SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

ANKTIVA 1.2 mg solution for subcutaneous injection. Each vial contains 1.2 mg of ANKTIVA in 0.6 mL solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nogapendekin alfa inbakicept is a complex consisting of two nogapendekin alfa bound to inbakicept, produced in a Chinese hamster ovary (CHO-K1) cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

Each vial contains 1.2 mg nogapendekin alfa inbakicept in 0.6 mL solution, delivering 1 mg.

3. PHARMACEUTICAL FORM

Nogapendekin alfa inbakicept is a clear to slightly opalescent, colourless to slightly yellow solution, pH 7.4.

Solution for subcutaneous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ANKTIVA is indicated in combination with immune checkpoint inhibitors for the treatment of adult patients with metastatic NSCLC with disease progression on or after standard of care (immune checkpoint inhibitors alone or in combination with chemotherapy). Patients with actionable genomic alteration should have disease progression on approved therapy for these alterations, before using ANKTIVA in combination with immune checkpoint inhibitors.

4.2 Posology and method of administration

Therapy

ANKTIVA is recommended at a fixed dose of 1 mg, administered subcutaneously once every 21 days, continued for the duration of immune checkpoint inhibitors.

Special populations

Elderly

No dose adjustments are necessary in the elderly population.

Hepatic and/or renal impairment

Safety and effectiveness have not been established in patients with severe renal or hepatic impairment due to exclusionary criteria for these populations in clinical trials; therefore dose adjustment parameters for impairment have not been established.

Paediatric population

There are no data from the use of ANKTIVA in the paediatric population for the indication of metastatic NSCLC with disease progression on or after standard of care.

Method of administration

For subcutaneous use only.

Do not shake.

For instructions on subcutaneous administration, see section 6.6.

ANKTIVA is administered subcutaneously.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Data is limited or not available currently for the following populations: pregnant and lactating women, paediatric populations, patients with severe hepatic and renal impairment, patients with active autoimmune disease, transplant recipients, and patients with significant immunosuppression, because these populations were excluded from clinical studies.

Excipients

This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.4.1 Traceability

For metastatic NSCLC, subcutaneous use only. ANKTIVA should NOT be administered by intravesical, intravenous, or intramuscular use.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed for metastatic NSCLC.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential / contraception

Women of childbearing potential are required to use effective contraception during treatment and for 1 week after the last dose.

Pregnancy

There are no data on the use of treatment 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 (see section 5.3). These results indicate a potential risk. Treatment is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

There are no data on the presence of ANKTIVA in either animal or human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, women are advised not to breastfeed during treatment with ANKTIVA and for 2 weeks after the final dose.

Fertility

There are no clinical data on the effects of treatment on fertility.

4.7 Effects on ability to drive and use machines

Treatment has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

4.8.1 Adverse Reactions

Tabulated list of adverse reactions

Adverse reaction frequency was determined according to the following criteria: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000). Adverse drug reactions (ADRs) organised by MedDRA System Organ Class (SOC) and by frequency are presented in Table 1.

The most common NAI-related adverse drug reactions from QUILT-3.055 were injection site reaction (86%), chills (46%), fatigue (32%), pyrexia (28%), nausea (16%), injection site erythema and injection site pruritus (15% each), injection site pain (14%), influenza like illness (13%), decreased appetite (10%).

More than one patient experienced the following grade ≥ 3 NAI related adverse reactions: fatigue, injection site reaction, and aspartate aminotransferase increased (3 patients, 2% each), chills, injection site pain, alanine aminotransferase increased, blood alkaline phosphatase increased, anaemia, diarrhoea, and rash maculo-papular (2 patients, 1%).

The following NAI related serious adverse reaction occurred in more than 1 patient: injection site reaction (4 patients, 3%). The following NAI related serious adverse reactions occurred in 1 patient each: influenza like illness, atrial fibrillation, pericardial effusion, tricuspid valve incompetence, diarrhoea, ileus, small intestinal obstruction, pneumonitis, respiratory failure, injection site cellulitis, and hypovolemic shock (1% each).

Table 1 lists adverse reactions in a clinical study (n=147) where ANKTIVA in combination with standard of care was administered to subjects (aged 30 to 88 years).

