PROJECT: MABX CLINIC

TARGET PRODUCT PROFILE (TPP) REPORT

Project Information

Product Type : Drug **TRL :** 4 **Sprint :** 1

Abstract:

mAb-X is a humanized IgG1 monoclonal antibody targeting the interleukin-2 receptor ?-chain (CD25) to inhibit T-cell activation and prevent allograft rejection. Early clinical evaluation in renal transplant recipients shows good tolerability and a dose-dependent reduction in activated lymphocytes. The antibody is administered intravenously every two weeks and demonstrates a favorable pharmacokinetic profile with sustained receptor occupancy. Ongoing studies aim to confirm its efficacy and safety in broader transplant populations

Sprint's originating question:

What is our current understanding of mAb-X and its process, and which key uncertainties remain ?

Start Date : 2025-08-04 **End Date :** 2026-05-15

Manager

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Contributors

No contributors assigned to this project.

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PRODUCT PROFILE

1. INTRODUCTION

1.1 Name or acronym of the project:

TPP

Project NOVA (New Optimized Validated Antibody) - mAb-X

1.2 More information about the sprint, or the sprint question:

TPP

Sprint objective: to define and secure a robust, scalable and controllable upstream/downstream process for the production of a clinical-grade monoclonal antibody, ensuring purity (low HCP, low DNA, low aggregates) and stability consistent with an early regulatory submission (ANSM/EMA) and later industrial transfer.

1.3 Development challenges or constraints:

TPP

The development of the NOVA-mAbX project faces several technical and regulatory challenges inherent to the production of complex biological medicinal products. These constraints primarily concern process robustness, analytical characterization, and compliance with the current expectations for monoclonal antibodies under the ICH Q8–Q11 framework.

Key development challenges include:
- Process scalability : ensuring consistent product quality when scaling up from laboratory to pilot and clinical manufacturing scales.
- Process robustness : controlling variability in upstream (cell culture) and downstream (purification) operations to guarantee reproducible Critical Quality Attributes (CQAs).
- Impurity control : achieving efficient removal of process-related impurities (host-cell proteins, residual DNA, Protein A, viral contaminants) and product-related impurities (aggregates, fragments).
- Analytical characterization : establishing validated methods capable of detecting subtle structural or functional variations, including glycosylation and aggregation profiles.
- Formulation stability : developing a formulation compatible with parenteral administration, maintaining antibody stability under storage and handling conditions.
-Regulatory compliance : aligning process development and documentation with the ANSM/EMA guidelines for biotechnology-derived products and the Common Technical Document (CTD) format.
-QbD implementation : defining the Quality Target Product Profile (QTPP), identifying CQAs and CPPs, and establishing an initial control strategy to support risk management and design-space justification.

2. MEDICAL NEED AND CURRENT STANDARD OF CARE

2.1 Therapeutic indication:

ANSM

Treatment of adult patients with active rheumatoid arthritis who have had an inadequate response or intolerance to at least one biological disease-modifying antirheumatic drug (bDMARD), and who require a biologic with an alternative mechanism of action.

2.2 disease overview:

ANSM

Rheumatoid arthritis is a chronic, systemic, autoimmune inflammatory disease characterized by persistent synovitis, joint pain and swelling, progressive joint destruction, functional impairment and reduced quality of life. The disease course is heterogeneous, and a significant proportion of patients do not achieve sustained low disease activity or remission under current therapies.

2.3 Current therapeutic options and standard of care:

ANSM

Chronic autoimmune and inflammatory diseases are managed through a stepwise approach combining symptomatic relief and immune modulation.
First-line therapy relies on conventional synthetic DMARDs (csDMARDs) such as methotrexate or leflunomide. In cases of inadequate response, biologic DMARDs (bDMARDs) targeting pro-inflammatory cytokines (e.g., TNF-?, IL-6) or immune checkpoints (CTLA-4-Ig) are introduced.
Targeted synthetic DMARDs (tsDMARDs), mainly JAK inhibitors, provide additional oral options but act on overlapping pathways.
Despite these therapies, non-response, loss of efficacy, and intolerance remain frequent, highlighting the need for new biologics targeting alternative immune axes, such as the IL-23/Th17 pathway.

References

Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3–18.
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Najm A. et al. IL-23 orchestrating immune cell activation in arthritis. Rheumatology. 2021;60(Suppl_4):iv4-iv12. doi:10.1093/rheumatology/keab439
European Medicines Agency (EMA). European Public Assessment Reports (EPARs) for Adalimumab, Tocilizumab, Abatacept, Baricitinib, and Guselkumab.
https://www.ema.europa.eu/en/medicines

2.4 Unmet medical need targeted by the product:

ANSM

Yes

2.4.1 Explanation of the unmet medical need:

ANSM

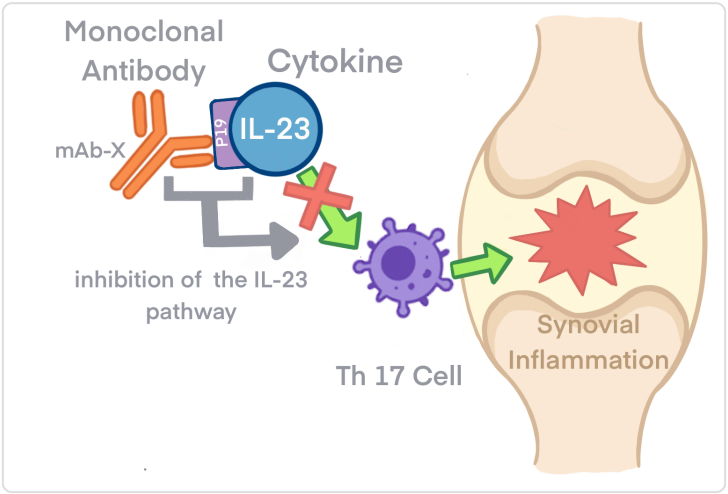
Current biologics mainly act on TNF-? or IL-6 pathways. Patients failing these agents have limited alternatives and may cycle between drugs with overlapping mechanisms, which does not always restore disease control. A monoclonal antibody specifically neutralizing IL-23 (p19) may:
reduce downstream pro-inflammatory mediators implicated in chronic synovitis;
offer an option in multi-refractory patients;
allow spacing of administrations if PK/PD is favorable.
This justifies development of a new mAb provided that its quality, purity, and safety are demonstrated through a controlled biotechnological process as described in the QbD modules.

2.5 Product profile

2.5.1 Mechanism of action of the product:

ANSM

mAb-X is a humanized IgG1 monoclonal antibody that binds selectively to the p19 subunit of interleukin-23, thereby preventing the interaction of IL-23 with its receptor and inhibiting the IL-23–driven differentiation and maintenance of Th17 cells. This leads to a reduction in the production of downstream pro-inflammatory cytokines and is expected to decrease synovial inflammation and joint damage.



2.5.2 Expected advantages or improvements over existing treatments:

ANSM

The NOVA-mAbX product offers an alternative mechanism of action for patients who have shown an inadequate or lost response to anti-TNF or anti-IL-6 biologics. By specifically targeting the IL-23/Th17 axis, it aims to modulate a distinct inflammatory pathway implicated in chronic autoimmune disease, potentially restoring disease control in refractory cases.

The treatment is being developed for intermittent intravenous administration, every four to eight weeks, which could improve patient adherence and convenience compared with more frequent dosing regimens.

