EU Risk Management Plan (RMP) for ANKTIVA (N-803)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

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Summary of significant changes in this RMP:

Not applicable – this is Version 1.0 of the RMP.

QPPV name: Dr. Marcus May

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The signature is available on file.

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ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BC	Bladder Cancer
BCG	Bacillus Calmette-Guérin
CHF	Congestive Heart Failure
CIS	Carcinoma *in situ*
CR	Complete Response
CSR	Clinical Study Report
DFR	Disease-free Rate
DFS	Disease-free Survival
DP	Drug Product
EAU	European Association of Urology
eCTD	Electronic Common Technical Document
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
EOS	End Of Study
EPAR	European Public Assessment Report
EU	European Union
FDA	Food And Drug Administration
GLP	Good Laboratory Practice
HG	High-grade
IDMC	Independent data monitoring committee
IL-2	Interleukin-2

IL-15	Interleukin-15
INN	International Non-Proprietary Name
IV	Intravenous
JAK	Janus Kinase
LTF	Long-term Follow-up
MAH	Marketing Authorisation Holder
MIBC	Muscle-invasive bladder cancer
MTD	Maximum Tolerated Dose
NA	Not Applicable
NK	Natural Killer (Cell)
NMIBC	Non-muscle Invasive Bladder Cancer
No	Number
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
PBS	Phosphate Buffered Saline
PD	Pharmacodynamic
PK	Pharmacokinetic
PS	Performance Status
PSUR	Periodic Safety Update Report
RC	Radical cystectomy
RD	Recommended Dose
ROA	Route of Administration
SAE	Serious Adverse Event
SC	Subcutaneous
SCS	Summary of Clinical Safety
SD	Study Day
SmPC	Summary of Product Characteristics
STAT	Signal Transducer and Activator of Transcription
TEAE	Treatment Emergent Adverse Event
TURBT	Transurethral Resection of The Bladder Tumour
ULN	Upper Limit of Normal

USA	United States of America
WHO	World Health Organization
WOE	Weight of Evidence

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Nogapendekin alfa: Interleukin 15 [72-aspartic acid] (Human IL-15N72D isoform) Inbakicept: Interleukin 15 receptor α chain (human sushi domain containing fragment) fusion protein with immunoglobulin G1 (human Fc fragment) (ANKTIVA)
Pharmacotherapeutic group(s) (ATC Code)	Therapeutic category: Interleukins ATC code: L03AC03
Marketing Authorisation Applicant	ImmunityBio Ireland Limited Grand Canal Square 2, 6th floor D02 A342 Dublin Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ANKTIVA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Immunological recombinant protein
	Summary of mode of action: Nogapendekin alfa inbakicept-pmln is an IL-15 receptor superagonist. IL-15 signals through a heterotrimeric receptor that is composed of the common gamma chain (γc) subunit, the beta chain (βc) subunit, and the IL-15-specific alpha subunit, IL-15 receptor α. IL-15 is *trans*-presented by the IL-15 receptor α to the shared IL-2/IL-15 receptor (βc and γc) on the surface of CD4+ and CD8+ T cells and NK cells. Binding of nogapendekin alfa inbakicept-pmln to its receptor results in proliferation and activation of NK, CD8+, CD4+, and memory T cells without proliferation of immuno-suppressive T_{REG} cells.
	IL-15 demonstrates a lack of activation of T_{REG} cells due to differential signal transduction pathways in T_{REG}cells downstream of IL-15α / IL-2 βγc engagement in comparison to NK cells, CD8+ killer T cells and memory T cells. This has also been demonstrated

	for the N-803 complex. In so far as the relevance of local administration of N-803 and specific activation of lymphocytes, there are several human and mouse studies detailing immune populations in the healthy bladder. These studies suggest that the bladder is not an immune-privileged site as resident T cells (CD4+ and CD8+), B cells, dendritic cells (Langerhans'-like DCs) and macrophages are present in the urothelium and/or the lamina propria in heathy individuals. BCG-activation of the tumour environment stimulates innate immunity resulting in further recruitment of adaptive immune cells. Within the bladder, DCs may capture antigens and migrate to secondary lymphoid organs and present antigen to T cells, resulting in activation. Important information about its composition: The ANKTIVA drug product (DP) is comprised of ANKTIVA in phosphate buffered saline (10 mM potassium phosphate, 10 mM sodium phosphate, 140 mM sodium chloride, pH 7.4). ANKTIVA DP is a clear to slightly opalescent, colourless to slightly yellow solution. Each vial of 0.4mL contains 400 micrograms of ANKTIVA in the delivered dose of 0.4 mL. Vial should not be shaken. **ANKTIVA must not be used for subcutaneous, intradermal, intramuscular or intravenous administration.**
Hyperlink to the Product Information	The product information including the Summary of Product Characteristics (SmPC) and the package leaflet is included within Module 1.3.1 of the electronic common technical document (eCTD) sequence.
Indication(s) in the EEA	Current: ANKTIVA in combination with BCG is indicated for the treatment of adult patients (≥18 years of age) with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS) with or without papillary tumours.
	Proposed: Not applicable
Dosage in the EEA	Current: For induction: 400 micrograms administered intravesically as a mixture with BCG recommended at a dose of 50 mg once a week for six weeks. A second induction course may be administered if complete response is not achieved at month 3 (re-induction). Re-induction is recommended in case of residual CIS +/- high grade Ta at the first assessment after induction (at week 12).

	For maintenance: 400 micrograms administered intravesically with BCG once a week for three consecutive weeks at months 4, 7, 10, 13 and 19 (for a total of 15 doses). Presence of a low-grade Ta will require a transurethral resection of bladder tumour (TURBT) procedure prior to instillation. Treatment may be delayed by up to 28 days after TURBT procedure if required. For patients with an ongoing complete response at month 25 and later, maintenance instillations with Anktiva and BCG may be administered once a week for three consecutive weeks at months 25, 31, and 37 for a maximum of 9 additional instillations.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Concentrate for intravesical suspension. Nogapendekin alfa inbakicept, 400 micrograms /0.4 mL clear to slightly opalescent, colourless to slightly yellow solution, pH 7.4, in single-dose vials (0.4 mL) for intravesical instillation after dilution.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Non-muscle Invasive Bladder Cancer

Incidence and Prevalence

In Europe, 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 (European Association of Urology 2022). 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).

Approximately 75% of bladder cancer patients present with a disease that is confined to the mucosa (Ta, CIS) or submucosa (T1), which are grouped under NMIBC (Gontero 2024). High-grade tumours in NMIBC, such as high-grade papillary are diagnosed in around 10% of patients (Tang and Chang 2015). The prognosis of patients with high-risk NMIBC is poor, with approximately 20% progressing to muscle-invasive disease and 14% of patients dying from BC. Most of these events occur relatively early, within about four years (van den Bosch and Witjes 2011).

BCG-unresponsive NMIBC

Some tumours recur during BCG treatment or after a short disease-free interval after receipt of BCG treatment. FDA Guidance for Industry: BCG-Unresponsive Non-muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment has defined BCG-unresponsive NMIBC as meeting at least one of the following criteria:

- Persistent or recurrent CIS (with or without 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
- 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
- T1 high-grade disease at the first evaluation following induction with BCG alone (at least 5 of 6 doses of an initial induction course).