Table 1 Treatment-Emergent, NAI-Related Adverse Events in QUILT 3.055

System organ class	Frequency category	Adverse reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia, Hyponatraemia, Dehydration, Hyperglycaemia, Hypoalbuminaemia, Blood alkaline phosphatase increased
Nervous system disorders	Common	Headache, Dysgeusia, Dizziness,
Gastrointestinal disorders	Very Common	Nausea
	Common	Diarrhoea, Vomiting, Abdominal pain, Abdominal distention, Colitis
Skin and subcutaneous tissue disorders	Common	Pruritus, Rash, Rash maculo-papular, Erythema
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia, Back pain
General disorders and administration site conditions	Very Common	Injection site reaction, Chills, Fatigue, Pyrexia, Injection site erythema, Injection site pruritus, Influenza like illness, Injection site pain
	Common	Injection site swelling, Peripheral swelling, Pain, Injection site rash, Malaise
Respiratory, thoracic and mediastinal disorders	Common	Cough, Pneumonitis, Dyspnoea
Blood and lymphatic system disorders	Common	Anaemia, Lymphocyte count decreased[a]
Vascular	Common	Hypotension
Injury, poisoning and procedural complications	Common	Contusion, Infusion related reaction, Injection related reaction
Investigations	Common	Weight decreased, Blood creatine increased, Aspartate aminotransferase increased, Alanine aminotransferase increased,

		Blood bilirubin increased
[a] Lymphocyte count decreased occurred in 2/147 (1%) participants		

Report any side effects to:

To report SUSPECTED ADVERSE REACTIONS, contact

- EDE Call Centre: 80033784
- E-mail: pv@ede.gov.ae

4.9 Overdose

There are no data indicating that an overdose may lead to any other symptoms than the described undesirable effects. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukins, ATC code: L03AC03

Mechanism of action

Nogapendekin alfa inbakicept is an IL-15 receptor agonist. 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 to its receptor results in proliferation and activation of NK, CD4+, CD8+, and memory T cells without proliferation of immuno-suppressive Treg cells.

Pharmacodynamic effects

Immunogenicity

Data regarding treatment-emergent anti-drug antibodies in subcutaneous dosing is pending.

Clinical efficacy and safety

QUILT-3.055

The efficacy of ANKTIVA in the treatment of lymphopenia was evaluated in QUILT-3.055, an open-label, multicohort Phase 2B trial in 147 adults with advanced solid tumors who had progressed following prior therapies, including checkpoint inhibitors (CPIs). All patients received subcutaneous ANKTIVA (15 µg/kg on Days 1 and 22 of each 6-week cycle) in combination with the same CPI on which they had progressed.

In cohorts 1 through 3, eligible participants were those who had disease progression following an initial response to treatment with PD-1/PD-L1 CPI therapy. In cohort 4, eligible participants were those who had disease progression after having stable disease for at least 6 months after treatment with PD-1/PD-L1 CPI therapy.

The major efficacy outcome measures were:

- Objective response rate (ORR), defined as investigator-assessed CR+PR, per RECIST v1.1.
- Prolongation of overall survival (OS) with NAI therapy by ALC response, where:
    - OS was defined as the time from first study drug administration to death resulting from any cause.
    - ALC response was defined as achievement or maintenance of an on-treatment ALC ≥ 1,000 cells/μL based on a mean on-treatment ALC ≥ 1,000 cells/μL.

Efficacy results are summarised in Table 2 and Table 3.

Table 2 ORR results in QUILT 3.055 – Safety Population

	NSCLC Participants (N=86)	**All Participants (N=147)**
Participants with confirmed CR or PR	6 (7%)	14 (10%)
95% CI	2.6, 14.6	5.3, 15.5
CR	0	0
PR	6 (7%)	14 (10%)

Table 3 OS results in QUILT 3.055 – Safety Population

	ANKTIVA plus CPI All NSCLC (N=79)	**Mean On-Treatment ALC < 1000/μL (N = 18)**	**Mean On-Treatment ALC ≥ 1000/μL (N = 61)**	**Log-rank P-value**	**Hazard Ratio 95% CI**
Number of deaths	58 (73%)	14 (78%)	44 (72%)	0.0369	0.52 (0.28, 0.97)
Median OS[a] (months)	14.6	11.8	16.2		
95% CI for the Median OS	12.0, 19.5	6.9, 14.1	13.8, 22.0		
Overall survival (OS) rate[b] at:					
Month 12	61.4% (49.5, 71.4)	44.1% (20.0, 65.9)	66.1% (52.6, 76.6)	-	-
Month 24	29.8% (19.8, 40.4)	12.6% (2.1, 33.0)	34.6% (22.7, 46.8)	-	-

ALC, absolute lymphocyte count; CI, confidence interval; NSCLC, non-small cell lung cancer; OS, overall survival.
[a] OS was defined as the time from the date of first study drug administration to the date of death from any cause. Participants who were alive at the end of follow up were censored at the last known date the participant was alive.
[b] OS rates were estimated using Kaplan-Meier analysis method.

The mechanistic primary endpoint was restoration of absolute lymphocyte count (ALC), defined as achieving a mean on-treatment ALC $\geq 1.0 \times 10^3$ cells/μL.