From a manufacturing standpoint, the process has been designed following Quality by Design (QbD) principles to ensure consistent product quality. The downstream purification strategy focuses on minimizing process-related impurities such as host-cell proteins, residual DNA, and Protein A, as well as product-related aggregates. This high level of purity is expected to reduce the risk of immunogenicity and contribute to an improved safety profile compared with existing monoclonal antibodies.

2.5.3 Expected efficacy:

TPP

For mAb-X, efficacy is expected to correlate with pharmacodynamic markers of IL-23 pathway inhibition. The main proxies of efficacy are:

Reduction of IL-17A / IL-17F levels, as these cytokines are downstream of IL-23 signaling.

Decreased Th17 cell activation or frequency in peripheral blood.

Reduction of inflammatory biomarkers such as CRP or ESR (exploratory, depending on clinical design).

Improvement in disease activity scores relevant to rheumatoid arthritis (e.g., DAS28), although these will only be evaluable in clinical phases.

At the current stage, IL-17A suppression is the strongest validated proxy based on in vitro and in vivo data.

2.5.4 Desired safety profile:

TPP

Given the mechanism of action of IL-23 blockade and existing data from similar p19-targeting monoclonal antibodies, the main safety aspects to monitor include:

Infection risk, particularly mild upper respiratory tract infections (reduced mucosal immunity linked to Th17).

Risk of reactivation of latent infections, including tuberculosis.

Liver function, as transient elevations of hepatic enzymes have been reported with related biologics.

Injection- or infusion-related reactions, common to monoclonal antibodies.

Immune dysregulation markers, in case of excessive IL-23 pathway suppression.

No target-organ toxicity is expected based on non-clinical data, but standard monitoring includes respiratory and hepatic systems.

2.5.5 Competitive landscape / existing products:

TPP

In the treatment of rheumatoid arthritis and other IL-23–driven autoimmune diseases, several biologics are already approved or in advanced development. Relevant competitors include:

Anti-TNF agents (adalimumab, infliximab, etanercept) – widely used but often ineffective in refractory patients.

Anti-IL-6 agents (tocilizumab, sarilumab).

JAK inhibitors (baricitinib, tofacitinib) – oral alternatives with distinct risk profiles.

Anti-IL-23p19 antibodies approved in other indications (guselkumab, risankizumab, tildrakizumab) but not yet broadly established in rheumatoid arthritis.

3. PRODUCT DESCRIPTION

3.1 Commercial name of the product:

ANSM

The commercial name has not yet been defined. For development and documentation purposes, the product is referred to as “mAb-X” throughout the project.

3.2 Generic or scientific name of the product:

ANSM

Humanized monoclonal antibody directed against the interleukin-23 (IL-23) p19 subunit, of the IgG1 isotype.

3.3 Development progress

ANSM

TRL (Technology Readiness Level): 4
Product Type: Drug

Medication type:

ANSM

Biological drug

Pharmacotherapeutic class:

ANSM

Immunomodulating agents – monoclonal antibodies.

Biological activity:

ANSM

Biological activity: ANSM Specific binding to the IL-23 p19 subunit, leading to inhibition of IL-23-dependent signaling pathways involved in chronic inflammation.

Innovation aspect:

ANSM

Integration of a Quality by Design (QbD) approach from the early development phase, with preliminary identification of Critical Quality Attributes (CQAs) (e.g., glycosylation, aggregation, HCP, residual DNA) and Critical Process Parameters (CPPs) (e.g., pH, temperature, chromatographic conditions). This strategy aligns with the process-design methodology and case studies presented in the Immerscio.bio QbD training modules

3.4 Composition / technology:

ANSM

The Drug Substance (DS) is produced by recombinant expression in a mammalian host cell line (Chinese Hamster Ovary – CHO). The upstream process involves a seed train expansion followed by a fed-batch bioreactor culture operated under controlled conditions of pH, temperature, and dissolved oxygen.
The Drug Product (DP) is formulated as a sterile aqueous solution of mAb-X in a histidine or phosphate buffer containing a non-ionic surfactant (e.g., polysorbate 80) and a stabilizing excipient (e.g., sucrose). The product is filled in Type I glass vials closed with rubber stoppers and aluminum seals.
This process follows the standardized monoclonal antibody platform

3.5 Route of administration / method of use:

ANSM

The product is intended for intravenous infusion in a hospital or clinical setting under medical supervision

3.6 Dose:

ANSM

The clinical dose will be defined on the basis of non-clinical pharmacokinetic/pharmacodynamic (PK/PD) studies and MABEL/NOAEL calculations. At the current stage (TRL 4), a starting dose in the range of 1–5 mg/kg IV every 4–8 weeks is envisaged as a preliminary target.

3.7 Dispositif de dosage / administration

3.7.1 Presence of a specific dosing or administration device: ANSM

Yes

3.7.2 If yes, describe the device: ANSM

No dedicated administration device is required; the product is compatible with standard hospital infusion equipment.

3.7.3 Is the device CE marked ?: ANSM

No

3.7.7 Additional comments on the device: ANSM

Accelerated and real-time stability studies are being conducted on the selected liquid formulation and primary packaging system (glass vial, rubber stopper). These studies follow ICH Q1A (R2) guidelines and aim to establish a preliminary shelf life to support clinical trial material supply.

3.8 Stability

3.8.1 Do preliminary stability observations exist for the product?: ANSM

Yes

3.8.1.1 – Describe any early stability observations (e.g., aggregation, degradation, viscosity changes).:

Low aggregation tendency at pH 6 and 2–8°C.
Slight aggregation detected during accelerated thermal stress (>40°C).
No significant degradation under short-term agitation.
Slight sensitivity to acidic conditions during Protein A elution.

3.8.1.2 – Which exploratory stability tests have been performed?:

Short-term stress tests (temperature, agitation)

3.8.2 Additional comments on stability: ANSM

Not provided

3.8.2 Are stability studies ongoing?: ANSM

Yes

3.8.2.1 – Stability study details:

Name	Function	Quantity	Origin	Nature	Duration	Storage	Comments
				Accelerated stability	6 months	25 °C ± 2 °C / 60 % RH ± 5 %	Preliminary evaluation of physical and chemical stability (appearance, pH, protein concentration, aggregation, purity by SEC, potency by ELISA).
				Long-term (real-time)	12–24 months	2–8 °C	Standard ICH Q1A(R2) long-term study on Drug Product vials (liquid formulation). Same attributes as accelerated study.
				Stress stability studies	2–4 weeks	40 °C ± 2 °C / 75 % RH ± 5 % and freeze–thaw cycles	Evaluate degradation pathways and identify critical parameters (temperature sensitivity, aggregation, pH drift).

3.8.2.2 – Identify key stability risks suspected at this stage (e.g., aggregation, deamidation, oxidation).:

Aggregation during acidic Protein A elution, oxidation of methionine residues, and potential deamidation during thermal stress.
These risks must be controlled before 500 L pilot-scale runs.

3.9 Treatment mode:

ANSM

Monotherapy

3.10 Target composition / key technical characteristics:

ANSM

The target composition of mAb-X is a sterile aqueous solution containing the monoclonal antibody as the active substance, formulated with:

a physiological buffer (histidine or phosphate, pH ? 6–7),
a non-ionic surfactant (e.g. polysorbate 80) to prevent surface aggregation,
and a stabilizer such as sucrose to ensure protein stability during storage.