The category of BCG-unresponsive tumours comprises BCG-refractory and some BCG-relapsing tumours. The European Association of Urology (EAU) recommends transurethral resection of the bladder tumour (TURBT) followed by intravesical full-dose BCG instillations for these patients, as this treatment has been shown to be superior to TURBT alone or TURBT with subsequent chemotherapy in preventing NMIBC recurrence (Gontero. 2024). However, BCG instillations still fail in up to 50% of patients (Meng 2019). A high rate of tumours persists or recur despite treatment with BCG bladder instillation (Kamat 2017). BCG-unresponsive NMIBC CIS patients are unlikely to benefit from further BCG treatment and are considered high-risk NMIBC patients with a poor prognosis. The 5-year survival rate decreases with disease progression from 69.5% for localized disease to 4.6% for metastatic disease (Saginala 2020).

Demographics of the population in the proposed indication and risk factors for the disease

The demographics of BC are evolving, reflecting an improved understanding of the human exposome and the changing nature of industrialisation (Jubber 2023). The worldwide age-standardised incidence rate for BC (per 100,000 person/years) is 9.5 in men and 2.4 in women. In the European Union, the age-standardised incidence rate is 20 in men and 4.6 in women (Gontero 2024). The male to female ratio for NMIBC is 3:1, and disease incidence increases with age. While rates of bladder cancer are higher in Caucasians than other ethnicities, disease specific survival is worse overall for African-Americans (Holzbeierlein 2024). In general, most important risk factors include tobacco smoking, occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, and pelvic radiation for BC (Gontero 2024). The longer duration of cigarette smoking, and more pack-years were both associated with higher risk of recurrence of NMIBC in a dose-dependent manner (Kwan 2022).

The main existing treatment options

The current standard of care for patients with intermediate or high-risk NMIBC is TURBT followed by treatment with an induction course (6-weekly instillations) with or without maintenance therapy (3-weekly instillations at three and six months thereafter for one to three 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 2024) A high rate of tumours persists or recur despite treatment with BCG (Kamat 2017). In such cases, a radical cystectomy 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). Importantly, many patients are poor candidates for radical cystectomy due to comorbidities or may strongly prefer bladder preservation treatment strategies (Gontero 2024; Packiam 2021).

Thus, there is a continuing unmet medical need for safe and effective therapies with a durable response for treatment of BCG-unresponsive NMIBC.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

BC incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and variations in access to, and delivery of, healthcare. The age-standardised mortality rate is 3.3 for men and 0.86 for women per 100,000 person/years (Gontero 2024; Saginala 2020). While the overall 5-year survival rate for BC is 77%, the frequency of recurrence and progression, accompanied by significant negative impacts on quality of life, act to increase disease burden (Saginala 2020). NMIBC has a high 5-year survival rate of over 88% but relapses after initial treatment in 50% to 70% and progresses to muscle-invasive bladder cancer (MIBC) in 10% to 30% of cases. This necessitates regular surveillance and follow-up procedures, which impose a high financial burden and can impact the quality of life (Bree 2022).

Important co-morbidities

There are no identified comorbid conditions specifically associated with NMIBC. Patients over 50 years of age diagnosed with NMIBC share comorbidities with other individuals in this age range, such as

hypertension, cardiovascular disease, diabetes, cerebrovascular disease, and pulmonary disease, which are commonly prevalent among this age group (Megwalu 2008; Barone 2023).

Part II: Module SII - Non-clinical part of the safety specification

The non-clinical program in support of this marketing authorisation application includes studies utilizing systemic and intravesical administration of ANKTIVA. A total of 16 toxicology studies were performed. The Sponsor conducted ten of these studies of which one was reported in the literature. The remaining six additional toxicology studies performed in collaboration with academic institutions were published in the literature.

Four non-GLP repeat-dose toxicity studies were conducted in mice to evaluate the toxicological effects and biological activity of ANKTIVA. Three of these studies involved a 4-week intravenous (IV) administration of N-803, while the fourth study used the subcutaneous (SC) route of administration. In addition, there were two safety studies that were conducted. There was a GLP 13-week SC repeat dose toxicity study in rats (20328204) and a non-GLP 1-month IV repeat dose toxicity study in cynomolgus monkeys (YLP-1203, YLP-1203 Addendum).The toxicology program in support of ANKTIVA is summarized in Table SII.1.

Table SII.1 – Toxicology Study Type and Duration

Study Type and Duration	GLP/non-GLP	Test Articles/Doses	Dosing Regimen	ROA	Species	Study No.
Repeat-Dose Toxicity						
1 month; recovery group to 36 days	Non-GLP	ANKTIVA (0.1, 1.0 or 4.0 mg/kg); PBS	4 weekly doses on SD 1, 8, 15, and 22	IV	Mouse (C57BL/6)	PC-ALT-803-41-11
1 month	Non-GLP	ANKTIVA (4.0 mg/kg); PBS	4 weekly doses on SD 1, 8, 16, and 22	IV	Mouse (BALB/c)	PC-ALT-803-04-12
1 month; recovery group to 50 days	Non-GLP	ANKTIVA (0.1 or 1.0 mg/kg); PBS	4 weekly doses on SD 1, 8, 15, and 22	IV	Mouse (C57BL/6)	PC-ALT-803-03-12
1 month	Non-GLP	ANKTIVA (1.0 mg/kg); PBS	4 weekly doses on SD 1, 8, 15, and 22	SC	Mouse (C57BL/6)	(Liu 2018), PC-ALT-803-04-15, PC-ALT-803-04-15 Amendment
13 weeks; recovery 90 to 126 days	GLP	ANKTIVA (0.1, 0.3 and 1.0 mg/kg); PBS	Once every two weeks on study days 1, 15, 29, 43, 57, 71, and	SC	Rat (Sprague Dawley)	20328204; 20328204 - ADA Report, Appendix 15; 20328204-IMP Report, Appendix

Study Type and Duration	GLP/non-GLP	Test Articles/Doses	Dosing Regimen	ROA	Species	Study No.
			85			16; 20328204-Cytokines Report, Appendix 17; 20328204-TK, Appendix 14
1 month; recovery group to 36 days	Non-GLP	ANKTIVA (0.03 or 0.1 mg/kg); PBS	4 weekly doses on SD 1, 8, 15, and 22	IV	Cynomolgus monkey	YLP-1203, YLP-1203 Addendum
						PC-ALT-803-02-13 (ADA aspect)
						PC-ALT-803-01-13 (PK aspect)
						YLP-1203NG (PD aspect)
Carcinogenicity						
Weight of Evidence (WOE) Assessment[a]	n/a	n/a	n/a	n/a	n/a	IB-CC-TR2025-001R
Reproductive and Developmental Toxicity						
Weight of Evidence (WOE) Assessment[a]	n/a	n/a	n/a	n/a	n/a	IB-ES-LA2020-001R

ADA: anti-drug antibody, GLP: good laboratory practices, IMP: immunophenotyping, IV: intravenous, No.: number, PBS: phosphate buffered saline, PD: pharmacodynamic, PK: pharmacokinetic, ROA: route of administration, SC: subcutaneous, SD: study day, TK: toxicokinetics, WOE: Weight of Evidence.
[a]As per (U. S. Food and Drug Administration Center for Drug Evaluation and Research 2019).

Additionally, literature search was conducted to identify articles that described studies with ANKTIVA that are in addition to the studies included in ImmunityBio study reports and publications. Thus, the objective of the literature search was to find articles that describe the pharmacology, pharmacokinetics, and toxicology of ANKTIVA.

