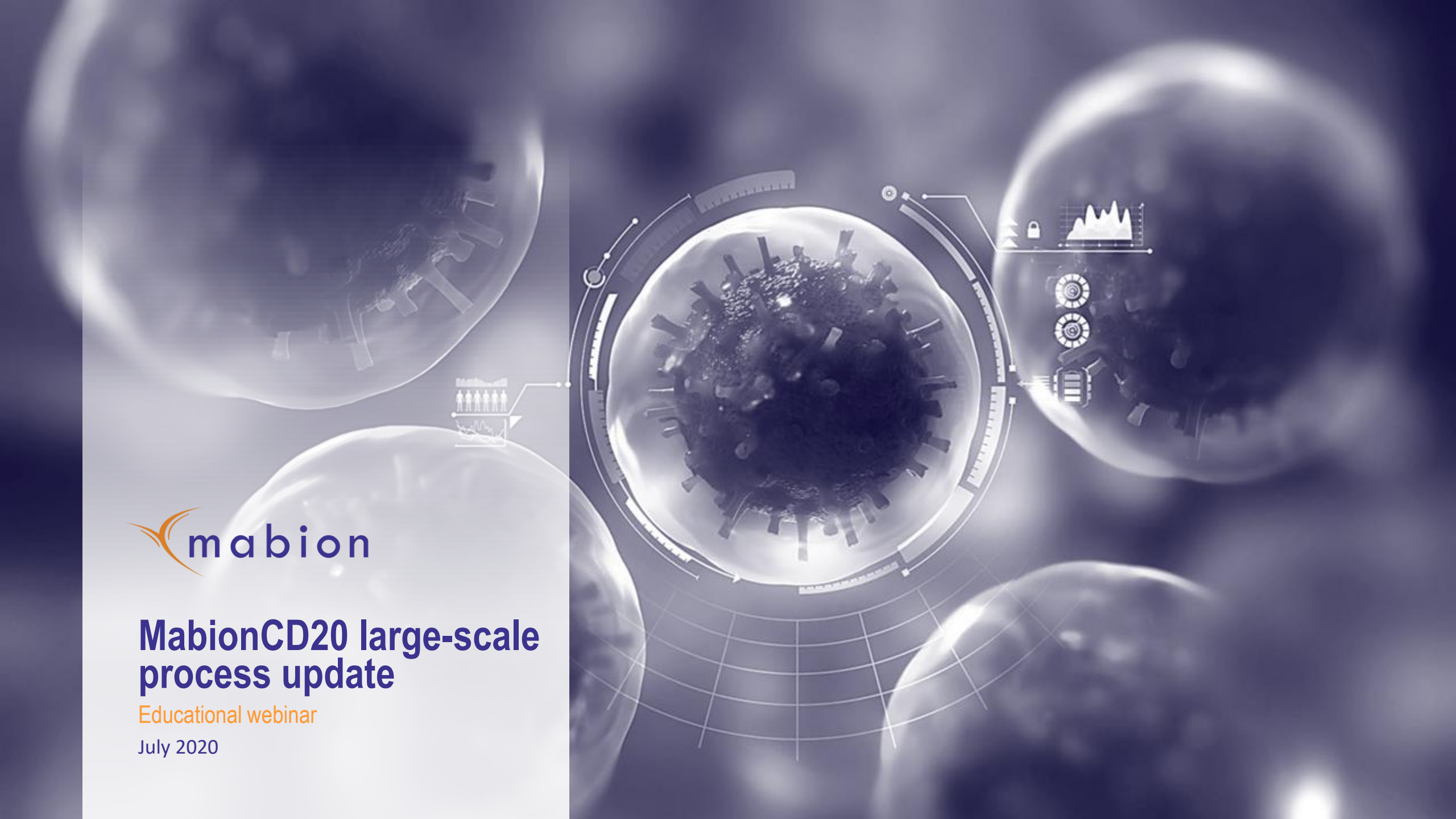

mabion

MabionCD20 large-scale process update

Educational webinar

July 2020

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Scientific Advice with EMA and the next steps

scope of the Scientific Advice (SA) documentation

April 2020
Mabion filed with EMA
large-scale manufactured MabionCD20 briefing package