Key quality characteristics include:
High purity (> 98 % monomer by SEC),
Controlled glycosylation pattern typical of CHO-expressed humanized IgG1,
Low levels of host-cell proteins (HCP), residual DNA, and Protein A,
Aggregate content below acceptable thresholds as defined in the CQAs.

3.11 Sterility

3.11.1 Is the product sterile?:

ANSM

Yes

3.11.2 Type of sterilization method used:

ANSM

Sterile filtration

3.11.3 Additional comments on sterility:

ANSM

The Drug Product is manufactured under aseptic conditions and filled into depyrogenated Type I glass vials with sterile closures.
Sterility assurance is based on:

validated filtration sterilization of the bulk solution through 0.22 µm filters;
aseptic filling operations in a controlled environment compliant with EU GMP Annex 1;
and sterility testing performed according to Ph. Eur. 2.6.1 and 2.6.14.
No terminal sterilization step is foreseen due to protein sensitivity.

3.12 Manufacturing process:

ANSM

The manufacturing process of mAb-X follows the standard monoclonal antibody platform and is developed under a Quality by Design (QbD) framework.

Upstream process (USP):
Recombinant CHO cells expressing the humanized IgG1 are expanded through a seed train and cultured in fed-batch bioreactors under controlled conditions (temperature, pH, dissolved oxygen, feeding profile).

Downstream process (DSP):
Includes cell-culture clarification, Protein A affinity capture, low-pH viral inactivation, ion-exchange and hydrophobic interaction chromatography for polishing, and ultrafiltration/diafiltration for buffer exchange and concentration adjustment.

Formulation and filling:
The purified antibody is formulated, sterile-filtered, and aseptically filled into glass vials.

3.13 Quality control:

ANSM

Quality control of mAb-X covers the Drug Substance and Drug Product levels, ensuring consistency, purity, and potency in line with ICH Q6B and Ph. Eur. monographs.

Representative analytical methods include:

Identity: peptide mapping, isoelectric focusing, binding ELISA to IL-23 p19;
Purity and impurities: SEC-HPLC (aggregates), SDS-PAGE, HCP ELISA, residual DNA qPCR, Protein A ELISA;
Potency: IL-23 neutralization bioassay or cell-based reporter assay;
Physicochemical properties: concentration, osmolality, pH, appearance;
Sterility and endotoxins: Ph. Eur. 2.6.1 / 2.6.14 / 2.6.30.

PRODUCT FORMULATION

4. PHARMACEUTICAL DEVELOPMENT STATUS

4.1 Formulations developed so far:

ANSM

A single liquid formulation of mAb-X has been developed at laboratory scale to support analytical characterization and stability assessments. The formulation consists of a sterile aqueous solution containing the antibody in a histidine buffer, with polysorbate 80 as a surfactant and sucrose as a stabilizer.
Preliminary stress and freeze–thaw studies have confirmed good physicochemical stability and low aggregation propensity under refrigerated conditions (2–8 °C).

4.2 Alternative formulations considered:

ANSM

Alternative formulations, including lyophilized and acetate-buffered solutions, were evaluated during early formulation screening. These options were discarded due to inferior solubility, increased viscosity at high concentrations, or reduced stability during thermal stress.

4.3 Completed pharmaceutical studies:

ANSM

At this stage, development activities have focused on:

- physicochemical characterization (pH, osmolality, viscosity, appearance, protein concentration, purity by SEC and SDS-PAGE);
- short-term stability studies under accelerated and stress conditions;
- preliminary compatibility assessment with container–closure components (Type I glass vial, bromobutyl stopper);
- filter compatibility and extractables/leachables screening.

All studies were conducted under laboratory conditions as part of the QbD-based formulation design described in the Immerscio.bio Module 3 – Case study on mAb purification.

4.4 Planned pharmaceutical studies:

ANSM

The next development phase will include:

- real-time stability studies under ICH Q1A (2–8 °C, 25 °C/60 % RH, 40 °C/75 % RH);
- photostability studies per ICH Q1B;
- freeze–thaw cycle robustness;
- microbial challenge testing and preservative efficacy (if applicable);
- scale-up verification of the formulation process (buffer preparation, sterile filtration, aseptic filling).

5. COMPOSITION AND COMPONENTS

5.1 Active ingredients:

TPP

The active substance, mAb-X, is a recombinant humanized IgG1 monoclonal antibody directed against the p19 subunit of interleukin-23 (IL-23). It is produced in CHO (Chinese Hamster Ovary) cells using a stable expression system and purified through a standard mAb downstream process involving Protein A affinity, polishing chromatography, viral inactivation, and ultrafiltration/diafiltration. The molecule displays high purity (> 98 % by SEC-HPLC) and is formulated as a sterile liquid for parenteral administration.

5.2 Excipients

5.2.1 Is there any excipient used in the formulation that is not listed in the European Pharmacopoeia?:

ANSM

No

5.2.2 Is there any novel excipient used in the formulation?:

ANSM

No

5.2.3 Is there any excipient of animal or human origin?:

ANSM

No

5.2.4 Is the TSE/BSE risk documented?:

ANSM

Yes

5.2.5 Excipients list:

TPP

Name	Function	Quantity	Origin
Histidine / Histidine HCl	Buffering agent	10 mM	Non-animal
Sucrose	Stabilizer / cryoprotectant	5 % w/v	Non-animal
Polysorbate 80	Surfactant (prevents aggregation)	0.01 % w/v	Non-animal
Water for Injection	Solvent	q.s. to 1 mL	Purified, Ph. Eur. grade

5.2.6 Specific characteristics or regulatory considerations:

ANSM

All excipients are widely used in parenteral formulations of therapeutic antibodies and are compliant with Ph. Eur. and ICH Q8–Q10 expectations.
Polysorbate 80 degradation and particle formation will be specifically monitored during stability studies as part of the control strategy.

5.3 Structure of the active substance

5.3.1 Molecular structure: ANSM

mAb-X is a humanized IgG1 composed of two identical heavy chains (= 50 kDa each) and two identical light chains (= 25 kDa each), covalently linked by disulfide bridges to form a tetrameric Y-shaped structure.

5.3.2 Molecular weight: ANSM

Approximate molecular mass: = 150 kDa (based on theoretical amino acid sequence and confirmed by mass spectrometry).

5.3.3 For biologics: amino acid sequence, 3D structure (if available): ANSM

The variable domains (VH and VL) contain framework regions of human IgG1 origin, with murine-derived complementarity-determining regions (CDRs) optimized for affinity to IL-23 p19.
The tertiary structure follows the typical IgG1 architecture with Fab and Fc regions, including a single conserved N-glycosylation site in the Fc domain.

5.4 Active Substance Regulatory and Quality Details

5.4.1 Is there an existing monograph for the active substance?: ANSM

No

5.4.3 Is this substance used in an EU-authorized medicinal product with the same process?: ANSM

No

5.4.5 Has the active substance been submitted in an ASMF or CEP dossier to the ANSM and accepted in support of a given pharmaceutical product?: TPP

No

5.4.7 Are any animal- or human-derived materials used in the process?: TPP

Yes

5.4.8 Specify the materials and their origin: ANSM

The production cell line (CHO) is of mammalian origin but considered an established and well-characterized recombinant cell substrate, not an “animal-derived material” under EMA/410/01.
All raw materials, culture media, and process reagents are of non-animal and non-human origin, with documented TSE/BSE compliance.