Among the five searches, there were 290 unique publications. A publication was considered relevant if it included N-803 or ALT-803 in the non-clinical studies that were reported in the publication. Reviews, editorials, clinical reports, and publications describing other IL-15 therapies (i.e., not N-803 or ALT-803) were considered not relevant. An overview of the 76 studies in the non-clinical program in support of ANKTIVA are shown in Table SII.2.

Table SII.2 – Summary of Non-clinical Pharmacology, Pharmacokinetic, and Toxicology Studies With ANKTIVA

Type of study	Number of Studies
Pharmacology Studies	
Primary Pharmacodynamics	25
Secondary Pharmacodynamics	20

Type of study	Number of Studies
Pharmacokinetic Studies	
Method of Analysis	11
Study Type	
Absorption	8
Distribution	2
Toxicology Studies	
Repeat - Dose Toxicity	6
Carcinogenicity	1
Reproductive and Developmental Toxicity	1
Other Toxicity Studies - Antigenicity	2
Total Number of Studies	76

Repeated Dose Toxicity Studies

A GLP repeated dose toxicity study (20328204) examined the potential toxicity of ANKTIVA, when given subcutaneously (0.1, 0.3, 1.0 mg/kg/day) once every other week for 13 weeks (on Days 1, 15, 29, 43, 57, 71, and 85;7 total doses) to Sprague Dawley rats, and to evaluate the potential reversibility of any findings. In addition, the toxicokinetics (20328204, Toxicokinetics Report, Appendix 14), immunogenicity (anti-N-803) (20328204, Anti-Drug Antibody Report, Appendix 15), flow cytometry (cell phenotypes) (20328204, Immunophenotyping Report, Appendix 16), and cytokines (20328204, Cytokines Report, Appendix 17) associated with ANKTIVA administration were determined. The results observed in this study are consistent with the immunostimulatory mechanism of action of ANKTIVA. Under the conditions of this study, the no observed adverse effect level (NOAEL) was considered to be 1.0 mg/kg.

A repeated dose non-GLP study in cynomolgus monkeys (YLP-1203, YLP-1203 Addendum) was conducted to determine the reversal or potential worsening of pharmacological/ toxicological effects, and/ or potential delayed toxic effects of ANKTIVA. The important safety pharmacology endpoints to reveal any functional effects on the major physiological systems, including the cardiovascular, central nervous, and respiratory systems were evaluated. The monkeys were dosed via intravenous (IV) route with either vehicle (Group A) or ANKTIVA at 0.03 mg/kg (Group B) or 0.1 mg/kg (Group C) once weekly for four consecutive weeks (days 1, 8, 15, and 22). The low-dose group (0.03 mg/kg) exhibited increased lymphocytic infiltration in the liver and lungs, though to a lesser extent than the high dose (0.1 mg/kg) group. The results observed in this study are consistent with the immunostimulatory mechanism of action of ANKTIVA. At the low dose (0.03 mg/kg), the immunostimulatory effects were present with the absence of adversity; thus, the lowest dose, 0.03 mg/kg, is the NOAEL for this study.

Overall, the toxicology data demonstrate that N-803 is well-tolerated even with systemic routes of administration.

Relevance to human usage

In general, the incidence and/or severity of toxicities was reversed by the end of the recovery period. ANKTIVA related haematology parameter changes are consistent with an ANKTIVA-mediated shift from erythropoiesis to leukocyte production, which is expected based on the immunostimulatory mechanism of action of ANKTIVA. The study did not find any abnormal pathology findings in the heart. Furthermore, there were no dose-related abnormalities based on electrocardiogram (ECG) evaluations recorded during the in-life phase. Similarly, there were no abnormal findings in brain weight or pathology that would be related to an effect in the brain. There were no indications of toxicological effects in the key safety pharmacology parameters or organs (central nervous system, cardiovascular, respiration) in the 13-week rat study and the one-month monkey study. Since ANKTIVA is administered intravesically with BCG and there is no systemic absorption, the findings are not relevant to human use.

Immunogenicity

The immunogenicity (antigenicity) of ANKTIVA was assessed by evaluating the development of anti-drug antibody (ADA) following administration of ANKTIVA in rats (20328204, Anti-Drug Antibody Report, Appendix 15) and monkeys (PC-ALT-803-02-13).

Relevance to human usage

Although ANKTIVA elicited antibodies in some of the monkeys there was no correlative impact to pharmacodynamics or post-dosing allergic reactions. Though local tolerance was not specifically assessed in non-clinical studies using intravesical administration of N-803, data from IV or SC routes of administration suggests that there are no local tolerance concerns.

Incidence of anti-drug antibodies in QUILT-2.005 Phase 2b study was low with only 5% of subjects testing positive at all post-baseline assessments. No neutralizing antibodies were detected. Similarly, in QUILT-3.032, only 3% of subjects tested positive for anti-drug antibodies at any post-baseline assessment and only 3 subjects tested positive for neutralizing antibodies. The low incidence of ADA is consistent with the mode of administration for both studies limiting systemic exposure and the fact that N-803 contains a human IL-15 moiety coupled to the human IL-15 alpha receptor which is identical to the native IL-15 alpha receptor. Based on the observed low rates of ADA, their low titers and low number of patients with neutralizing antibodies, it is unlikely that ADA will have safety concerns or effects on exposure and efficacy.

Reproduction and Postnatal Development

The typical patient diagnosed with NMIBC is between 50 and 70 years old and thus, most female patients with NMIBC are likely to be past childbearing age. Despite these demographics, consideration still needs to be made for any patient that may be of reproductive potential. The approach taken here to address reproductive toxicity of ANKTIVA for NMIBC CIS follows FDA's Guidance for Industry, "Oncology Pharmaceuticals: Reproductive Toxicity and Labeling Recommendations" (U. S. Food and Drug Administration Center for Drug Evaluation and Research 2019). In lieu of animal reproductive toxicity studies, a written assessment utilizing a weight-of-evidence (WOE) approach was generated (IB-ES-LA2020-001R), combining the results of a comprehensive literature search, with the results of internal non-clinical and clinical studies, to present a systematic assessment of the risk of ANKTIVA to fertility, pregnancy, and embryo-foetal development to patients with NMIBC CIS.

The literature-based assessment suggests that there are risks if ANKTIVA were to be systemically absorbed. However, because intravesical administration of ANKTIVA has no systemic absorption, maternal use is not expected to result in foetal exposure to the drug. Similarly, because intravesical administration of ANKTIVA has no systemic absorption, maternal use is not expected to result in exposure of a child while breastfeeding. However, it is recommended to verify pregnancy status in females of reproductive potential prior to initiating ANKTIVA. Additional information on pregnancy and lactation is provided in Module 2.4.

Carcinogenesis, Mutagenesis, Impairment of Fertility

ANKTIVA has not been tested for its carcinogenesis or mutagenesis potential (Module 2.6.6 Section 2.6.6.4, Module 2.6.6 Section 2.6.6.5). In lieu of a chronic rat carcinogenicity study, a written assessment utilizing a weight-of-evidence approach was generated (IB-CC-TR2025-001R), combining the results of a comprehensive literature search, with the results of internal nonclinical and clinical studies, to present an assessment of the carcinogenicity risk of N-803. Based on this assessment, there was little to no evidence for potential carcinogenicity as the result of intravesical administration of N-803 in BCG-unresponsive patients with NMIBC. No studies on the effects of ANKTIVA on fertility have been conducted. IL-15 was used as a surrogate molecule for ANKTIVA in a literature-based assessment to aid in the determination of embryo-foetal development, pregnancy, and reproductive toxicity risks of

ANKTIVA in the unlikely event that it was to be systemically absorbed following intravesical administration.