July 2020
Mabion received written advice from the regulator referring to the **scope and format of data to be included in the large-scale application for MabionCD20**

7 questions from the regulator touching on the following areas:

1) Question on defining a Quality Attribute (glycoforms) in a way more representative of biological activity – **Neutral/Challenging**
2) Presented 5000L scale data sufficient to show biosimilarity to MabThera? **Neutral/Positive**
3) Question on proposed comparability (500L/5000L) approach – **Negative**, with guidance on how to improve data package
4) Question on the QTPP (Quality Target Product Profile) - **Neutral**
5) Question on needing a Phase I bridging study – **Neutral/Expected** – bar for filing without any clinical data high
6) Question on design of Phase I study, if required – **Positive** – proposed design accepted with one exception
7) Need for additional safety/immunogenicity data (assuming we run the Phase I study) – **Positive** – data considered sufficient

Mabion addressing SA queries to reach strategic goal

Mabion's goals

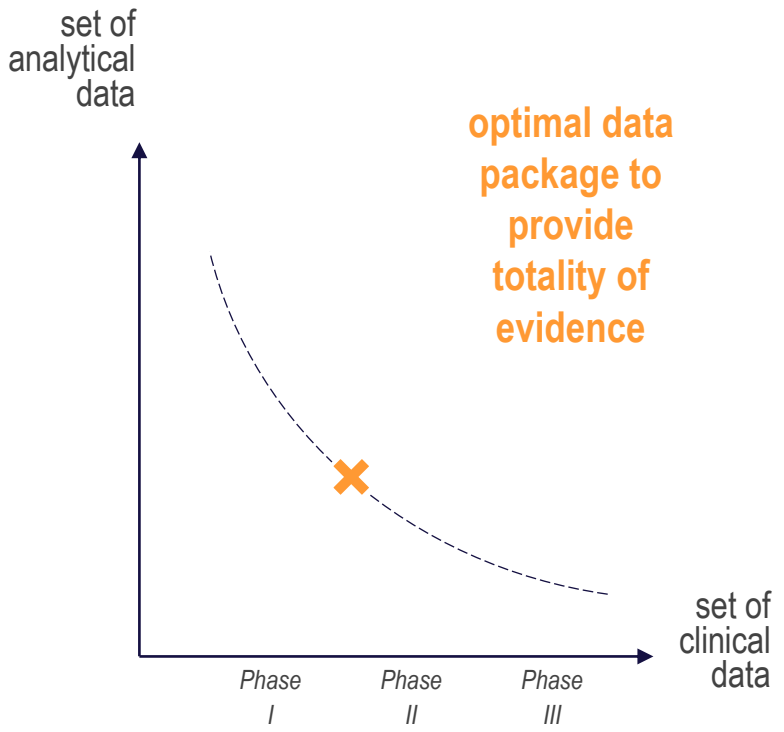
provide convincing data package (totality of evidence) for the large-scale application

sustainable risk management to maximize likelihood of approval (avoid „minimum-set-of-data" approach)

get EMA approval for the commercial scale product (the Company's actual goal) and launch it as early as possible

Mabion's consulted scope of data within the taken approach

analytical data package	⇨ set of more than 50 state-of-the-art analytical methods
clinical data package	⇨ Phase 1/2 trial to demonstrate the biosimilarity between MabionCD20 and comparators – clinical „bridging" data: - 3-armed study: MabionCD20, MabThera (EU reference product) and Rituxan (US reference product) - scope of trial: pharmacokinetics (PK), and safety endpoints - clinical indication: rheumatoid arthritis - estimated enrollment: estimated <80 patients per arm
volume of manufactured batches	⇨ minimum 3 batched required by international standards ⇨ increasing number of batches: - improves visibility of data space (supports regulatory purposes and reduces unknowns) - signals to Mabion's partners that the Company is convinced of the product's quality - batches can be marketed after clearance (inventory building for launch)



Through Scientific Advice the Company has reconnected with the Agency and improved understanding of expectations

why does additional clinical trial data improve the quality of the MAA?