5.4.9 Have impurities been qualified during non-clinical studies?: TPP

Yes

5.4.10 Add details on the impurities: ANSM

To be assessed in upcoming non-clinical tox program (GLP studies).

5.5 Packaging and handling objective

5.5.1 Describe the packaging used for the product.: TPP ANSM

mAb-X is filled into Type I borosilicate glass vials (2 mL nominal fill volume) sealed with bromobutyl rubber stoppers and aluminum overseals. All components are compliant with Ph. Eur. and USP <381>.

5.5.2 Storage instructions (temperature, humidity, light exposure, etc.): TPP ANSM

Store at 2–8 °C, protected from light. Do not freeze.
Short excursions up to 25 °C for less than 24 hours are acceptable during handling or transport.

5.5.3 Handling recommendations (e.g. reconstitution, transport, precautions): TPP ANSM

Administer by intravenous infusion using standard aseptic technique.
Do not shake the vial; inspect visually for particles or discoloration before use.
Transport under controlled refrigerated conditions in accordance with GDP guidelines.

5.5.4 Shelf life (under recommended storage conditions): TPP ANSM

Preliminary data support a provisional shelf life of 6 months at 2–8 °C for the laboratory-scale batch. Real-time stability studies are ongoing to refine the final expiry dating.

MECHANISM OF ACTION

6. MECHANISM OF ACTION OVERVIEW

6.1 Type of primary pharmacological action: ANSM

mAb-X acts as a targeted immunomodulator, designed to selectively neutralize the cytokine interleukin-23 (IL-23) by binding to its p19 subunit. This inhibition prevents IL-23 from engaging its receptor (IL-23R) on effector T cells, thus modulating the inflammatory response driven by the Th17 pathway.

6.2 Main biological target (name and type):

ANSM

The primary target is Interleukin-23 (IL-23), a heterodimeric cytokine composed of p19 and p40 subunits. mAb-X specifically recognizes the p19 subunit, leaving IL-12 (which shares the p40 chain) functionally intact.

6.3 Involved signaling or metabolic pathway:

ANSM

IL-23 binds to the IL-23 receptor complex (IL-23R and IL-12R?1) expressed on Th17 lymphocytes and innate immune cells, activating JAK2/TYK2 kinases and downstream STAT3 phosphorylation.
This signaling cascade maintains Th17 cell proliferation and the release of pro-inflammatory cytokines such as IL-17A, IL-17F, and TNF-?, which contribute to chronic joint inflammation and tissue destruction.
By blocking IL-23, mAb-X indirectly suppresses this pro-inflammatory loop.

6.4 Link between the target and expected therapeutic effect:

ANSM

In rheumatoid arthritis and related autoimmune diseases, the IL-23/Th17 axis plays a key role in sustaining chronic inflammation independently of TNF-? and IL-6 pathways.
Neutralization of IL-23 is expected to reduce Th17-mediated cytokine production, leading to a decrease in synovial inflammation, pain, and structural damage.
This mechanism complements existing therapies targeting TNF or IL-6 and provides an alternative for patients who fail these biologics.

6.5 Downstream effects or predictable side effects:

ANSM

Pharmacological inhibition of IL-23 may cause:

increased susceptibility to mild upper respiratory infections, due to reduced Th17-mediated mucosal immunity;
potential reactivation of latent infections (e.g. tuberculosis), as reported with similar IL-23p19 antagonists;
transient elevation of liver enzymes or mild injection-site reactions.

No direct cytotoxic or metabolic adverse effects are expected given the selective extracellular mechanism of action.

6.6 Scientific references or supporting non-clinical data:

ANSM

The proposed mechanism of action (selective neutralization of IL-23 via binding to the p19 subunit, leading to downstream inhibition of Th17-mediated inflammation) is consistent with published data on the IL-23/IL-17 axis in autoimmune diseases (Gaffen et al., 2014; Croxford et al., 2012) and with clinical experience from approved or late-stage IL-23p19 monoclonal antibodies (antibodies already existing : guselkumab, risankizumab, tildrakizumab) showing efficacy and an acceptable safety profile in chronic immune-mediated inflammatory diseases (McInnes et al., 2021; Feagan et al., 2017; Reich et al., 2019). Regulatory assessments from EMA/FDA for risankizumab (BLA 761105) further support the clinical relevance of IL-23p19 blockade.

7. INDICATION FOR USE – EXTENDED

7.1 Primary therapeutic indication:

ANSM

Treatment of adult patients with moderate-to-severe rheumatoid arthritis who have shown inadequate response or intolerance to at least one biologic Disease-Modifying Antirheumatic Drug (DMARD).

7.2 Secondary indications (if applicable):

ANSM

Potential future extensions include other IL-23–driven autoimmune disorders such as psoriatic arthritis and Crohn's disease, pending supportive non-clinical and clinical data.

7.3 General overview of the targeted disease:

ANSM

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent inflammation of the synovial membrane, progressive cartilage destruction, and bone erosion.
The disease affects approximately 0.5–1 % of the adult population, with a higher prevalence in women.
Despite advances in biologic therapy, up to 30 % of patients fail to achieve sustained remission, highlighting a continued need for innovative treatments targeting alternative immune pathways.

7.4 Dosage, posology, and duration of treatment:

ANSM

The dosage will be established from non-clinical PK/PD and toxicology studies.
Based on analogs in the same class, an initial intravenous dose of 1–5 mg/kg every 4–8 weeks is anticipated.
Treatment duration is expected to be long-term, depending on disease activity and clinical response.

7.5 Drug administration method

7.5.1 Method of administration:

ANSM

mAb-X is given as a slow intravenous infusion, typically over 30 to 60 minutes, using standard sterile infusion equipment (PVC or PE lines, in-line 0.22 µm filter).
The solution is supplied ready for use and does not require reconstitution or dilution prior to administration.
Infusion should be performed under aseptic conditions by trained healthcare personnel, with the patient observed during and after administration.

7.5.2 Special administration conditions (if any):

ANSM

Administration in a controlled hospital or outpatient clinical setting.
No dilution or reconstitution required; inspect the solution visually before use.
Infuse over 30–60 minutes at room temperature.

7.6 Dosage forms and strengths:

ANSM

Liquid sterile concentrate for infusion, containing 100 mg/mL mAb-X in a buffered isotonic solution.
Filled in 2 mL Type I glass vials.

7.7 Contraindications:

ANSM

Known hypersensitivity to monoclonal antibodies or formulation excipients.
Active or latent tuberculosis infection.
Severe uncontrolled infections or immunocompromised state.

7.8 OVERDOSE

7.8.1 Toxic concentrations:

ANSM

No data available; dose-limiting toxicity not observed in non-clinical models up to 50 mg/kg.

7.8.2 Signs and symptoms of overdose:

ANSM

Potential exaggerated pharmacologic effects such as transient leukopenia or increased infection risk.

7.8.3 Potential complications of overdose:

ANSM

Secondary infections or immune dysregulation in case of chronic overexposure.

7.8.4 Hazardous quantities:

ANSM

Exposures >10× the therapeutic range could be considered potentially hazardous until toxicology data confirm safety margins.

7.8.5 Treatment of overdose:

ANSM

Exposures >10× the therapeutic range could be considered potentially hazardous until toxicology data confirm safety margins.