Relevance to human usage

Since IL-15 has been shown to be a key component of the embryo implantation process, maternal exposure to ANKTIVA could affect fertility and early pregnancy through both foetal exposures, as well as through the expansion and activation of uterine natural killer cells and CD8+ T cells and the resultant pro-inflammatory impact on the maternal immune system. Therefore, ANKTIVA has the potential to pose a risk to fertility, foetal development, and pregnancy maintenance based on exposure to higher levels of IL-15.

There are no data on the use of ANKTIVA in pregnant women. Animal reproduction studies have not been conducted with ANKTIVA. 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. These results indicate a potential risk. ANKTIVA is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to ANKTIVA following intravesical administration is negligible (below the limit of quantitation). There are no data on the presence of ANKTIVA in human milk, or the effects on the breastfed child, or on milk production. ANKTIVA can be used during breast-feeding.

Overall, the toxicology data demonstrate that ANKTIVA is well-tolerated even with systemic routes of administration. Based on clinical data (Module 2.7.2), what is known about the biological properties of ANKTIVA (Module 3.2.S.1.3), and the physiology of the bladder wall there is no detectable absorption following intravesical administration of ANKTIVA. Safety margins have not been evaluated for intravesical administration and the highest dose of 400 micrograms is well-tolerated in clinical studies. In conclusion, the non-clinical toxicology program data suggest that intravesical administration of ANKTIVA is safe, and results in minimal toxicities.

Part II: Module SIII - Clinical trial exposure

The clinical safety data supporting the use of ANKTIVA in the proposed indication of BCG-unresponsive NMIBC CIS with or without Ta or T1 papillary disease comes from QUILT-3.032 (cohorts A, B and C) and QUILT-2.005 P1b/2b (cohorts A and B). The overall clinical program is provided in Table SIII. 1 and include the protocol number, the study status, the report date (or data cut-off date), the study type, the primary objective, the population and the number of subjects exposed to study drug, the dose and dosing regimen, and the type of data collected.

The pharmacokinetics and pharmacodynamics of ANKTIVA after subcutaneous (SC) administration was determined in a study in healthy subjects (QUILT-1.004). The QUILT-1.004 is included to provide pharmacokinetic, pharmacodynamic, and safety data after SC administration for comparison to the results after bladder instillation.

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.

Table SIII. 1 – Clinical Studies Supporting ANKTIVA 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: ANKTIVA SC Administration					
QUILT-1.004; Completed 13 Mar 2018	Single centre, open-label	Determine PK profile after SC ANKTIVA administration	Healthy adult volunteers 20 subjects	10 micrograms/kg ANKTIVA, followed 15 days later by 20 micrograms/kg ANKTIVA	Safety PK PD
NMIBC: ANKTIVA Bladder Instillation					
QUILT-2.005 Phase 1b; Completed 14 Aug 2017	Phase 1b dose-escalation, multicentre, open-label, single-arm	MTD and RD of ANKTIVA+BCG for BCG-naïve NMIBC	Adults with BCG-naïve NMIBC 9 subjects	ANKTIVA (100 micrograms, 200 micrograms, or 400 micrograms) 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, multicentre	CR rate (for CIS) or DFS (papillary) of ANKTIVA plus BCG versus BCG alone	BCG-naïve NMIBC 195 total Cohort A (CIS ± Ta/T1): 120 Cohort B (HG Papillary): 75	ANKTIVA (400 micrograms) 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 ANKTIVA	Enrolment in QUILT-3.032 or QUILT-2.005 phase 2b 1 subject	ANKTIVA (400 micrograms) 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 July 2024	Phase 2/3, open-label, single-arm, three-cohort, multicentre	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	ANKTIVA (400 micrograms) 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, SC: subcutaneous.

[a]Enrolment in the PK sub-study 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.

The clinical development program providing efficacy data in support of ANKTIVA plus BCG for patients with BCG-unresponsive high-grade NMIBC (CIS) is comprised of one study (QUILT-3.032), which is a phase 2/3, open-label, single-arm, three-cohort, multicentre study of intravesical ANKTIVA plus BCG or ANKTIVA alone in subjects with BCG-unresponsive high-grade (HG) NMIBC. The data cut-off for this study was 15 July 2024. A total of 286 subjects with NMIBC received intravesical administration of ANKTIVA plus BCG, 98 subjects received BCG only, and 10 subjects received ANKTIVA alone. A total of three subjects received intravesical ANKTIVA at a dose of 100 micrograms, three subjects a dose of 200 micrograms, and 290 subjects at a dose of 400 micrograms. Further detail on exposure is presented in Module 2.7.4 Section 2.7.4.2.3.**2**. and summarized by treatment regimen for the combined analysis population in Table SIII.2.

The demographic profile of all subjects exposed to ANKTIVA plus BCG or BCG is summarised in Table SIII.3.

Table SIII.2 – Summary of Subjects Exposed to ANKTIVA by Dose and Population - Safety Population

Dose	Healthy Subjects (QUILT-1.004)	BCG Naïve (QUILT-2.005-P1b/P2b)			BCG Unresponsive (QUILT-3.032)			Total Subjects with NMIBC			Total Subjects
	(n)	CIS (n)	HG Pap (n)	All (n)	CIS (n)	HG Pap (n)	All (n)	CIS (n)	HG Pap (n)	All (n)	
SC Administration											
10 micro grams /kg	20	NA	NA	NA	NA	NA	NA	NA	NA	NA	20
20 micro grams /kg	14[a]	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
Intravesical Bladder Administration (micrograms/instillation)											
100 micro grams	NA	0	3	3	NA	NA	NA	0	3	3	3
200 micro grams	NA	1	2	3	NA	NA	NA	1	2	3	3
400 micro grams	NA	60	40	100	110	80	190	170	120	290	290
Total Subjects											
n	20[a]	61	45	106	110	80	190	171	125	296	316

BCG: Bacillus Calmette-Guérin, CIS: carcinoma *in situ*, HG: high grade, kg: kilogram, micrograms: microgram, NA: not applicable, NMIBC: non-muscle invasive bladder cancer, SC: subcutaneous.
[a]A total of 14 of the 20 subjects who received 10 micrograms/kg ANKTIVA in study period 1 also received 20 micrograms/kg ANKTIVA in study period 2. Thus, a total of 20 subjects received ANKTIVA SC.
Source: QUILT-1.004 Clinical Study Report (CSR), QUILT-2.005-P1b CSR Table 14.1.3, SCS Table 2.1.1, SCS Table 2.1.2, SCS Table 2.1.3.