- certain changes in the manufacturing process **implicate necessity to reassess comparability** of the biological product by the regulator (comparable quality attributes)
- assessment of comparability is a **standard procedure** required by the Regulator **in case of changes to the manufacturing process,** both during development and after approval (different requirements are applied depending on the scope of change and following the evaluation of the quality attributes)
- reasons for such changes include improvements to the manufacturing process or up-scaling
- **clinical trial data adds to the totality of evidence substantially increasing the comfort of the Regulator in the assessment procedure**

provide data from clinical trial (limited-scope) → **to prove comparability of the biological product (MabionCD20) across the manufacturing process changes**

development of the large-scale manufacturing process – validation, stability and analytical similarity and comparability data

1 **validation of manufacturing process**

confirming that it is feasible to repeatedly achieve the required quality of the product by using defined process control parameters

☑ **validation pursued in line with the initial schedule**

3 batches of drug substance manufactured; drug product ready for release (final step of validation)

! **preliminary analytical tests show that all manufactured batches meet requirements regarding quality attributes**

2 **stability study**

controlling natural differences in structure of the biological product and potential undesired immunogenicity due to impact of physical conditions (particularly temperature influencing time and storage method)

☑ **started**

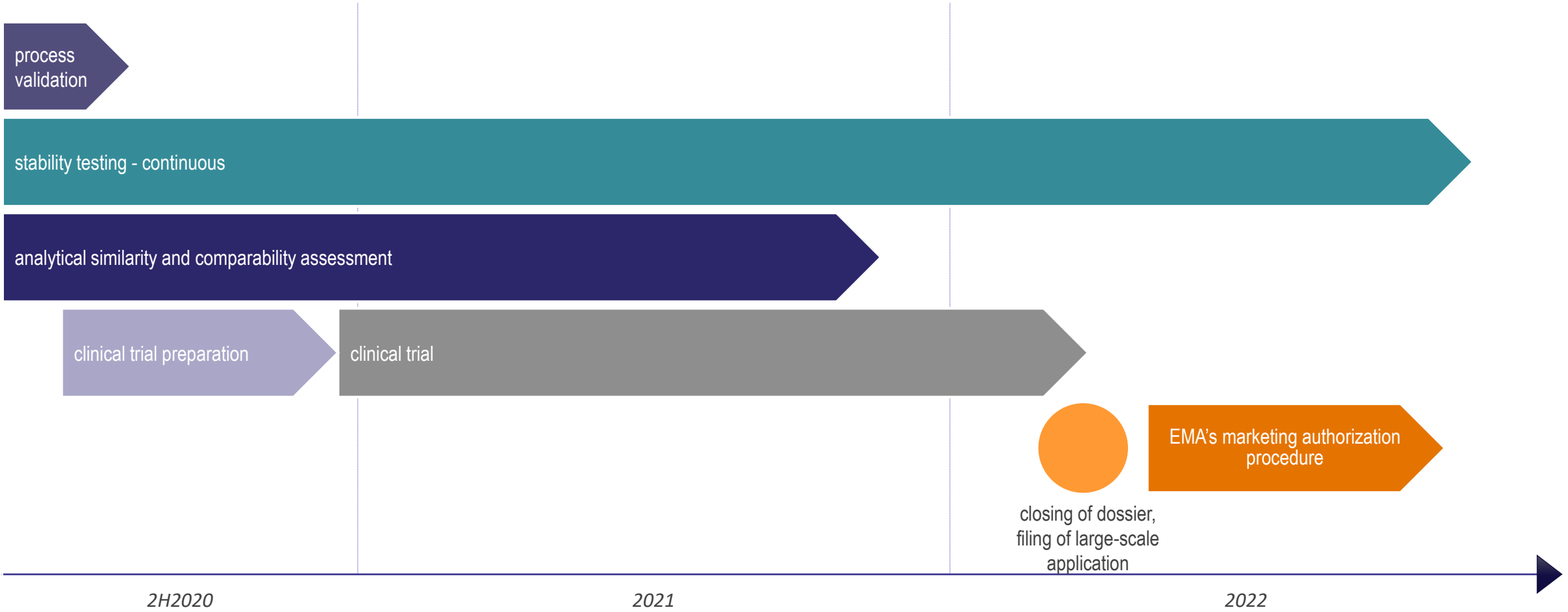
3 batches in stability study

3 **analytical similarity and comparability assessment**

in vitro assays aimed at comparing biological and physicochemical attributes of biosimilar and reference drug through statistical analysis of results based on qualified analytical methods with verified sensitivity. Analytical similarity assessment involves identification of critical quality attributes (CQAs) that are relevant to clinical outcomes.

☐ **to be performed**

assumed timeline of large-scale application processing in EMA



development of the large-scale dossier and near-term activities

accomplished

- ☑ scientific advice document received and analyzed
- ☑ 3 batches of product manufactured