PRECLINICAL EXPERIMENTS

8. NON-CLINICAL EXPERIMENTS

8.1 Key development milestones and go/no-go criteria before entering clinical phases (PoC & GLP):

TPP

A series of in vitro and in vivo studies were carried out to characterize the mechanism of action, pharmacological activity, and preliminary safety profile of mAb-X.
The experimental work followed a QbD-aligned design, emphasizing consistency, reproducibility, and control of analytical variability.
In vitro studies included:
- Binding affinity assessment of mAb-X to human IL-23 (p19 subunit) by ELISA and surface plasmon resonance (SPR).
- Functional neutralization assay on human Th17-differentiated PBMCs (inhibition of IL-17A secretion).
- Cross-reactivity analysis using a human tissue microarray (no unexpected off-target binding detected).
In vivo studies (pilot stage):
- Proof-of-concept efficacy in a murine collagen-induced arthritis (CIA) model.
Treatment with mAb-X significantly reduced joint inflammation scores and serum IL-17A levels compared with vehicle.
- Preliminary pharmacokinetic study in rodents (single IV dose): measurable plasma concentrations up to 7 days post-injection, consistent with expected IgG1 half-life.

8.2 Protocols of experiments already conducted:

ANSM

A series of in vitro and in vivo studies were carried out to characterize the mechanism of action, pharmacological activity, and preliminary safety profile of mAb-X.
The experimental work followed a QbD-aligned design, emphasizing consistency, reproducibility, and control of analytical variability.

In vitro studies included:
- Binding affinity assessment of mAb-X to human IL-23 (p19 subunit) by ELISA and surface plasmon resonance (SPR).
- Functional neutralization assay on human Th17-differentiated PBMCs (inhibition of IL-17A secretion).
- Cross-reactivity analysis using a human tissue microarray (no unexpected off-target binding detected).

In vivo studies (pilot stage):

- Proof-of-concept efficacy in a murine collagen-induced arthritis (CIA) model.
Treatment with mAb-X significantly reduced joint inflammation scores and serum IL-17A levels compared with vehicle.
- Preliminary pharmacokinetic study in rodents (single IV dose): measurable plasma concentrations up to 7 days post-injection, consistent with expected IgG1 half-life.

8.3 Protocols for upcoming experiments:

ANSM

Planned studies include:

Repeat of PK/PD study in cynomolgus monkeys (most relevant species for cross-reactivity).
4-week repeat-dose toxicity study (GLP compliant) to define NOAEL and support first-in-human (FIH) dose calculation.
Extended tissue cross-reactivity (TCR) panel using immunohistochemistry on human and monkey tissues.
Stability and comparability assessments of DS/DP lots used in the toxicology batch relative to the clinical batch.

9. PRELIMINARY DATA

9.1 Mechanism of action corroboration

9.1.1 Proof of concept:

ANSM

mAb-X demonstrated dose-dependent suppression of IL-23–induced Th17 activation in vitro and significant reduction of arthritis severity in vivo.
These findings confirm the expected pharmacological activity via IL-23 blockade, in line with published evidence for IL-23p19 neutralization in autoimmune models (Cutrona G, Gobbi M, Bongiorno D, et al. Microenvironmental Regulation of the IL-23R/IL-23 Axis Overrides Chronic Lymphocytic Leukemia Indolence. Sci Transl Med. 2018;10(428):eaal1571; Teng et al., Nat Rev Immunol 2015).

9.1.2 Pharmacodynamics:

ANSM

In vitro: IC50 for inhibition of IL-17A release ? 100 pM.

In vivo: Dose-dependent reduction in serum IL-17A and IL-22 levels following IV administration in the CIA mouse model.

Biomarker correlation: reduction of paw swelling correlated with suppression of Th17 cytokines ($R^2 > 0.8$).

9.1.3 Pharmacokinetics:

ANSM

Name	Function	Quantity	Origin	Species	Dose	Route	Bioavailability	Auc	Cmax	Tmax	T Half	Vd
				Mouse (n=6)	5 mg/kg	IV	100%	2000	50	0.5	120	0.1

9.1.3.1 Description of the elimination pathways:

As an IgG1 monoclonal antibody, mAb-X is expected to undergo catabolic clearance via FcRn-mediated recycling and lysosomal degradation in the reticuloendothelial system. No renal excretion is anticipated.

9.2.1 Choice and Justification of Animal Models

9.2.1.1 Species used:

ANSM

Mouse (collagen-induced arthritis), cynomolgus monkey planned

9.2.1.2 Relevance to human pathology:

ANSM

Both species express IL-23p19 with high homology to the human form, allowing translational relevance for PK and PD data.

9.2.1.3 Rationale for selection:

ANSM

The CIA model recapitulates key immunopathological features of rheumatoid arthritis (Th17-mediated inflammation, joint destruction). The cynomolgus monkey provides an adequate safety species for toxicology and cross-reactivity.

9.2.2 Summary of Main Results

9.2.2.1 Study design:

ANSM

single and repeat IV dosing (1–10 mg/kg)

9.2.2.2 Endpoints evaluated:

ANSM

clinical score, paw thickness, serum cytokines, histopathology.

9.2.2.3 Key findings:

ANSM

dose-related efficacy with no adverse clinical signs up to 10 mg/kg

9.2.2.4 Conclusions:

ANSM

The available non-clinical data provide a solid foundation to proceed toward Good Laboratory Practice (GLP)-compliant toxicity studies and First-in-Human (FIH) clinical planning.
In vitro and in vivo findings consistently demonstrate that mAb-X exhibits a potent and selective blockade of IL-23 signaling, translating into measurable pharmacodynamic effects in disease-relevant models (notably, reduction of Th17 cytokines and clinical improvement in the collagen-induced arthritis model).

No unexpected off-target activity or adverse pharmacological findings were observed, and preliminary pharmacokinetic data indicate predictable antibody disposition and an exposure window compatible with chronic administration.

Collectively, these results support the initiation of formal GLP toxicity studies in the cynomolgus monkey, the most relevant non-rodent species for safety assessment with the objective of establishing the No-Observed-Adverse-Effect Level (NOAEL), refining the MABEL-based starting dose, and confirming safety margins required for the upcoming FIH submission.

9.3 Off-target effects:

ANSM

No off-target binding was detected in human tissue cross-reactivity assays.
In vitro cytokine release testing using human PBMCs showed no abnormal activation, suggesting low risk of cytokine-release syndrome.

9.4 Safety Pharmacology

9.4.1 Cardiovascular system:

No

9.4.2 Central nervous system:

No

9.4.3 Respiratory system:

No

9.4.4 Other systems (renal, hepatic...):

within reference limits

10. TOXICITY NON CLINICAL

10.1 Toxicology Data:

ANSM

Preliminary non-GLP toxicity studies in rodents showed no mortality or severe adverse events. Mild transient infusion-related reactions (piloerection, reduced mobility) resolved spontaneously.

