4.1. Uncertainties and limitations about unfavourable effects

- The limited size of the safety population, including data from BCG-naïve subjects receiving BCG in combination with N803 in QUILT-2.005 (Phase 1b/2b), does not allow for the identification of rare ADRs. In addition, the single-arm design of QUILT-3.032 limits the ability to characterise the individual safety profile of N-803. However, this uncertainty is partially mitigated by the supportive safety data from the QUILT-2.005 Phase 2b, which included both N-803 in combination with BCG and BCG-monotherapy arms, allowing for a limited comparison between N-803 in combination with BCG and BCG monotherapy. Further safety data will be provided as part of the agreed SOBs under the CMA which will further support the evaluation of the safety profile.
- Due to the limited safety follow-up after treatment completion or discontinuation, long-term safety data are lacking and the risk for late-onset ADRs remains largely uncharacterised. As a result, long-term safety is reflected as missing information in the RMP. In addition, long-term safety will be further characterised through extended 5-year follow-up in the ongoing study

QUILT-3.032 and provided as part of the SOB by 31/12/2029.

- Although the currently available data on immune-related AEs (irAEs) do not raise specific concerns, N-803 is an immune-stimulating agent with a new mechanism of action, and the overall safety database is still relatively limited. Thus, there is some uncertainty regarding the potential risk for local immune activation to trigger systemic immunological reactions, including irAEs. Therefore, irAEs are reflected as an important potential risk in the RMP, to be monitored in PSURs and further characterised in the agreed SOBs under the CMA.

9.5. *Effects Table*

Table 66 Effects Table for Anktiva in combination with BCG for the treatment of adult patients with BCG-unresponsive NMIBC with CIS with or without papillary tumours (data cut-off: 15 July 2024).

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
	Cohort A, Anktiva + BCG (N = 100)	**Cohort C, Anktiva (N = 10)**			
Complete Response (CR) Rate at any time (95% CI)	71% (61, 80)	20%		**SoE:** high concordance between local and central pathology reviewer for CR at any time (95%) **Unc:** limited external validity and comprehensiveness	Study QUILT-3.032
Median Duration of CR (DoR) (95% CI) (months)	26.6 (13.0, 49.9)	-			Study QUILT-3.032

Unfavourable Effects*					
Event	**QUILT-3.032** BCG + Anktiva (n=180)	**QUILT 2.005** BCG + Anktiva (n=106)	**QUILT 2.005** BCG only (n=98)	Safety population n =286 Comparator n=100	**QIULT-3.032 and QUILT-2.005**
Disseminated BCG infection	0	1 (1%)	0	"	"
Bacteraemia	3 (2%)	0	0	"	"
Sepsis	2 (1%)	1 (1%)	1 (1%)	"	"
Renal and urinary disorders	120 (67%)	85 (80%)	76 (78%)	"	"
Fatal adverse events	4 (2%)	1 (1%)	0		
Treatment-emergent	2 (1%)	0	0		
Treatment-related	0	0	0		

SAEs	27 (15%)	11 (10%)	10 (10%)		
Treatment-related	2 (1%)	3 (3%)	2 (2%)		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; <sBA: serum bile acids>; <PELD: paediatric end-stage liver disease>; <MELD: model for end-stage liver disease score>; <SBD: surgical biliary diversion>; <OLT: orthotopic liver transplantation>; <PE: primary endpoint>; <SE: secondary endpoint>; <OR: odds ratio>.

* Incidence of treatment-emergent and non-treatment-emergent AEs

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Radical cystectomy (RC) remains the only potentially curative option for patients with BCG-unresponsive NMIBC, but it is a major surgical intervention associated with significant morbidity and impact on quality of life. Delaying or avoiding cystectomy in patients who are unwilling or unfit to undergo radical surgery, as well as delaying progression in patients not deemed eligible for cystectomy, are considered valid treatment goals and represent an unmet medical need in the EU.