- ☑ tender documentation for CROs in final preparation
- ☑ clinical trial protocol drafted
- ☑ application for public grant filed

near-term activities

- ☐ opening tenders for CROs
- ☐ advancing stability study
- ☐ commencing similarity and comparability studies

strengths and opportunities

- ☑ **continuation of relations with EMA's assessors (reduced risk of misinterpretation of previous issues resolved)**
- ☑ regulatory experience earned over the previous application process
- ☑ support from partners

financing of the large-scale development and regulatory process until approval from EMA

main areas of spending*

** does not include running costs and CAPEX for increasing capacity*

R&D	stability tests
R&D	analytical similarity and comparability assessment
R&D	clinical trial (incl. CROs)
M&M	Manufacturing & Maintenance (additional batches)
QA QC	Quality Assurance & Quality Control & Regulation
	(including sourcing in the reference product)

70%

estimated at total PLN 75-85 m (net)

set of activities necessary to meet regulator's requirements for the MAA remains unchanged (would have followed small-scale approval)

sources of financing

- equity raise
- loans (including loans from founders)
- new public grants

additional funding

- partnering
- EBI loan

MabionCD20 operational and regulatory pathway in the US

- **continuation of the initiated regulatory process in the US**
  - ongoing consultation with US FDA regarding clarification of the scope of the bridging study (following Type 3 BPD meeting protocol)
  - next expected regulatory step will comprise Type 2 meeting (confirmed timing: first half of August 2020)

- **ongoing process of building data package for the US application**
  - proposed bridging study for the EU process (Rituxan arm) can be used in the US application as a part of data package
  - large-scale data for the EU market with Rituxan arm increase the value of MabionCD20 asset for the potential partner

- **active business development aimed at partnering of MabionCD20 in the US**

Withdrawal assessment report contents

WAR redaction – „Recommendations" section

„Based on the review of the data on quality, safety and efficacy, **on 12th of December 2019**

the CHMP considers that the application for Rituximab Mabion (also referred MabionCD20), in the treatment of

Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Rheumatoid arthritis (RA), Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