10.2 Single-dose toxicity studies:

ANSM

Species	Dose(s)	Route	Toxicity	Lethal Dose	0	1	2	3	4
					Mouse	10 mg/kg	IV	None	Not reached

10.3 Repeated-dose toxicity studies:

ANSM

Species	Dose(s)	Route/duration	NOEL	NOAEL	Exposure	Toxic Effects	0	1	2	3	4	5	6	Name	Function	Quantity	Origin
							Mouse	1, 3, 10 mg/kg, once weekly	IV / 4 weeks	Not identified (exploratory study)	10 mg/kg (no adverse findings observed)	Exposure proportional to dose; t½ compatible with IgG1	Mild infusion-related transient signs at high dose, no organ toxicity				
							Monkey	1, 3, 10 mg/kg	IV, once weekly, 4 weeks + 4 weeks recovery	To be determined	To be determined	Target: 5–10× projected human AUC to ensure safety margin	No specific toxicity expected based on class; monitor immune and injection-site reactions				

10.4 Genotoxicity, Reprotoxicity, and Special Toxicology

10.4.1 Genotoxicity: ANSM

No

10.4.2 Reproductive Toxicity: ANSM

No

10.4.3 Phototoxicity: ANSM

Not provided

Justify Phototoxicity results:

Not provided

Justify Phototoxicity results (not applicable):

Not provided

10.4.4 Juvenile Toxicity: ANSM

No

10.4.5 Carcinogenesis / Fertility: ANSM

No

11. FIRST IN HUMAN DOSE SELECTION

11.1 Starting Dose

11.1.1 Criteria retained for starting dose selection: ANSM

MABEL

11.1.2 Details and justification: ANSM

The MABEL was derived from the in vitro IL-23 neutralization curve and in vivo efficacy threshold in the CIA model, integrating exposure–response data.
A conservative starting dose of 1 mg/kg IV every 4–8 weeks is proposed for the first-in-human study.

11.2 Scaling Approach

11.2.1 Method for extrapolation:

ANSM

Allometric (HED)

11.2.2 Justification of the scaling method:

ANSM

Allometric extrapolation using body surface area (HED) and PK modelling from rodent data.
This approach aligns with EMA Guideline on strategies to identify and mitigate risks for first-in-human trials

11.3 Safety Margin

11.3.1 Calculated safety margins (AUC, Cmax):

ANSM

Preliminary allometric extrapolations based on rodent pharmacokinetic data indicate that the exposure achieved at the projected clinical starting dose (1 mg/kg IV) corresponds to approximately one-tenth of the exposure associated with the No-Observed-Adverse-Effect Level (NOAEL) expected from the upcoming GLP monkey study.
Simulations using antibody PK models (IgG1, FcRn-mediated recycling) suggest:
AUC (clinical starting dose) ? 200 µg·h/mL
AUC (predicted NOAEL) ? 2 000 µg·h/mL
Cmax ratio (human/NOAEL) ? 1:12

These estimates provide an anticipated safety margin of ? 10-fold on both systemic exposure and peak concentration.

11.3.2 Calculation method:

ANSM

Safety margins were derived by integrating:
Allometric conversion of animal PK data (mouse ? human) normalized by body surface area;
Scaling of clearance and distribution using IgG1-specific parameters;
Comparison of predicted human exposure (MABEL-based dose) to NOAEL exposures (rodent + planned monkey data).

The most conservative parameter (Cmax) was used to determine the margin, in line with EMA's FIH risk-mitigation guideline.
Final calculations will be updated once GLP toxicology and monkey PK data are available.

11.4 Additional Considerations

11.4.1 Justification of dosing interval:

ANSM

The proposed dosing interval of 4 to 8 weeks is supported by the predicted elimination half-life of mAb-X (approximately 10–14 days in rodents), consistent with other IgG1 antibodies targeting cytokines.
Model-based extrapolation to humans anticipates a terminal half-life around 20 days, which allows a monthly or bimonthly administration schedule, compatible with standard hospital infusion regimens.

The interval will be further refined during Phase I based on observed PK, PD markers (IL-17A suppression), and immunogenicity data.

11.4.2 Maximum dose to be administered in Phase I:

ANSM

A maximum single dose of 10 mg/kg IV is proposed for the Phase I escalation study, corresponding to approximately 10× the projected starting exposure and remaining below the anticipated NOAEL.
This upper limit provides sufficient range to explore dose-response while maintaining safety margins defined in the non-clinical package.
Subsequent dose increases will follow a modified Fibonacci scheme with sentinel dosing for the first cohort.

11.4.3 Stopping criteria and risk mitigation:

ANSM

he clinical protocol will include predefined stopping criteria aligned with current EMA guidance for biologics:
Occurrence of serious infusion reactions or cytokine-release-like events
Any Grade 3–4 laboratory abnormality attributable to study drug
Exposure (AUC or Cmax) exceeding twice the predicted safe threshold
Emergence of anti-drug antibodies (ADA) associated with altered PK or immune activation.

Risk-mitigation strategies include:
Sentinel dosing of the first subjects in each cohort
Real-time PK monitoring before dose escalation
Immediate medical supervision during and after infusion
Use of pre-defined pause and review rules by the safety committee.

CLINICAL CONSIDERATIONS

12. CLINICAL DEVELOPMENT STATUS

12.1 Clinical Trials Conducted and Ongoing

12.1.1 Clinical trials already conducted or ongoing with the investigational medicinal product (or with a closely related product if the IMP has never been tested in humans).:

ANSM

Not provided

12.1.2 Number of clinical trials conducted or ongoing: ANSM

Not provided

12.1.3 Total number of patients enrolled (France and overall): ANSM

Study	Total Patients	Patients in France	Patients Outside France

12.2 Synoptic Tables of Clinical Trials

12.2.1 Tables of Clinical Trials ANSM

12.2.1.a Overview of Study Characteristics:

Study title	Objectives	Design	Population	Investigational product	Dosage

12.2.1.b Efficacy Study:

Endpoints	Efficacy results	Safety results

13. PLANNED CLINICAL DEVELOPMENT

13.1 Synoptic Tables of Planned Clinical Trials

13.1.1 Patient management in case of toxicity foreseen?: ANSM

Not provided

Patient management in case of toxicity:

Not provided

13.1.2 Stopping criteria: ANSM

Not provided

Explain stopping criteria if different from standard (per patient, per cohort, for the study):

Not provided

13.1.3 DSMB presence: ANSM

Not provided

Explain DSMB if applicable.:

Not provided

13.2 Synoptic Summary of Planned Clinical Studies

13.2.1 For each planned clinical study, provide the following details ANSM

13.2.1.a Study Overview:

Title (and EudraCT number) and phase	Objectives (primary / secondary)	Study design

13.2.1.b Clinical Details:

Study population	Justification of population and treatment line	Dose regimen	Endpoints (primary / secondary / exploratory)

14. RISK: LIMITATIONS AND PRECAUTIONS

14.1 Use limitations: TPP

Not provided

14.2 Special concerns: TPP

Not provided

REGULATORY CONSIDERATIONS

15. REGULATORY INFORMATION

15.1 Regulatory Status

15.1.1 Orphan Designation: ANSM

Not provided

If yes, specify date of designation and procedure number:

Not provided

15.1.2 Pediatric Investigation Plan (PIP): ANSM

Not provided

If applicable, specify date and procedure number:

Not provided

15.1.3 Marketing Authorization (MA/AMM): ANSM

Not provided

If obtained, specify date and procedure type: ANSM

Not provided

15.1.4 Scientific Advices Received: ANSM

Not provided

If yes, specify dates and type: ANSM

Not provided

15.1.5 PRIME Designation Considered: ANSM

Not provided

If yes, provide details on the PRIME designation: ANSM

Not provided

15.1.6 Other relevant regulatory statuses (specify if any): ANSM

Not provided

15.2 Regulatory Compliance ANSM

15.2.1 List of guidelines or reference documents considered in product development: ANSM

Not provided

15.2.2 If "EMA", "FDA" or "Other" selected, specify the guideline name(s) or references: ANSM

Not provided

FINANCIAL ASPECTS

16. MARKET INFORMATION

16.1 Targeted country or region for commercialization: TPP BPI

Not provided

16.2 Targeted population (e.g. age group, specific condition, etc.): TPP BPI

Not provided

16.3 Market access strategy (e.g. hospital use, retail pharmacy, compassionate use): TPP BPI

Not provided

16.4 Expected pricing strategy (if known): TPP BPI

Not provided

16.5 Key existing competitors or reference products on the market: TPP BPI

Not provided

16.6 Comparison in terms of cost-effectiveness: TPP BPI

Not provided

16.7 Expected advantages for payers (e.g. reduced hospitalizations, fewer side effects): TPP BPI

Not provided

16.8 Planned reimbursement strategy (if applicable): TPP BPI

Not provided

17. FINANCIAL OBJECTIVES

17.1 Expected potential economic value (e.g. return on investment, budget impact): TPP BPI

Not provided

17.2 CANVAS model or economic business model (if applicable): TPP BPI

Not provided

Quality Target Product Profile (QTPP)

QA

QUALITY

Quality Attribute	Target	Justification
Identity	Primary and tertiary structure consistent with reference mAb-X (LC-MS + peptide mapping).	Confirms that the produced antibody is the correct molecule, with no sequence or structural deviation.
Purity	? 98% monomer by SEC-HPLC.	Ensures high-quality material and supports interpretation of scale-up data.
Major Impurities (HCP/DNA/Protein A)	HCP < 100 ppm DNA < 10 pg/mg Protein A < 10 ppm	Standard expectations for pre-FIH monoclonal antibodies.
Aggregation level :	aggregates <2%	: reduces immunogenicity risk during pilot-scale production
Initial stability	no major degradation products in short-term stress	ensures the antibody remains intact during scale-up handling

SAFETY

Quality Attribute	Target	Justification
Toxic impurities	No impurity with known toxicological alerts above reporting threshold.	Prevents unexpected toxicity during animal studies.
Preliminary genotoxicity	No mutagenic signal in early genotoxicity assay	Mandatory check before initiating GLP toxicology
Pilot in vivo tolerability signals	No severe adverse events or unexpected toxicity in exploratory in vivo studies at planned exposure levels.	Supports safe transition to formal GLP tox & FIH dose selection.
Degradation-related toxicological risk	no degradation species of toxicological concern.	ensures toxicity studies reflect the intact antibody
Cytotoxicity profile	no excessive cytotoxicity in relevant cell systems	screens for unexpected off-target effects

EFFICACY

Quality Attribute	Target	Justification
Mechanism of Action consistency	Inhibition of IL-23–induced IL-17A/IL-6 production in vitro	Confirms MoA remains functional at pilot scale.
Preliminary pharmacokinetics	Exposure in cynomolgus compatible with predicted human dose	Needed to define safe starting dose for FIH (MABEL/HED logic).
Stability in biological matrices	stable in serum/plasma over assay duration	avoids artefacts caused by degradation
Potency	IC50 within the predefined window.	confirms alignment with the mechanism of action

Unit 1: UPSTREAM

Steps:

Step 1.1: Cell Revival

Material Attributes:

- Medium composition (glucose, glutamine, salts, growth factors)
- Medium lot quality

Performance Parameters:

- Inoculation density (starting viable cell concentration)
- Incubation temperature (typically 37 °C)
- CO2 level (around 5 %)
- Timing of thawing

In-Process Controls (Step)

IPC Name	Specification
Cell count and viability	rypan Blue or automated cell counter
pH and osmolality of the medium	*No specification*
Glucose and lactate levels	*No specification*
Microscopic observation	morphology, contamination check

Step 1.2: Inoculum Preparation

Material Attributes:

- Inoculum medium composition

Performance Parameters:

- Passage ratio (split ratio)
- Culture duration
- pH and temperature
- Dissolved oxygen (DO) and agitation
- Final inoculum volume

In-Process Controls (Step)

IPC Name	Specification
Viable cell density	target range before transfer
Metabolite monitoring	glucose, glutamine, lactate, ammonia
Osmolality	*No specification*
Growth rate	microscopy
Absence of contamination	visual or rapid tests

Step 1.3: Bioreactor Production

Material Attributes:

- Feed composition
- • Basal medium quality
- Bioreactor type

Performance Parameters:

- Feed rate and schedule
- Culture duration
- Headspace pressure
- Agitation speed
- Temperature
- Temperature
- Aeration rate & oxygen flow
- Feeding mode

In-Process Controls (Step)

IPC Name	Specification
pH, temperature, Disolve Oxygen	real-time probes
Viable cell density and viability	Daily sampling
Glucose, lactate, glutamine, ammonia concentration	*No specification*
CO? and O? gas flow rates	*No specification*
Product titer	ELISA or HPLC for monitoring yield
Agitation speed and aeration rate	measurement of actual physical process variables

Step 1.4: Centrifugation

Material Attributes:

- Broth viscosity

Performance Parameters:

- Rotation speed (g-force)
- Centrifugation duration
- Feed flow rate
- Process temperature

In-Process Controls (Step)

IPC Name	Specification
Supernatant turbidity or optical density	clarity check
Temperature monitoring	*No specification*
Volume recovery yield	*No specification*

Step 1.5: Depth Filtration

Material Attributes:

- Product viscosity and stability
- Colloidal charge and liquid composition

Performance Parameters:

- Filtration flow rate
- Differential pressure limit
- Filter type and pore size

In-Process Controls (Step)

IPC Name	Specification
Differential pressure across the filter	*No specification*
Filtration flow rate	*No specification*

IPC Name	Specification
Conductivity and pH of filtrate	*No specification*

In-Process Controls (IPCs)

IPC Name	Specification	Step
Cell count and viability	rypan Blue or automated cell counter	Cell Revival
pH and osmolality of the medium	*No specification*	Cell Revival
Glucose and lactate levels	*No specification*	Cell Revival
Microscopic observation	morphology, contamination check	Cell Revival
Viable cell density	target range before transfer	Inoculum Preparation
Metabolite monitoring	glucose, glutamine, lactate, ammonia	Inoculum Preparation
Osmolality	*No specification*	Inoculum Preparation
Growth rate	microscopy	Inoculum Preparation
Absence of contamination	visual or rapid tests	Inoculum Preparation
Supernatant turbidity or optical density	clarity check	Centrifugation
Temperature monitoring	*No specification*	Centrifugation
Volume recovery yield	*No specification*	Centrifugation
Differential pressure across the filter	*No specification*	Depth Filtration
Filtration flow rate	*No specification*	Depth Filtration
Conductivity and pH of filtrate	*No specification*	Depth Filtration

IPC Name	Specification	Step
pH, temperature, Disolve Oxygen	real-time probes	Bioreactor Production
Viable cell density and viability	Daily sampling	Bioreactor Production
Glucose, lactate, glutamine, ammonia concentration	*No specification*	Bioreactor Production
CO? and O? gas flow rates	*No specification*	Bioreactor Production
Product titer	ELISA or HPLC for monitoring yield	Bioreactor Production
Agitation speed and aeration rate	measurement of actual physical process variables	Bioreactor Production