Table SIII.3 – Demographics: Safety Population – Study 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 + ANKTIVA (N = 286)
	BCG + ANKTIVA (N = 180)	BCG + ANKTIVA (N = 106)	BCG (N = 98)	
Age groups				
Median	73.0	68.0	67.0	70.5
Min, max	46, 93	26, 91	41, 89	26, 93
Age groups (years), n (%)				

Variable Category/Statistic	**BCG Unresponsive (QUILT-3.032)**	**BCG-Naïve (QUILT-2.005-P1b/P2b)**		**All Subjects Receiving BCG + ANKTIVA (N = 286)**
	BCG + ANKTIVA (N = 180)	**BCG + ANKTIVA (N = 106)**	**BCG (N = 98)**	
< 65	38 (21%)	38 (36%)	39 (40%)	76 (27%)
≥ 65	142 (79%)	68 (64%)	59 (60%)	210 (73%)
Gender				
Female	34 (19%)	17 (16%)	16 (16%)	51 (18%)
Male	146 (81%)	89 (84%)	82 (84%)	235 (82%)
Race				
American Indian or Alaska Native	2 (1%)	1 (1%)	1 (1%)	3 (1%)
Asian	3 (2%)	9 (8%)	3 (3%)	12 (4%)
Black or African American	9 (5%)	7 (7%)	3 (3%)	16 (6%)
Native Hawaiian or other Pacific Islander	1 (1%)	1 (1%)	1 (1%)	2 (1%)
White	161 (89%)	85 (80%)	84 (86%)	246 (86%)
Not reported	1 (1%)	0	0	1 (0%)
Other	1 (1%)	1 (1%)	2 (2%)	2 (1%)
Unknown	2 (1%)	2 (2%)	4 (4%)	4 (1%)
Ethnicity				
Hispanic or Latino	6 (3%)	3 (3%)	2 (2%)	9 (3%)
Not Hispanic or Latino	170 (94%)	95 (90%)	89 (91%)	265 (93%)
Not reported	2 (1%)	6 (6%)	4 (4%)	8 (3%)
Unknown	2 (1%)	2 (2%)	3 (3%)	4 (1%)
Baseline weight (kg)				
Median	87.45	82.50	83.30	85.05
Min, max	41.7, 160.3	54.4, 165.0	46.7, 127.7	41.7, 165.0
Baseline ECOG performance status, n				
0 – 1	175 (97%)	105 (>99%)	97 (99%)	280 (98%)
2	5 (3%)	1 (1%)	1 (1%)	6 (2%)

Note: Includes QUILT-3.032 subjects treated with BCG plus N-803 at 400 micrograms/instillation (N = 180); QUILT-2.005 phase 2b subjects treated with BCG plus N-803 at 400 micrograms/instillation (N = 97) or BCG alone (N = 98); QUILT-2005 phase 1b subjects treated with BCG plus N-803 at 400micrograms/instillation (N = 3), at 200 micrograms/instillation (N = 3), and at 100 micrograms/instillation (N = 3). BCG: Bacillus Calmette-Guérin, ECOG: Eastern Cooperative Oncology Group, max: maximum, min: minimum, PS: performance status.
Reference: SCS Table 1.2.3.

Safety analyses are based on the safety population, which consisted of all subjects who received at least one dose of BCG and/or N-803. Safety was assessed by the incidence and severity of TEAEs, AESIs, clinical laboratory tests, changes in vital signs, treatment exposure, concomitant medications, immunogenicity, and physical examinations for all subjects who received at least one dose of study treatment.

QUILT-3.032 is ongoing and long-term safety data will be assessed including participants who are in the follow-up phase of the study (up to month 60) and added to the safety database.

The combination of ANKTIVA plus BCG was well-tolerated by subjects with NMIBC, and the safety profile was consistent with the established profile for subjects receiving BCG only. The most common TEAEs reported after ANKTIVA plus BCG administration were related to bladder instillation of drug treatment and were generally grade 1-2. The most common (>10% of subjects) TEAEs were renal and urinary disorders, including dysuria (37%), haematuria (34%), pollakiuria (32%), micturition urgency (22%), and urinary tract infection (24%). Fatigue (26%), chills (14%), pyrexia (12%), nausea (11%), and hypertension (11%) were also commonly reported. Treatment-related grade ≥3 TEAEs, treatment-related serious adverse event (SAEs), and treatment related TEAEs leading to study drug discontinuation were all rare, each occurring in ≤5% of subjects. Observed toxicities were manageable, seldom requiring dose delays or supportive treatment. No treatment-related deaths occurred after administration of ANKTIVA plus BCG.

In QUILT-3.032, when compared with ANKTIVA plus BCG (Cohorts A and B), treatment with ANKTIVA monotherapy was well-tolerated and associated with lower incidence of TEAEs (including those associated with drug discontinuation and drug interruption) (Module 2.7.4 Section 2.7.4.3.1.2), lower severity of TEAEs, and lower incidence of SAEs (Module 2.7.4 Section 2.7.4.3.1.4). However, with ANKTIVA administered alone, the treatment duration was limited to induction only due to the lack of therapeutic effect. Thus, safety results from QUILT-3.032 support two conclusions: 1) results from QUILT-3.032 provide evidence that ANKTIVA plus BCG treatment was associated with low toxicity and high tolerability; 2) the safety profile of ANKTIVA administered alone provides evidence that compared to the BCG package insert, ANKTIVA plus BCG does not raise new safety concerns.

Treatment administered in QUILT-2.005 P1b/P2b enabled comparison of safety in patients with the same NMIBC treatment history (BCG-naïve) receiving ANKTIVA plus BCG versus BCG alone. The overall safety profile was similar in these two treatment groups; there were no clinically meaningful differences in the safety profile of intravesical ANKTIVA plus BCG treatment when compared with intravesical BCG treatment. The most common grade ≥3 TEAE of hypertension occurred at comparable levels between treatments arms (11% of subjects receiving ANKTIVA plus BCG and 12% of subjects receiving BCG alone) (Module 2.7.4 Section 2.7.4.3.1.2). Treatment-emergent SAE occurred in 10% of subjects receiving both ANKTIVA plus BCG and BCG only (Module 2.7.4 Section 2.7.4.3.1.2). The similar safety profiles of ANKTIVA plus BCG versus BCG alone provide additional evidence that, compared to the BCG package insert, the safety profile of ANKTIVA plus BCG does not raise new safety concerns.

Overall, these findings support the conclusions that ANKTIVA plus BCG has an acceptable safety profile for the treatment of subjects with BCG-unresponsive NMIBC and is comparable to BCG monotherapy which is approved for the treatment of patients with NMIBC. The safety profile of ANKTIVA in combination with NMIBC is unchanged with over two years treatment of subjects with NMIBC.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Population with recurrence of BCG unresponsive Ta/T1 disease (without presence of CIS) more than six months after last BCG instillation or BCG unresponsive CIS more than 12 months after last BCG instillation.	For the disease to be considered unresponsive to BCG, it must occur within six or 12 months (depending on the staging) of the last instillation of BCG. Reflects the indication.	No	The population does not reflect the proposed indication.
Population with 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 five years that is progressing or requires active treatment.	Previous cancers within the last five years or active cancers, and the respective therapy of these, influence the effectivity and safety of a local bladder cancer therapy.	No	The population does not reflect the proposed indication.
Population with concurrent febrile illness, active urinary tract infection, active tuberculosis.	The application of ANKTIVA in combination with BCG in patients with a febrile or infective disease, such as urinary tract infection and tuberculosis, might impact the course of these diseases. Patients with febrile illness, active urinary tract infection, active tuberculosis should not be treated with BCG.	No	The application of ANKTIVA in combination with BCG, a live-attenuated vaccine, in the bladder could influence the inflammatory response caused by the previous urinary tract infection, which could increase the undesired symptoms and complicate the treatment of the infection. When given systemically, ANKTIVA has an immunostimulatory effect which, in