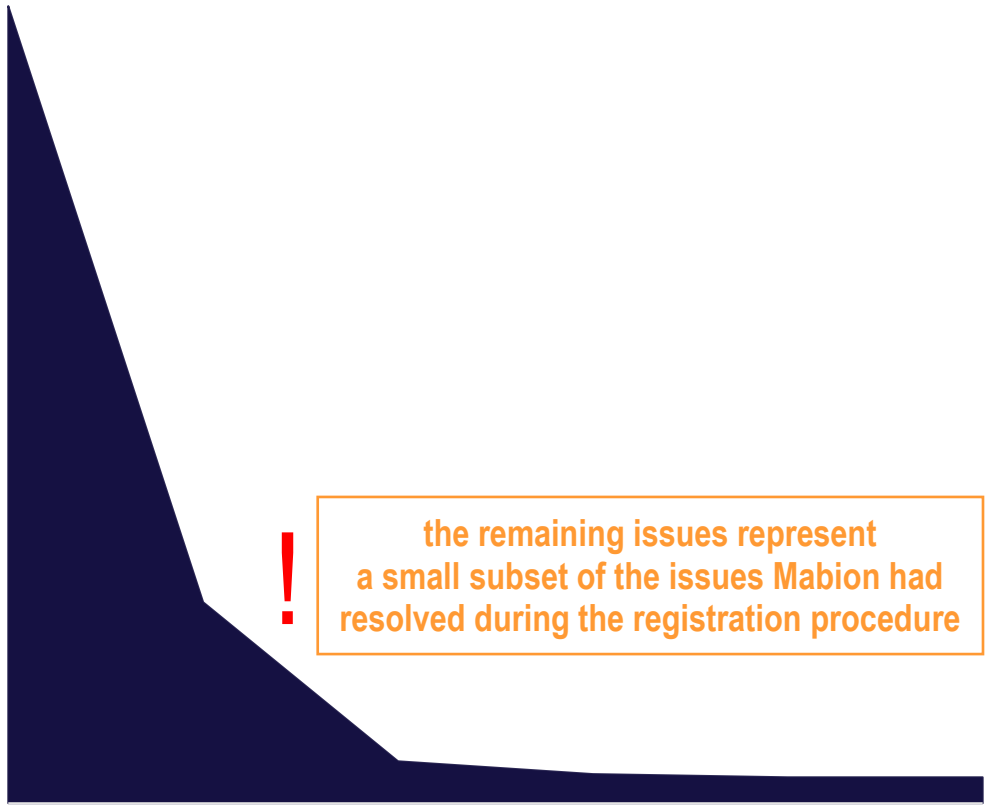
is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation **at the present time**."

The major objections* precluding a recommendation of marketing authorization, pertain to the following principal deficiencies:

- Biosimilarity of MabionCD20 to the originator MabThera-EU has not been demonstrated on several levels as follows:
  - Status of the commercial process; no use of commercial product in clinical trials;
  - GMP compliance has been confirmed for Konstantynów Łódzki manufacturing site, however some deficiencies were noted during development. Improvements in the quality system are acknowledged;
  - Questions regarding non-clinical models;
  - Questions regarding difference between originator and biosimilar based on sub-analysis. Higher ACR20 response rates for MabionCD20 and MabThera in Mabion RA study which questions the study sensitivity to prove biosimilarity;
  - Data handling after findings from GCP inspection.

** For the day of 12th of December 2019*

consistent and methodical work on resolving the Regulator's questions



! the remaining issues represent a small subset of the issues Mabion had resolved during the registration procedure