Unit 2: DOWNSTREAM

Steps:

Step 2.1: Capture Chromatography

Material Attributes:

- Resin type (Protein A, affinity, ion exchange, etc.)
- Binding capacity of the resin
- Buffer composition and conductivity
- Product stability in buffer
- Feed turbidity and viscosity

Performance Parameters:

- Column loading volume (residence time, mg protein/mL resin)
- Flow rate and pressure
- Elution gradient (salt concentration or pH)
- Column equilibration and regeneration conditions

In-Process Controls (Step)

IPC Name	Specification
UV absorbance (280 nm) to monitor elution peak	*No specification*
Protein concentration in load and eluate	*No specification*
Pressure drop across the column	*No specification*

Step 2.2: Intermediate Chromatography

Material Attributes:

- Buffer composition and stability of product under acidic conditions
- Product concentration and formulation

Performance Parameters:

- pH and exposure time (e.g., pH 3.5 for 60 min)
- Mixing speed and temperature
- Neutralization buffer volume and rate

In-Process Controls (Step)

IPC Name	Specification
pH measurement and control during inactivation	*No specification*
Product integrity (via HPLC or UV absorbance) after neutralization	*No specification*

Step 2.3: Polishing Chromatography

Material Attributes:

- Resin type (cation/anion exchange)
- Buffer quality and ionic strength
- Feed impurity profile

Performance Parameters:

- Column loading and flow rate
- Buffer pH, conductivity
- Gradient elution program
- Wash and regeneration cycles

In-Process Controls (Step)

IPC Name	Specification
UV absorbance during elution	*No specification*
Conductivity and pH monitoring	*No specification*
Pressure drop across the column	*No specification*

Step 2.4: Viral Filtration

Material Attributes:

- Resin type (e.g., hydrophobic interaction, size exclusion)
- Buffer composition

Performance Parameters:

- Column flow rate and loading
- Buffer composition and pH
- Column temperature

In-Process Controls (Step)

IPC Name	Specification
UV absorbance (protein peak separation)	*No specification*
Product purity (SDS-PAGE, SEC-HPLC)	*No specification*

IPC Name	Specification
Conductivity and pressure	*No specification*
Yield and concentration	*No specification*

Step 2.5: Concentration / Diafiltration (TFF)

Material Attributes:

- Filter membrane compatibility (protein adsorption)
- Buffer composition

Performance Parameters:

- Filtration pressure and flow rate
- Filter type (pore size ~20 nm)
- Feed temperature and viscosity

In-Process Controls (Step)

IPC Name	Specification
Differential pressure (?P) across filter	*No specification*
Filtrate turbidity and clarity	*No specification*
Filtrate flow rate	*No specification*
Filter integrity test (before/after run)	*No specification*

Step 2.6: Sterile Filtration (0.22 ?m)

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (IPCs)

IPC Name	Specification	Step

UV absorbance (280 nm) to monitor elution peak	*No specification*	Capture Chromatography
Protein concentration in load and eluate	*No specification*	Capture Chromatography
Pressure drop across the column	*No specification*	Capture Chromatography
pH measurement and control during inactivation	*No specification*	Intermediate Chromatography
Product integrity (via HPLC or UV absorbance) after neutralization	*No specification*	Intermediate Chromatography
UV absorbance during elution	*No specification*	Polishing Chromatography
Conductivity and pH monitoring	*No specification*	Polishing Chromatography
Pressure drop across the column	*No specification*	Polishing Chromatography
UV absorbance (protein peak separation)	*No specification*	Viral Filtration
Product purity (SDS-PAGE, SEC-HPLC)	*No specification*	Viral Filtration
Conductivity and pressure	*No specification*	Viral Filtration
Yield and concentration	*No specification*	Viral Filtration
Differential pressure (?P) across filter	*No specification*	Concentration / Diafiltration (TFF)
Filtrate turbidity and clarity	*No specification*	Concentration / Diafiltration (TFF)

Filtrate flow rate	*No specification*	Concentration / Diafiltration (TFF)
Filter integrity test (before/after run)	*No specification*	Concentration / Diafiltration (TFF)

Unit 3: FILL & FINISH

Steps:

Step 3.1: Formulation & Sterile Filtration

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

Step 3.2: Filling

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

Step 3.3: Quality Control & Packaging

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (IPCs)

No IPCs available

In-Process Controls (IPCs)

Unit 1 : UPSTREAM

IPC Name	Specification	Step
Cell count and viability	rypan Blue or automated cell counter	Cell Revival
pH and osmolality of the medium	*No specification*	Cell Revival
Glucose and lactate levels	*No specification*	Cell Revival
Microscopic observation	morphology, contamination check	Cell Revival
Viable cell density	target range before transfer	Inoculum Preparation
Metabolite monitoring	glucose, glutamine, lactate, ammonia	Inoculum Preparation
Osmolality	*No specification*	Inoculum Preparation
Growth rate	microscopy	Inoculum Preparation
Absence of contamination	visual or rapid tests	Inoculum Preparation
Supernatant turbidity or optical density	clarity check	Centrifugation
Temperature monitoring	*No specification*	Centrifugation
Volume recovery yield	*No specification*	Centrifugation
Differential pressure across the filter	*No specification*	Depth Filtration
Filtration flow rate	*No specification*	Depth Filtration
Conductivity and pH of filtrate	*No specification*	Depth Filtration
pH, temperature, Disolve Oxygen	real-time probes	Bioreactor Production
Viable cell density and viability	Daily sampling	Bioreactor Production

IPC Name	Specification	Step
Glucose, lactate, glutamine, ammonia concentration	*No specification*	Bioreactor Production
CO? and O? gas flow rates	*No specification*	Bioreactor Production
Product titer	ELISA or HPLC for monitoring yield	Bioreactor Production
Agitation speed and aeration rate	measurement of actual physical process variables	Bioreactor Production

Unit 2 : DOWNSTREAM

IPC Name	Specification	Step
UV absorbance (280 nm) to monitor elution peak	*No specification*	Capture Chromatography
Protein concentration in load and eluate	*No specification*	Capture Chromatography
Pressure drop across the column	*No specification*	Capture Chromatography
pH measurement and control during inactivation	*No specification*	Intermediate Chromatography
Product integrity (via HPLC or UV absorbance) after neutralization	*No specification*	Intermediate Chromatography
UV absorbance during elution	*No specification*	Polishing Chromatography
Conductivity and pH monitoring	*No specification*	Polishing Chromatography

IPC Name	Specification	Step
Pressure drop across the column	*No specification*	Polishing Chromatography
UV absorbance (protein peak separation)	*No specification*	Viral Filtration
Product purity (SDS-PAGE, SEC-HPLC)	*No specification*	Viral Filtration
Conductivity and pressure	*No specification*	Viral Filtration
Yield and concentration	*No specification*	Viral Filtration
Differential pressure (?P) across filter	*No specification*	Concentration / Diafiltration (TFF)
Filtrate turbidity and clarity	*No specification*	Concentration / Diafiltration (TFF)
Filtrate flow rate	*No specification*	Concentration / Diafiltration (TFF)
Filter integrity test (before/after run)	*No specification*	Concentration / Diafiltration (TFF)