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			combination with BCG, might influence the course of disease of tuberculosis or febrile illness.
Population with ongoing chronic systemic steroid therapy required (e.g. more than 10 mg oral prednisone daily of equivalent)	Immunocompromised participants may have impaired immune responses which might affect the treatment.	No	Immunosuppressants might affect the mechanism of action of ANKTIVA which is based on the stimulation, proliferation and activation of natural killer and lymphocytes cells. Since ANKTIVA is administered intravesically with BCG and there is no systemic absorption, systemic exposure is negligible. The safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Pregnant, breastfeeding, or planning to become pregnant during the study	Clinical development generally does not initially investigate benefit/risk in pregnant women.	No	There are no data for the use of ANKTIVA in pregnant women; and animal reproduction studies have not been conducted with ANKTIVA The systemic exposure of breastfeeding woman to ANKTIVA is negligible, therefore no effects are expected on the breastfed newborn/infant. Fertility studies with ANKTIVA have not been conducted.
Liver function abnormalities as indicated by ongoing hepatic enzyme	Clinical development generally does not initially investigate benefit/risk in patients with moderate to	No	There are no or limited amount of data for the use of ANKTIVA in patients

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
elevation (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) >2X upper limit of normal	severe hepatic impairment.		with impaired hepatic function; since ANKTIVA is administered intravesically with BCG and there is no systemic absorption, systemic exposure is negligible. The safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Renal insufficiency as indicated by a creatinine level >3X upper limit of normal	Clinical development generally does not initially investigate benefit/risk is patients with moderate to severe renal impairment	No	There are no or limited amount of data for the use of ANKTIVA in patients with impaired renal function; since ANKTIVA is administered intravesically with BCG and there is no systemic absorption, systemic exposure is negligible. The safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Any of the following clinical laboratory values at the time of enrollment: a) Absolute neutrophil count (ANC) < 800/µL b) Platelets < 50 000/µL	Individuals with low ANC may have impaired immune responses which might affect the treatment. Further, low platelet count might increase the risk of bleeding during the procedure.	No	There are no or limited amount of data for the use of ANKTIVA in patients with low ANC or low platelet count; since ANKTIVA is administered intravesically with BCG and there is no systemic absorption, systemic exposure is negligible. The safety profile is not expected

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
History or evidence of uncontrollable central nervous system disease	History or evidence of uncontrollable central nervous system might affect the ability to provide informed consent or adhere to the trial protocol.	No	There are no or limited amount of data for the use of ANKTIVA in patients with uncontrollable central nervous system disease; since ANKTIVA is administered intravesically with BCG and there is no systemic absorption, systemic exposure is negligible. The safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Active systemic infection requiring parenteral antibiotic therapy. All prior infections must have resolved following optimal therapy.	The application of ANKTIVA in combination with BCG, a live-attenuated vaccine, in the bladder could influence the inflammatory response caused by the systemic infection, which could increase the undesired symptoms and complicate the treatment of the infection.	No	When given systemically, ANKTIVA there is no systemic absorption, systemic exposure is negligible. The safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile
Symptomatic congestive heart failure (CHF), New York Heart Association (NYHA) Class III or IV heart failure or other clinical signs of severe cardiac dysfunction. Severe/unstable angina pectoris, or myocardial	Clinical development generally does not initially investigate benefit/risk is patients with moderate to severe heart impairment	No	There are no or limited amount of data for the use of ANKTIVA in patients with impaired heart function; since ANKTIVA is administered intravesically with BCG and there is no

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
infarction within 6 months prior to study entry			systemic absorption, systemic exposure is negligible. The safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Paediatric Population	The disease does not occur in any subset of the paediatric population	No	Bladder cancer in paediatric patients occurs very rarely, with incidence rates reported at 0.1-0.4%. The tumours are typically low-grade ad non-invasive. The European Medicines Agency has waived the obligation to submit the results of studies with ANKTIVA in all subsets of the paediatric population in the treatment of bladder cancer.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or repeated exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1 – Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	

Type of special population	Exposure
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Refer to Table SIII.3 for exposure information by ethnic origin from the studies.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Marketing authorisation (MA) for ANKTIVA has been granted in the USA on 22 April 2024 to Altor BioScience, LLC, an indirect wholly-owned subsidiary of ImmunityBio, Inc., and 63 doses of ANKTIVA have been distributed in the market since May 2024. No adverse events have been reported to the Sponsor. Post-authorisation exposure is calculated using monthly shipment reports from commercial operations. Additionally, ImmunityBio pharmacovigilance team monitors any AE/SAEs reported on ANKTIVA. The two data sources are combined to calculate the total exposure value.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

ANKTIVA is a soluble complex consisting of a human IL-15N72D super agonist and a dimeric human IL-15 receptor α (IL-15Rα), used in the treatment of NMIBC. The interleukins are non-habit forming, non-narcotic and have no potential for misuse. There is no potential for recreational use.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients:

- Irritable bladder symptoms during instillation, dysuria, pollakiuria, urinary tract infection, nocturia, micturition urgency and haematuria.
- Systemic adverse events including fatigue, chills, pyrexia, nausea, increased creatinine, diarrhoea, musculoskeletal pain, headache, pruritus, rash, and malaise.

Other reasons for considering the risks not important:

- Anaphylactic reactions: This is considered as a potential risk since, as with any other drug, rarely allergic or hypersensitivity reactions could occur in individuals allergic/hypersensitive to any components of the product. However, no cases of anaphylaxis have been reported in clinical or non-clinical trials with ANKTIVA.
- Medication errors: There is potential of medication errors with ANKTIVA if not administered as per the instructions given in the package leaflet. An inaccurate administration may traumatize the urinary tract or introduce contaminants into the urinary system. However, this is a preventable risk, and no cases of medication errors were observed in the clinical trials.

There are no data on the use of ANKTIVA in pregnant women. Animal reproduction studies have not been conducted with ANKTIVA; however, 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. These results indicate a potential risk. ANKTIVA is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

Risks	Risk-benefit impact
None	Not Applicable

Important Potential Risks

Risks	Risk-benefit impact
Immunological adverse reactions	This is a potential risk inherent to any immune-modulatory therapy. The currently available data on immunological adverse reactions do not give raise to specific concern but the safety database is still relatively limited. N-803 is not locally resorbed and the systemic exposure is negligible, but the local immunologic reaction might trigger a systemic reaction. Given the medical need, the extremely limited treatment options for patients with BCG-unresponsive NMIBC, and the good safety profile, the therapeutic benefit seen with N-803 plus BCG of a 71% CR rate outweighs the risk.

Missing information

Risks	Risk-benefit impact
Long-term safety	QUILT-3.032 is an ongoing study so not all safety data has been collected to date. Long-term safety data will be collected and assessed through long-term safety monitoring including for participants who are in the follow-up phase of the study (up to month 60) and this information will be added to the safety database.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable as this is the initial RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Immunological adverse reactions

Potential mechanisms:

Although the systemic exposure to N-803 is negligible following intravesical instillation, the immuno-stimulatory mechanism of N-803 may be associated with a potential risk of immunological adverse reactions, including the triggering of autoimmune diseases.

Evidence source(s) and strength of evidence:

In subjects that received intravesical administration of N-803, reported adverse events were predominantly local genitourinary events and mild systemic symptoms (e.g., chills, pyrexia). Immune-mediated AEs were not specifically reported. However, as N-803 is an immunostimulatory agent with a novel target, and the current safety database is still relatively limited, immunological adverse reactions are considered as an important potential risk.