The single-arm phase 2 study QUILT-3.032 met the primary endpoint showing a CR rate at any time of 71% (95% CI: 61.1, 79.6), which exceeded the lower bound of the 95% CI of 20%, which was the prespecified success criteria. The median DoR was 26.6 months (95% CI: 13.0, 49.9).

In the overall population of QUILT-3.032, 17% of subjects underwent cystectomy during the study, including 8 responders and 9 non-responders. Overall, 10% of patients developed muscle-invasive or metastatic disease during the study. Notably, a higher proportion of patients (5/30) who received a second induction course (re-induction) progressed to muscle-invasive or metastatic disease, compared with patients responding to first induction (5/70). A warning has been added in section 4.4 of the SmPC on the risk of progression to muscle invasive and metastatic bladder cancer with delayed cystectomy.

In summary, the antitumoral activity of Anktiva in combination with BCG has been demonstrated. However, residual uncertainties remain, primarily concerning the durability of long-term efficacy and the precise magnitude of clinical benefit relative to standard of care. These uncertainties warrant further characterisation post-authorisation and will be addressed through specific obligations in the context of the conditional marketing authorisation.

The safety profile of Anktiva in combination with BCG was consistent with expectations for this treatment modality and the combination was generally well tolerated. However, the small study population, the single-arm, open-label design of study QUILT-3.032 and the limited duration of long-term safety follow-up, limit the characterisation of the safety profile. The available data are insufficient for the identification of less common adverse reactions, and the long-term safety profile remains incompletely characterised. These aspects will be further characterised through the agreed SOBs.

With regards to patients that remain eligible for radical cystectomy after losing response to BCG, treatment with Anktiva in combination with BCG, appears to be a reasonable treatment option based on the high CR rate and observed duration of complete response. However, a risk of progression to muscle-invasive or metastatic disease with delayed cystectomy needs to be considered by patients and prescribers when considering alternative treatment strategies. A warning has been included in section 4.4. of the SmPC, to inform healthcare professionals on the key factors relevant to this decision, including the risk of progression to muscle-invasive or metastatic disease associated with a lack of

response to initial induction. While a second induction course (re-induction) may be given, this should be accompanied by a careful reassessment of the appropriateness of proceeding to radical cystectomy. The risk of developing muscle-invasive or metastatic bladder cancer increases the longer cystectomy is delayed in the presence of persisting CIS.

There is a recognised unmet medical need in patients with BCG-unresponsive NMIBC who are ineligible for radical cystectomy, as well as those who are eligible, but who decline the procedure due to its impact on quality of life. In these populations, the benefit-risk profile of Anktiva in combination with BCG is considered positive.

In view of the uncertainties described above under (9.3.1. 9.4.1.) and further elaborated below (9.6.3.), the available data are considered not comprehensive. Therefore, a conditional marketing authorisation is appropriate.

9.6.2. Balance of benefits and risks

Based on the available efficacy data and the acceptable safety profile in this setting, the benefit-risk is considered positive in the proposed indication and a conditional approval of Anktiva is supported.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Conditional marketing authorisation

9.6.3.1.1. Applicant's request for Conditional Marketing Authorisation

The applicant initially sought a full marketing authorisation. However, during the assessment, in response to concerns raised by the CHMP regarding the non-comprehensiveness of the data submitted, the applicant requested that the application be considered under the provisions for a conditional marketing authorisation.

The applicant acknowledged the non-comprehensive nature of the clinical dossier and provided a justification to support the eligibility of Anktiva for a CMA, addressing the four required criteria:

a) A positive benefit-risk balance:

The applicant considers that the benefit-risk is positive in the target population based on the high CR rate at any time, and the durability of response, together with an acceptable safety profile.

b) It is likely that the applicant will be able to provide comprehensive data post-authorisation:

Two specific obligations (SOBs) are proposed and relate to ongoing clinical studies:

- The applicant has committed to providing longer-term follow-up data from the ongoing **QUILT-3.032** study. The estimated completion of the study and submission of the results, including the 5-year follow up period for all subjects, is expected by December 2029.
- In addition, the applicant proposed **QUILT-2.005 Phase 2b** as a second SOB. This is an ongoing, phase 2b, randomized, open-label, multicenter study in BCG-naïve NMIBC patients. In this study, Anktiva in combination with BCG is compared to BCG monotherapy, with CR rate as the primary endpoint and DFS as a key secondary endpoint. An interim analysis will be performed on Cohort A by an independent data monitoring committee (IDMC) to assess

futility and determine whether a sample size increase is warranted. The outcome of the interim analysis is expected by Q3 2026. Final study results from QUILT-2.005 Phase 2b will be submitted upon completion, expected by June 2027.

This study directly evaluates the added value of N-803 in a controlled setting by including a comparator arm, thereby allowing contextualisation of the antitumor activity of N-803. Although conducted in a different patient population (i.e., BCG-naïve NMIBC patients), results from this trial are expected to further inform the contribution of N-803 to the overall efficacy of the combination. In addition, the randomised design is expected to further support a more robust assessment of efficacy while providing a larger and comparative safety dataset in a related disease setting.

c) The medicine fulfils an unmet medical need:

Anktiva addresses a well-defined unmet medical need in adult patients with BCG-unresponsive NMIBC, with CIS with or without papillary tumours, when used in combination with BCG. No medicinal product is currently approved in the European Union for this specific indication.

Current standard of care options for BCG-unresponsive NMIBC with CIS include systemic immunotherapy, intravesical chemotherapy, and RC with urinary diversion. RC is the current preferred treatment after BCG and systemic immunotherapy failure. Although RC is considered curative for patients with high-risk NMIBC, it is associated with substantial perioperative morbidity and mortality, and a clinically relevant negative impact on quality of life. In addition, many patients are medically ineligible for cystectomy due to comorbidities or decline the procedure because of its impact on quality of life. As a result, a large proportion of patients remain without effective or acceptable therapeutic options.

d) The benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required:

The applicant notes that residual uncertainties primarily concern long-term efficacy durability, attribution of AEs to Anktiva, and the precise magnitude of benefit relative to standard of care. These uncertainties, however, are limitations inherent to the design and sample size of the pivotal study, but do not indicate emerging safety signals. The risk of underestimating adverse reactions due to limited exposure is addressed through ongoing safety monitoring, the proposed risk minimisation measures and the completion and submission of ongoing confirmatory studies providing long-term follow up and comparative data.

Given the established potential for clinical benefit, particularly in patients who are ineligible for or unwilling to undergo cystectomy, immediate availability provides a public health benefit that outweighs the risks associated with remaining uncertainties.

9.6.3.1.2. Discussion on the non-comprehensiveness of data in the context of a Conditional Marketing Authorisation

In regard to the request for a conditional marketing authorisation, the CHMP considers that the following is to be accounted in terms of non-comprehensiveness of the dossier:

Due to the limitations in the pivotal study design, including the absence of a randomised comparator arm as well as a limited sample size, the available data are not considered comprehensive within the meaning of the CMA legislation. As outlined above, these uncertainties include the risk of inaccurate ascertainment of CR ("false positives"), the challenge in quantifying the potential risk of progression to muscle-invasive or metastatic disease when cystectomy is delayed in eligible patients and the limited follow-up, which is not considered sufficient to fully characterise long-term outcomes. With respect to

safety, the main uncertainties include the theoretical risk of systemic immune-related AEs due to local immunogenicity and the risk of rare and late-onset ADRs.

9.6.3.1.3. Conclusions and recommendation on Conditional Marketing Authorisation

As comprehensive data on the product are not available, as discussed above, the applicant requested that the application be considered under the provisions for a conditional marketing authorisation.

