EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc Ref: EMADOC-360526170-2157788
Human Medicines Division

Initial Qualification Opinion List of Issues

Molecule-independent device bridging approach (MIDBA)

Summary

The main purpose of this request for Qualification Advice is to seek the Agency's advice on the applicability of a molecule-independent device bridging approach (MIDBA), an alternative methodology for clinical bridging from manual subcutaneous (SC) injection via a handheld syringe (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform (YpsoMate 2.25 and 1.0 AIs) for monoclonal antibodies (mAbs). With the MIDBA, it is proposed that individual clinical device qualification for mAbs using the YpsoMate AI platform is replaced by referring to available PK comparability data generated with other mAbs for the same AI platform. This approach would omit the need to generate molecule-specific PK comparability assessments for new mAbs using the YpsoMate AI.

Pivotal clinical studies are frequently conducted using a PFS or HHS, while a standardized and more convenient AI may not be available before starting the Phase III program. Subsequently, pharmacokinetic (PK) comparability studies may be conducted to demonstrate clinical comparability for administration of the same molecule across two SC injection procedures, that is, to allow presentations to transition from HHS or PFS to AI. To facilitate access to a convenient SC delivery system, the Applicant is applying the YpsoMate AI platform for the administration of different mAbs across the portfolio.

The underlying prerequisites for applying the MIDBA are that:

1. the AI contains the same formulation (i.e., including the same excipients at the same concentrations) as used for manual injection,
2. the injection volume is either the same as in the pivotal Phase III study or bracketed by the range of volumes established for manual injection in the pivotal Phase III study for the respective mAb, and
3. the injection sites were previously qualified with manual injection.

Technical design verification and validation, including a summative human factors study, would still be conducted for each individual mAb medicinal product.

As the main Context of Use (CoU) (see further below), the Applicant intends to apply the MIDBA as a novel methodology for generating clinical evidence for the **YpsoMate AI platform** for use with **mAbs**. The proposed methodology was already discussed with the Agency for selected molecules within the Applicant's pipeline [redacted].

[redacted]

Context of Use

The Applicant intends to apply the MIDBA as an alternative methodology to conducting dedicated clinical PK comparability studies between manual and automated subcutaneous injection drug delivery device platforms for eligible monoclonal antibodies [redacted]products. The Applicant proposes applying the novel MIDBA methodology across a number of different context of use (CoU) scenarios, each supported by a distinct scientific evidence base. This approach is expected to enable a tailored discussion on the regulatory qualification of this novel methodology for each CoU.

In **CoU scenario 1,** the integral mAb drug-YpsoMate 1.0 mL and 2.25 mL AI device combination product presentation to be submitted with the marketing authorisation application (MAA) contains the same injection volume of a mAb formulation as that used in the pivotal clinical studies (manual injection using a PFS or HHS). The total dose volume is administered with one injection both with the AI and the PFS or HHS.

[redacted]

Scientific discussion

An advantage can be seen of not having to conduct comparative PK studies for each and every comparison when the device bridging part is very similar across products, for different monoclonal antibodies with different molecular targets, but otherwise comparable PK and physicochemical properties. It is acknowledged that the need for clinical bioavailability data for new injection devices is not described in any detail in currently available EMA guidelines. Development of the MIDBA can therefore be understood and endorsed.

While the proposed prerequisites are broadly followed based on common sense, the manner the Applicant builds their argumentation cannot be completely followed. The proposed steps (components) for the qualification of the different COU are supported. However, the rather descriptive approach is not supported. Quantitative approaches should be proposed to establish the appropriateness of the clinical validation set, as well as the criteria for assessment of the eligibility of mAb's based on PK characteristics, mAb formulation physicochemical and device characteristics spaces. This is currently lacking throughout all the COUs. Hence, most of the identified issues with the overall approach are also applicable to all questions and respective COUs. Below, more specific comments related to each CoU are listed.