Characterisation of the risk:

Mode of action of N-803 is immune activation through IL-15 receptor agonism. Potentially, immune-mediated inflammatory events across different organ systems could be triggered by this unspecific immune activation (e.g., pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, myocarditis). In clinical trials with N-803 no signal for immune-mediated toxicity was reported. After intravesical administration at the approved dose, systemic exposure was below the limit of quantitation, which biologically reduces the likelihood of systemic immune activation and immune-related adverse events. However, there is a theoretical potential risk based on the mechanism of action (IL-15 receptor agonism activates NK and CD8+ T cells), despite the low systemic exposure with the approved intravesical route. Subject information is summarized in Table SVII.1.

Table SVII.1 Immune-Related Adverse Events in QUILT-3.032

System Organ Class Preferred Term	Relationship to Study Drug	Subject Number	Age	Gender	Grade	Outcome	Treatment Start to Incident (days)
Infections and infestations							
Conjunctivitis	Unrelated	[redacted]	71	[redacted]	1	Recovered/ Resolved	112
Conjunctivitis	Unrelated	[redacted]	71	[redacted]	2	Recovered/ Resolved	113
Skin and subcutaneous tissue disorders							
Alopecia	Unrelated	[redacted]	77	[redacted]	1	Recovered/ Resolved	1
Psoriasis	Unlikely	[redacted]	[redacted]	[redacted]	2	Recovering/ Resolving	532
Musculoskeletal and connective tissue disorders							
Rheumatoid arthritis	Possible	[redacted]	72	[redacted]	1	Recovered/ Resolved	144
Respiratory, thoracic and mediastinal disorders							
Idiopathic pulmonary fibrosis	Unrelated	[redacted]	79	[redacted]	1	Not Recovered/ Not Resolved	416
Gastrointestinal disorders							
Pancreatitis acute	Unrelated	[redacted]	65	[redacted]	3	Recovered/ Resolved	337
Immune system disorders							
Drug hypersensitivity	Unrelated	[redacted]	73	[redacted]	3	Recovered/ Resolved	28
Drug hypersensitivity (Cipro and Bactrim DS)	Unrelated	[redacted]	79	[redacted]	1	Not Recovered/ Not Resolved	360
General disorders and administration site conditions							
Systemic inflammatory response syndrome	Unrelated	[redacted]	73	[redacted]	3	Recovered/ Resolved With Sequelae	48

System Organ Class Preferred Term	Relationship to Study Drug	Subject Number	Age	Gender	Grade	Outcome	Treatment Start to Incident (days)
Source: Listing 16.2.4.1, Listing 16.2.3, Listing 16.2.7.							

A total of 8 subjects had 1 or more of these TEAEs: subject [redacted] had two instances of conjunctivitis (grade 1 and 2, considered unrelated to study drug); [redacted] had alopecia (grade 1, unrelated); [redacted] had psoriasis (grade 2,unlikely related); [redacted] had rheumatoid arthritis (grade 1, possibly related); [redacted] had idiopathic pulmonary fibrosis (grade 1, unrelated); [redacted] had acute pancreatitis (grade 3, unrelated); [redacted] had drug hypersensitivity and systemic inflammatory response (both grade 3, unrelated); and subject [redacted] had drug hypersensitivity (grade 1, unrelated).

Risk factors and risk groups:

There are no identified risk factors for the development of immunological adverse reaction following N-803 intravesical administration. Conditions that might increase systemic absorption (e.g., traumatic catheterization, gross haematuria with disrupted urothelium) could in theory raise a risk.

Preventability:

There are currently no reliable predictors of susceptibility of individual patients to develop immunological adverse events following intravesical N-803 treatment. Generally, the product is for intravesical administration only; parenteral administration is explicitly not permitted by the SmPC. Standard bladder-instillation precautions are to be applied to minimize mucosal trauma and inadvertent systemic exposure. Routine pharmacovigilance activities will include targeted queries for immune-mediated terms (MedDRA) in ICSRs and periodic reports to proactively surveil for immunological adverse reactions.

Impact on the risk-benefit balance of the product:

The overall number of potential immunological adverse events reported in clinical trials was low and assessed as not related to the study treatment. The benefit-risk balance of ANKTIVA is considered positive based upon its safety profile and the overall survival rate. The magnitude of benefit seen with N-803 plus BCG of a 71% CR rate, a 26.6 month median duration of response, and a 90.9% probability of absence of progression at 24 months in responders.

Public health impact

This risk has minimal public health impact beyond its effect on individual patient.

SVII.3.2. Presentation of the missing information

Missing Information: Long-term Safety

Evidence Source:

Due to the relatively limited safety database and a short follow-up duration in the pivotal trial, long-term safety is considered as missing information.

Population in need of further characterisation:

Patients with BCG-unresponsive NMIBC. Long-term safety assessments will include extended follow-up of responders to evaluate the durability of response and to identify any late-onset adverse events.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII. 1 – Summary of safety concerns

Important Identified Risk	None
Important Potential Risk	Immunological adverse reactions
Missing information	Long-term safety

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the safety profile of the product.

Planned global pharmacovigilance procedures for monitoring and collection of safety of Anktiva will include weekly regulatory intelligence searches to remain up to date on current on applicable global regulations, scientific literature monitoring using MedLine, International Pharmaceuticals Abstracts (IPA) and Inside Conferences (CON), quarterly Increased Frequency reviews on a compound level and weekly searches of the FAERS, Eudravigilance, and WHO VigiAccess databases for Anktiva reports. Should new information arise from any data source that impacts the marketing authorization or product safety, the Safety Review Committee will convene to review and determine if the emerging safety issue or signal meets the definition of an emerging safety issue according to, GVP-Module IX Signal Management. If warranted, EMA will be notified within 3 working days after establishing that a signal or a safety issue from any source is confirmed as an emerging safety issue. If the new or changed risk requires a change to the product information and /or Risk Management Plan, a variation application will be submitted rather than a separate stand-alone signal notification. All pharmacovigilance activities for Anktiva will be detailed and documented within the Pharmacovigilance System Master File (PSMF).

Specific adverse reaction follow-up questionnaires:

No specific adverse reaction follow-up questionnaires are proposed by the Marketing Authorisation Holder (MAH).

Other forms of routine pharmacovigilance activities:

None proposed.

III.2 Additional pharmacovigilance activities

Based on the safety data analysis from three clinical trials (QUILT-2.005-P1b, QUILT-2.005-P2b, and QUILT-3.032), intravesical BCG plus ANKTIVA has a comparable safety profile to intravesical BCG monotherapy in high-risk NMIBC (Module 2.7.4). QUILT-3.032 is ongoing and long-term safety data and incidence of immunological adverse reactions will be assessed including for those participants who are in the follow-up phase of the study (up to month 60) and any report information will be added to the safety database. Otherwise, no additional pharmacovigilance activities are proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

The interim analysis of QUILT-3.032, which is an on-going trial was the basis of the ANKTIVA BLA 761336 FDA approval. As part of the FDA approval post-marketing commitments (22 April 2024), the Sponsor committed to completing the trial as provided below (Table Part IV. 1).

In addition to the QUILT-3.032 data, a comprehensive analysis will ultimately be performed on the BCG-naive population in QUILT-2.005 Phase 2b.

QUILT-2.005 is an on-going, Phase 2b, randomized, open-label, multicentre study in BCG-naive NMIBC. The respective milestones for the QUILT-2.005 are presented in the table below.

Table Part IV. 1 – Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation

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.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Although no immune-mediated toxicities have been identified in the clinical development or postmarketing experience with intravesical ANKTIVA, there is a theoretical potential for immunological adverse reactions given its immune-activating mechanism and class effects observed with systemic immunotherapies. At present, routine risk minimization measures and routine pharmacovigilance are considered adequate.