The product falls within the scope of Article 14-a(1) of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease. Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance of Anktiva in combination with BCG for the treatment of adult patients with BCG-unresponsive NMIBC with CIS with or without papillary tumours is positive, as discussed above
- It is likely that the applicant will be able to provide comprehensive data post-authorisation: the measures proposed by the applicant concerning QUILT-2.005 and QUILT-3.032 (see Table 67) are considered appropriate to address the above-mentioned uncertainties (sections 9.3.1. and 9.4.1. that currently render the dataset non-comprehensive. Since the studies proposed are ongoing, with clearly defined timelines, it is considered likely that comprehensive data will be provided post-authorisation.
- An unmet medical need will be addressed: it is agreed that Anktiva addresses an unmet medical need in the EU. Anktiva provides a major therapeutic advantage over radical cystectomy, which is associated with significant peri-operative morbidity and mortality ranging from 0.8% to 8%. Anktiva is a bladder-sparing option and serves as an alternative for patients who are ineligible for RC or refuse the procedure because of its impact on quality of life. There are currently no medicinal products approved for this indication.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required, given the established potential for clinical benefit, particularly in patients who are ineligible for or unwilling to undergo cystectomy, and the lack of alternatives in this setting

The CHMP considers the following measures necessary to address the missing data in the context of conditional marketing authorisation:

Table 67 Specific obligations in relation to the CMA

Description	Due date
In order to confirm the efficacy and safety of nogapendekin alfa inbakicept in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours, the MAH shall submit the results of the ongoing open-label randomized phase IIB QUILT-2.005 study to evaluate the efficacy and safety of intravesical BCG in combination with nogapendekin alfa inbakicept versus BCG alone in patients with BCG-naïve NMIBC.	30 June 2027
In order to confirm the efficacy and safety of nogapendekin alfa inbakicept in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS) with or without papillary tumours, the MAH shall submit the final results including the 5-years follow up period for patients of the ongoing open-label single-arm	31 December 2029

Description	Due date
phase II/III QUILT-3.032 study.	

9.7. Benefit-risk conclusions

9.7.1. At Day 210 – Final CHMP conclusions

The benefit-risk of Anktiva in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours, is positive, based on the high CR rate at any time, and the durability of response, together with an acceptable safety profile.

10. Appendix

CHMP AR on new active substance claim

Nogapendekin alfa inbakicept is a dimeric fusion protein acting as an interleukin-15 (IL-15) superagonist. The fusion protein contains IL-15 with an N72D substitution (IL-15N72D), which is non-covalently bound with high affinity to an IL-15Rα sushi domain fused to IgG1 Fc. The mode of action for nogapendekin alfa inbakicept is mediated by the biological activity of IL-15N72D, which includes lymphocytic activation of T cell and NK cell antitumor responses without initiating an adverse T regulatory (Treg) cell-mediated response. The activity exerted by nogapendekin alfa inbakicept in NK and CD8+ T cell proliferation assays is vastly enhanced by the engineered N72D substitution.

The Applicant has based the NAS claim of nogapendekin alfa inbakicept on indent 1, as the introduced changes of nogapendekin alfa inbakicept have a significant impact on its biological function compared to the wild-type IL-15. Further, no IL-15-based medicinal product has been previously authorized in the EU for the proposed target population of nogapendekin alfa inbakicept. The Applicant has conducted searches in relevant databases, including the European Medicines Agency (EMA) Medicine finder for medicinal products for human use, the Union Register of medicinal products for human use, as well as consulted the MRI Product Index of the Heads, and scientific publications, to confirm that no similar active substance is currently authorised in the EU.

The approach to conduct searches in established databases, including terms related to interleukin-15 in general, the individual basic structural elements (IL-15N72D, nogapendekin alfa; IL-15RαSu/IgG1Fc, inbakicept; IL-15N72D:IL-15RαSu/IgG1Fc, nogapendekin alfa inbakicept) is in line with the Reflection paper on criteria to be considered for the evaluation of new active substance status of biological substances. In addition, supportive data from the database searches and sequence comparisons have also been provided as requested from the Reflection paper on NAS. Based on the review of available data on the active substance, the CHMP considers that nogapendekin alfa inbakicept is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.