CoU1, mAb drug-YpsoMate AI device combination, 1:1 scenario

The underlying prerequisites for mAb-products to be eligible for application of the MIDBA, the are that the YpsoMate AI contains the same formulation (i.e., including the same excipients at the same concentrations) as used for manual injection, and the injection volume is either the same as in the pivotal Phase III study or bracketed by the range of volumes established for manual injection in the pivotal Phase III study for the respective mAb.

The Applicant proposes to limit the application of MIDBA to products with PK characteristics and formulation properties within the studied design space where *in vivo* data is available (isotype, injection volume, concentration, injection time, formulation ingredients, bioavailability values, Tmax values). The Applicant has however not defined which actual limits for these parameters they have in mind, and the Applicant is therefore invited to present the proposed "design space" more explicitly if a qualification is envisaged.

Moreover, it is noted that for one of the model drugs, gantenerumab, the formulations were different. The relevance of this this model drug could therefore be questioned, as it seems to prove that the prerequisite is not really needed. The second prerequisite related to bracketed volume is difficult to follow in the absence of more elaborate description of quality comparability (including Critical Bioavailability Attributes (CBA), Critical material attributes (CMAs), Critical quality attributes (CQAs) and design space.

The relevance of the two proposed "model mAbs" (omalizumab and gantenerumab) should be supported by a discussion on the Critical Bioavailability Attributes (CBA), and Critical quality attributes (CQAs), which is currently lacking.

With respect to safety and local tolerability for the mAb product administered using the Ypsomate AI platform, such data will be available for manual SC administration using PFS or HHS from previous clinical trials and should encompass injection volumes that cover the range of injection volumes foreseen to be delivered with the YpsoMate AI platform. The formulation will be the same. Based on these prerequisites, a similar safety and local tolerability profile would be expected for the PFS/HHS vs. the AI device; the latter for which no clinical data would be available. However, for the reference mAbs (omalizumab and gantenerumab), the rates of injection site reactions (ISRs) were somewhat higher for the AI vs. PFS/HHS in the PK comparability studies. The Applicant is asked to elaborate on reasons for this (e.g. differences in speed of injection between devices) and whether this pattern has been observed for other mAb products.

[redacted]

[redacted]

[redacted]

List of issues to be addressed in writing and during the discussion meeting

Based on the coordinators' reports the Scientific Advice Working Party (SAWP) determined that the Applicant should discuss the following points, before advice can be provided:

Issues to be addressed in writing by 5 February 2025 and during the discussion meeting

Issues on Clinical and Chemical, Pharmaceutical and Biological development

Overarching question applicable to all CoUs

1. Please discuss the need for a more quantitative approach to establish the appropriateness of the clinical validation set, as well as the criteria for assessment of the eligibility of mAb's based on PK characteristics, mAb formulation physicochemical and device characteristics spaces. This is currently lacking throughout all the proposed COUs.

CoU1

2. The Applicant proposes to limit the application of MIDBA to products with PK characteristics and formulation properties within the studied design space where *in vivo* data is available (isotype, injection volume, concentration, injection time, formulation ingredients, bioavailability values, Tmax values). In line with the general question above, the Applicant has however not defined which actual limits for these parameters they have in mind and is therefore invited to present the proposed "design space" more explicitly, including a justification of the relevance of the proposed reference drugs for COU1.

3. Using the MIDBA, no clinical safety or tolerability data would be available for the device bridged to (e.g. from PFS/HHS to AI). In the BE studies with the reference mAbs omalizumab and gantenerumab, the rates of ISRs were somewhat higher for the AI vs. PFS/HHS (24% vs. 14% for omalizumab and 40.7% vs. 27.5% for gantenerumab). The issue is therefore not only the injection volume but the amount/time (rate) that might be higher with the AI and have an impact on the safety and tolerability. This should be discussed.

4. There seem to be no robust data supporting that injection times for the YpsoMate AI remain consistent and within the injection time range of the vial syringe or prefilled syringe. This should also be discussed.

[redacted]

[redacted]