supported by experienced advisors: **Mylan** **Parexel**

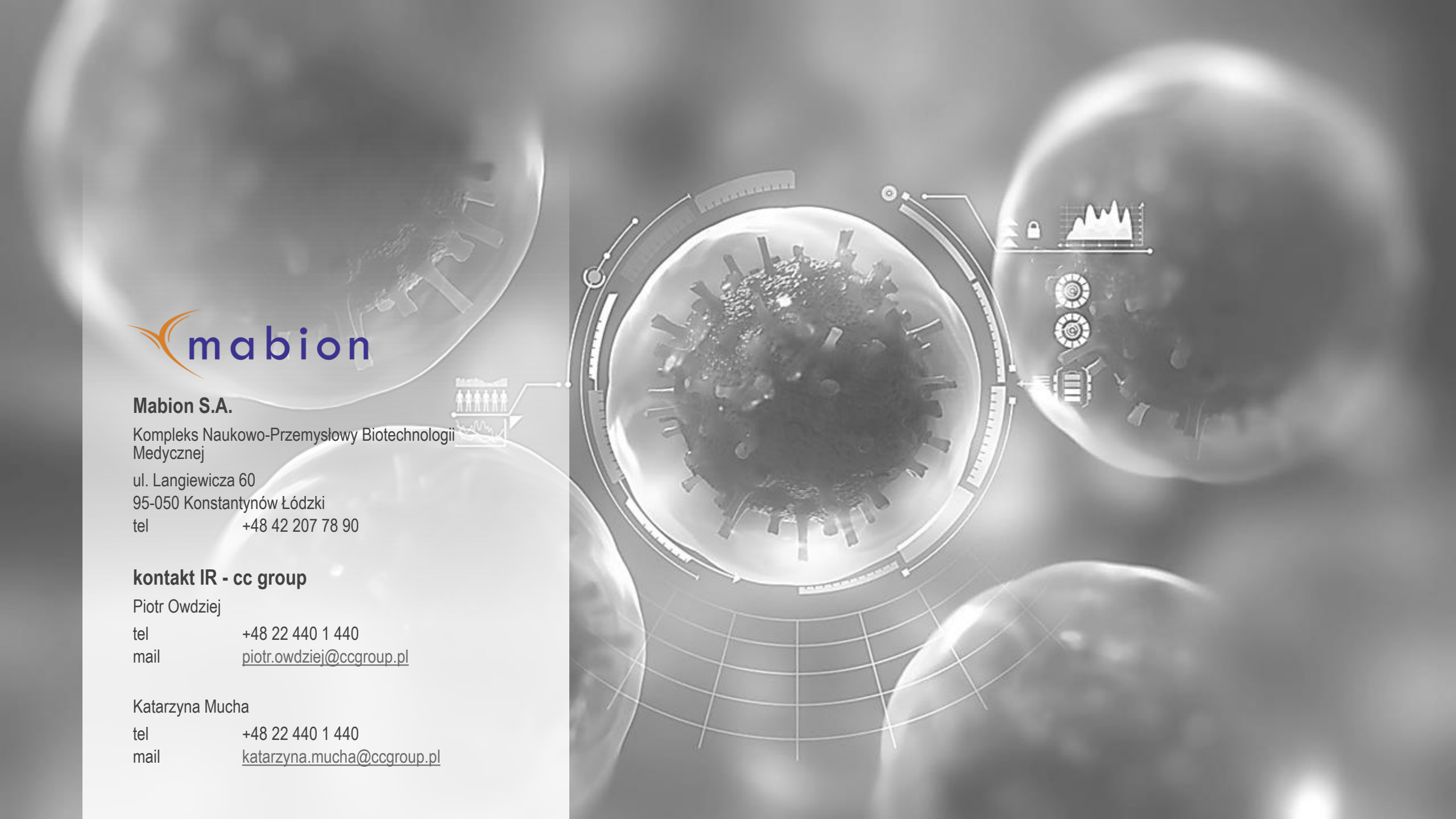
assessment report for MabionCD20 was drafted for the „Day 195", i.e. status in Nov/Dec2019, when a number of unresolved issues remained. They were further addressed and largely solved by the Company in the responses to the Agency submitted in 1Q 2020.

publication of the withdrawal assessment report stands for the last step in the small-scale application procedure and completes the procedure

Day 181+ (1)
refers to the list of outstanding issues received by Mabion in December 2019 (as reflected in the last adopted AR)

Day 181+ (2)
refers to the assessment report received by Mabion in February 2020

Day 181+ (3)
refers to the assessment report received by Mabion in February 2020 prior to oral explanations



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