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

V.2. Additional Risk Minimisation Measures

No additional risk minimisation measures are required for ANKTIVA. Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immunological adverse reactions	Routine risk minimisation measures: • SmPC section 4.8 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • QUILT-2.005 – final study report due 30/06/2027 • QUILT-3.032 – final study report due 31/12/2029
Long-term safety	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • QUILT-2.005 – final study report due 30/06/2027 • QUILT-3.032 – final study report due 31/12/2029

Part VI: Summary of the risk management plan

Summary of risk management plan for ANKTIVA (hIL-15N72D/hIL-15RαSu-Fc complex Interleukin 15 [72aspartic acid] (Human IL-15N72D isoform))

This is a summary of the risk management plan (RMP) for ANKTIVA (hIL-15N72D/hIL-15RαSu-Fc complex Interleukin 15 [72aspartic acid] (Human IL-15N72D isoform)). The RMP details important risks of ANKTIVA, how these risks can be minimized, and how more information will be obtained about ANKTIVA risks and uncertainties (missing information).

ANKTIVA summary of product characteristics (SmPC) and its package leaflet gives essential information to healthcare professionals and patients on how ANKTIVA should be used.

This summary of the RMP for ANKTIVA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ANKTIVA in RMP.

I. The medicine and what it is used for

ANKTIVA is authorised for use in combination with Bacillus Calmette–Guérin (BCG) for the treatment of patients with BCG-unresponsive or non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS) with or without papillary tumours. It contains a soluble complex consisting of nogapendekin alfa (a human IL-15N72D receptor agonist variant) bounded with high affinity to inbakicept (a dimeric human IL-15 receptor α (IL15Rα) sushi domain/human IgG1 Fc fusion protein) as active substances and it is given via intravesical injection. The medicinal product is for treatment use only.

Further information about the evaluation of ANKTIVA benefits can be found in ANKTIVA EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ANKTIVA, together with measures to minimise such risks and the proposed studies for learning more about ANKTIVA risks, are outlined below.

Measures to minimise the risks identified for medicinal products are:

- Specific information, such as adverse reactions; posology and method of administration; contraindications; warnings and precautions, in the package leaflet addressed to healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of ANKTIVA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ANKTIVA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine):

List of important risks and missing information	
Important Identified Risk	None
Important Potential Risk	Immunological adverse reactions
Missing information	Long-term safety

II.B Summary of important risks

Important Potential Risk: Immunological adverse reactions	
Evidence for linking the risk to the medication	Given that N-803 is an immunostimulatory with a novel target, and the current safety database is still relatively limited, immunological adverse reactions are considered as an important potential risk.
Risk factors and risk groups	There are currently no reliable predictors of susceptibility of individual patients to develop immunological adverse events following N-803 treatment. Standard bladder-instillation precautions should be applied to minimize mucosal trauma and inadvertent systemic exposure.
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.8 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • QUILT-2.005 • QUILT-3.032 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures • None Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • QUILT-2.005 • QUILT-3.032 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Owing to the single arm nature and limited sample size of the pivotal study QUILT-3.032, a full marketing authorisation (MA) is presently not warranted by the EMA. Therefore, a conditional marketing authorisation (CMA) is requested under Article 4 of Commission Regulation (EC) No 507/2006 for Anktiva, an interleukin-15 (IL-15) receptor superagonist intended in combination with Bacillus Calmette-Guérin (BCG) for use in adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours. The justification for the CMA is based on NMIBC—particularly when unresponsive to standard BCG therapy—meeting the criteria of a seriously debilitating and life-threatening disease. It affects a substantial patient population, imposes significant clinical and quality-of-life burdens, and carries a well-documented risk of progression to invasive and metastatic cancer. Based on these data, the condition clearly falls within the scope of Article 2(a) of Commission Regulation (EC) No 507/2006, supporting its eligibility for conditional marketing authorisation.

The request is based on the four statutory criteria for CMA which are addressed in the paragraphs below: (A) positive benefit-risk balance, (B) ability to supply comprehensive data post-authorisation, (C) unmet medical need, and (D) benefit of immediate availability.

A: ANKTIVA in combination with BCG confers substantial clinical benefit - durable CR, bladder preservation, and favourable survival - while exposing patients to limited and manageable risks by delaying RC which is comparable to initial BCG therapy and the associated delay in RC. The benefit-risk balance is therefore positive and supports the grant of a conditional MA.

B: In terms of supplying comprehensive data post-authorisation, concrete plans are in place to provide the comprehensive clinical data currently lacking, via continuing monitoring of ongoing patients thereby meeting the criterion of likely data provision and serving to confirm the clinical benefit conferred by ANKTIVA in combination with BCG in BCG unresponsive NMIBC.

C: Taking into account the morbidity and mortality rates following radical cystectomy (RC), there is a big unmet medical need for a bladder-sparing treatment that can help patients avoid the procedure. Saving lives and avoiding the detrimental effects to the patients' quality of life. RC is ultimately received by only <25% of patients with BCG-unresponsive NMIBC, due to

ineligibility (45%) or patient refusal related to quality-of-life concerns, this can be concluded of patient data from UK, Germany, Spain, France and Italy (Chun 2020). As bladder cancer is especially prevalent in older people, there are a considerable amount of patients ineligible for RC due to age or comorbidities. This leaves tens of thousands of patients per year across the EEA without treatment. With cystectomy avoidance rate of 83%, ANKTIVA provides an important clinically-meaningful advance in therapy compared to currently available options for patients with a diagnosis of high-risk BCG unresponsive and BCG-refractory or BCG-relapsed NMIBC.

D: The potential for benefit in a large, undertreated patient population, particularly those ineligible for or declining cystectomy, provides strong public health justification for immediate access. In addition, the public health benefit of granting access without delay is significant and supported by a favourable early assessment of the benefit risk profile in a setting of high unmet medical need. Given the scale and urgency of this need, and the capacity to address the remaining uncertainties through ongoing studies and real world evidence, it is considered that the benefits to public health of immediate availability clearly outweigh the risks associated with the incomplete data, in line with Article 4(d) of Commission Regulation (EC) No 507/2006.

The following studies are specific obligations for conditional marketing authorisation:

QUILT-3.032

QUILT-3.032 is an ongoing phase 2/3, open-label, multicenter study of intravesical N-803 (400 µg) plus BCG or N-803 alone in subjects with BCG-unresponsive high-grade NMIBC.

The primary objective is 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.

QUILT-2.005

QUILT-2.005 is an ongoing phase 2b, randomized, open-label, multicenter study of intravesical BCG plus N-803 versus BCG alone in BCG-naïve patients with high-grade NMIBC. Subjects are enrolled into 1 of 2 study cohorts and randomized 1:1 to be treated with either BCG plus N-803 or BCG alone. Cohort A includes subjects with CIS disease (with or without Ta/T1) and Cohort B includes subjects with high-grade papillary disease (Ta/T1 only).

The primary objective for Cohort A is to determine the efficacy of the combination of N-803 plus BCG compared to BCG alone in patients with CIS disease (with or without Ta/T1) in terms of complete response (CR) rate at 6 months. The primary objective for Cohort B is to determine the efficacy of the combination of N-803 plus BCG compared to BCG alone in patients with high-grade papillary disease (Ta/T1 only) in terms of disease-free survival (DFS) using cystoscopy, confirmatory bladder biopsy (if required), and urine cytology.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for ANKTIVA.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

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