PROJECT: MABX CLINIC

TARGET PRODUCT PROFILE 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.

TARGET PRODUCT PROFILE

Project overview

1.1 Name or acronym of the project

Nova - New optimized validated Antibody - mAbX

1.2 More information about the sprint, or the sprint question

for this sprint, our objective is to identify which process lever most strongly affects two key attributes of mAb-X: its IC50, and its glycan profile, especially the G2F ratio. This is the guiding question for the sprint, and it will orient the entire QbD analysis that follows.

1.3 Development challenges or constraints

mAb-X faces several TRL5-level constraints typical of monoclonal antibody scale-up:
• Process scalability (5 L ? 200–500 L)
• Glycosylation control
• Aggregation risk
• Impurity clearance (HCP, DNA, Protein A)

Product overview

3.1 Commercial name of the product

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

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

3.3 Development progress

Product type : Drug
TRL (Transfer Readiness Level) : 4
Medication type : Biological drug
Pharmacotherapeutic class : Immunomodulating agents – monoclonal antibodies.
Biological activity : 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 : 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

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

Indication

2.1 Therapeutic indication

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

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

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.
https://doi.org/10.1136/ard-2022-223356
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

Yes

2.4.1 Explanation of the unmet medical need

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.

Mechanism of action

2.5.1 Mechanism of action of the product

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.

Expected benefit

2.5.2 Expected advantages or improvements over existing treatments

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.

Formulation

4.1 Formulations developed so far

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).

7.6 Dosage forms and strengths

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

3.10 Target composition / key technical characteristics

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.

5.1 Active ingredients

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.

Route of administration

3.5 Route of administration / method of use

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

Expected efficacy

2.5.3 Expected efficacy

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.

Desired safety profile

2.5.4 Desired safety profile

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.

Stability

3.8.1 Do preliminary stability observations exist for the product?

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)

3.8.2.2 – 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.

Pharmacodynamics and pharmacokinetics

9.1.2 Pharmacodynamics

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

Species	Dose	Route of Administration	Bioavailability	AUC (ng·h/ml)	Cmax (ng/ml)	Tmax (h)	T1/2	Vd
Mouse (n=6)	5 mg/kg	IV	100%	2000	50	0.5	120	0.1

Preclinical development plan

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

Preclinical proof-of-concept has been established: mAb-X binds IL-23, shows functional neutralization, and reduces inflammation in a murine model.
A preliminary PK study confirmed an exposure profile consistent with an IgG1.
Before entering first-in-human studies, the remaining milestones are:
• completion of GLP toxicology,
• viral clearance validation,
• production of a 200–500 L pilot-scale GMP batch.

Competitive landscape (optional)

2.5.5 Competitive landscape / existing products

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.