Among the 140 participants in the safety population , 78% (109/140) achieved the ALC restoration threshold. In the NSCLC subgroup (N=79), 77% (61/79) achieved the ALC restoration threshold . The median increase in ALC was approximately 21% during the first treatment cycle and was sustained with continued therapy.

Restoration of ALC was associated with improved overall survival (OS).

- In the NSCLC cohort, median OS was 16.2 months in ALC responders compared to 11.8 months in non-responders (Hazard Ratio [HR] 0.52; 95% CI 0.28–0.97; P=0.0369).
- In the full study population, median OS was 15.8 months for responders vs 11.8 months for non-responders (HR 0.59; 95% CI 0.37–0.95; P=0.0281).

These data support the mechanism of action of ANKTIVA as an IL-15/IL-15Rα superagonist that reverses lymphopenia and improves survival in patients with CPI-refractory tumors by expanding NK cells and $CD8^+$ memory T cells without promoting T-regulatory cell proliferation.

5.2 Pharmacokinetic properties

A study of systemic exposure of ANKTIVA demonstrate an apparent mean half-life (t1/2) estimates of 0.835 to 0.862 day (~20-21 hr).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of toxicity using intravenous or subcutaneous administration since the clinical systemic exposure to nogapendekin alfa inbakicept (ANKTIVA) following intravesical administration is negligible.

Animal reproduction studies have not been conducted with ANKTIVA. The IL-15 pathway is thought to be involved in maintaining tolerance to the foetus during pregnancy. A secondary signalling mechanism of IL-15 has been shown in murine models of pregnancy to increase uterine natural killer cells. This produces interferon-gamma (IFN-γ), which disrupts maternal tolerance to the foetus and has been shown to result in an increase in embryofoetal loss.

Animal fertility studies have not been conducted with nogapendekin alfa inbakicept (ANKTIVA). In a 13-week and 1-month repeat-dose toxicology study in rats and monkeys, respectively, there were no notable effects in the male and female reproductive organs. However, the monkeys were not sexually mature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate
Potassium dihydrogen phosphate
Sodium chloride
Water for injections
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 C-8°C).
Do not freeze. Do not shake.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.6 mL solution in a glass vial with a serum stopper (chlorobutyl elastomer with a Flurotec B2-40 coating) and an aluminium alloy seal containing a blue plastic polypropylene flip-off cap.

Pack size: 1 single-dose vial.

6.6 Special precautions for disposal and other handling

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if visible particles are observed.

Do not shake the vial. Using aseptic technique, remove the flip-off cap and disinfect the stopper. Withdraw 0.6 mL of ANKTIVA using a sterile syringe and needle. Administer the entire contents by subcutaneous injection using standard technique.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for biological pharmaceutical waste.

Standard precautions for handling parenteral biologics apply. Gloves should be worn during preparation and administration. No additional protective measures are required specific to ANKTIVA.

7. MARKETING AUTHORISATION HOLDER

ImmunityBio, Inc.

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation

9. DATE OF REVISION OF THE TEXT

LABELLING

10

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

ANKTIVA
nogapendekin alfa inbakicept
1.2 mg per 0.6 mL
(1.2 mg / 0.6 mL)
solution for subcutaneous injection

2. STATEMENT OF ACTIVE SUBSTANCE

One vial (0.6 mL) contains 1.2 milligrams nogapendekin alfa inbakicept.

3. LIST OF EXCIPIENTS

Excipients: Disodium phosphate, potassium dihydrogen phosphate, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for subcutaneous injection
1 single-dose vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. MANUFACTURING AND EXPIRY DATE

MFG
EXP

Read the leaflet for the shelf life of the reconstituted medicine.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. MANUFACTURER NAME

Manufacturer Responsible for Batch Release:
Millmount Healthcare Ltd
Block 7, City North Business Campus
Stamullen
K32 TD60
Ireland

12. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ImmunityBio, Inc.
9920 Jefferson Blvd
Culver City, CA 90232
United States

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

N/A

15. DATAMATRIX

16. GLOBAL TRADE ITEM NUMBER

GTIN: 00381481000056

17. SERIAL NUMBER

S/N

12

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ANKTIVA
nogapendekin alfa inbakicept
1.2 mg per 0.6 mL
(1.2 mg / 0.6 mL)
solution for subcutaneous injection
For subcutaneous use.

2. METHOD OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.

3. MANUFACTURING AND EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 mL

6. SPECIAL STORAGE CONDITIONS

N/A

7. OTHER

N/A

8. DATAMATRIX

N/A

9. GLOBAL TRADE ITEM NUMBER

N/A

10. SERIAL NUMBER

N/A