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Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion for Molecule-independent device bridging approach (MIDBA)

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[1] Last day of relevant committee meeting

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Qualification Opinion

The molecule-independent device bridging approach (MIDBA) is qualified as an alternative methodology for clinical bridging from manual subcutaneous (SC) injection via a handheld syringe (HHS) or prefilled syringe (PFS) to an autoinjector (AI) device for monoclonal antibodies (mAbs). With the MIDBA, referring to available PK comparability data generated with other mAbs for the same AI device is proposed as an alternative to generating molecule-specific PK comparability assessments for new mAbs between HHS or PFS and AI. The validity of the approach is demonstrated with YpsoMate 2.25 and 1.0 AIs and with omalizumab and gantenerumab as reference mAbs. Consequently, in regulatory submissions, the following conditions must be fulfilled for MIDBA to be accepted for device bridging of monoclonal antibodies from manual (HHS/PFS) to automated subcutaneous injection.

- Same monoclonal antibody
- Same dose and formulation
- Same injection volume (which should be between 0.5 and 2 mL)
- Same injection site(s)
- An exposed needle length between 4 and 8 mm
- Slow absorption after SC injection
- Similar physicochemical properties to at least one reference mAb

Applying the MIDBA to a different AI device and/or changing any of the proposed specifications need to be supported by additional data and/or justification, along the lines presented for YpsoMate 2.25 and 1.0 in this qualification opinion.

Scientific Discussion

PK comparability aspects

The CHMP *Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins* (CHMP/EWP/89249/2004) states that "The bioavailability might differ between administration sites e.g. thigh, abdomen, and relative bioavailability with respect to each administration site should be clinically investigated if alternative administration sites are to be suggested". More detailed requirements are not expressed in the guideline, though. The potential need for clinical bioavailability data for new injection devices is not described in any detail in currently available EMA guidelines.

Considering the observed injection-site-dependent PK for a number of mAbs, the Applicant proposes that only injection sites previously qualified with manual injection via HHS/PFS (abdomen, upper arm or thigh) in pivotal clinical trials or other clinical pharmacology studies evaluating injection sites would be eligible for use with the YpsoMate AI. This is endorsed.

PK comparability data previously generated for two reference mAbs with the YpsoMate AI device have been used to support the concept.

The Applicant proposes to limit the application of MIDBA to products with PK characteristics and formulation properties similar to the ones of the reference mAb(s), where in vivo data are available (isotype, injection volume, concentration, injection time, formulation ingredients, bioavailability values, Tmax values). However, the Applicant was not able to define a "design space" as asked, and there are no actual limits defined for these parameters. Therefore, any difference from the reference mAbs' key attributes—those expected to directly affect absorption rate or injection performance—must be fully justified as not leading to clinically relevant changes in PK.

The Applicant proposed the MIDBA to rely mainly on data from two specific reference mAbs, i.e. mAbs for which comparative PK studies have been performed to support bridging between different devices. The two mAbs were omalizumab and gantenerumab and, for these two mAbs, PK comparability data

for HHS/PFS versus YpsoMate AI have been previously generated. For these two cases, similar PK was demonstrated for SC administration via HHS/PFS and via Ypsomate AI. This would then support a similar device bridging strategy for other mAb products with similar PK and physicochemical properties, for which the other prerequisites are met (i.e. same formulation, same injected volume, etc.). While this approach appeared reasonable, the relevance of the two proposed reference mAbs (omalizumab and gantenerumab) needed further support by a discussion on the Critical Bioavailability Attributes (CBA), and Critical Quality Attributes (CQAs).

In response to the request from the SAWP to use a more quantitative approach, the Applicant created an overview of the prerequisites for the application of MIDBA. These are presented in the following table.

Table 1 Prerequisites for the application of MIDBA to mAbs in order to achieve comparable PK between manual and automated injection

Parameter	**Prerequisite**	**How addressed**
Formulation[1]	The same for manual and automated[2] administration	Control strategy
Deliverable volume	The same for manual and automated[2] administration	
Monoclonal antibody[3]	The same for manual and automated[2] administration	
Exposed needle length[4]	Between 4 and 8 mm for automated device	
Injection site	The same for manual and automated[2] administration	Specified in medicinal product information
Absorption rate	mAbs characterized by slow absorption into systemic circulation[4]	Selection of molecules with Tmax within "Design space"

[1]Including quality and quantity of excipients.

[2]Autoinjector

[3]Including the production process and control.

[4]Supported with additional literature data for a more quantitative approach.

As stated above, to qualify for the MIDBA, the *formulation* must remain the same as that used for manual injection in the pivotal clinical studies, including overall *injection volume* and identical excipients, at the same concentrations. The same technical quality control processes will be applied to confirm the comparability of the drug product, intermediates, and development process (EMA Guideline on quality documentation for medicinal products when used with a medical device. 2021; EMA Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues. 2007; ICH Q5E Comparability of biotechnological/biological

products. 2005).

The *monoclonal antibody* used for both manual and automated injection must be the same, i.e. any changes related to the cell line, production processes, or control framework compared to the mAb material studied in the pivotal clinical trials must be justified and supported with appropriate evidence according to applicable EMA guidance.

Only *injection sites* permitted for PFS or HHS injection (abdomen, upper arm, or thigh) based on clinical trial data would be eligible for use with the YpsoMate AI device. This will be specified in the product information of the mAb-device combination product.

For the *exposed needle length*, a systematic survey of biological products approved by FDA's Center for Drug Evaluation and Research (Hu et al. 2020), was referred to, including 17 biologics license applications (BLAs) with both PFS and AI presentations for SC administration. This survey revealed that most PK comparability studies met bioequivalence (BE) criteria. In addition to the injection site, the injection depth of the AI as determined by the needle length was suggested as a potential factor influencing the outcome of the PK comparability study. It was hypothesized that, in cases where BE criteria were not met, this may be attributed to AI presentations typically being administered at a 90° angle, where the extended needle length influences the effective injection depth and at a needle length >8 mm may lead to inadvertent intramuscular (IM) administrations. This differs from PFS/HHS presentations, which are generally injected at a 45° angle, without specific control over the needle length piercing the skin. Results suggest that, with a 90° insertion angle, a minimum injection depth of 4 to 5 mm is required for subcutaneous administration. A needle length of less than 8 mm would favour preventing accidental IM injection, particularly in the limbs of males and individuals with a BMI < 25 kg/m². Based on this only exposed needle length of between 4 and 8 mm for the AI device can be endorsed by the CHMP.

For the parameter *absorption rate*, the Applicant suggests that monoclonal antibody therapeutics falling within the scope of using an AI device qualified via MIDBA are generally characterized by slow absorption rates following SC injection. This reflects a slow transition from the injection site into the systemic circulation, primarily occurring via convection to the absorbing lymphatic vessels, followed by convection through the lymphatic vessels that drain into the blood (e.g., T_{max} of approximately 2 to 13 days) (Zhao et al. 2013). Thus, the underlying rationale for assuming that the PK profiles for SC administration of mAbs using HHS or PFS and AI devices will be similar is that, in such situations, the release from the interstitial space via lymph flow (Ryman and Meibohm 2017), rather than the specifics of the SC injection method, is expected to be the rate-limiting factor for absorption into the systemic circulation. This view is endorsed in principle by the CHMP. However, the design space of the MIDBA approach with respect to Tmax and injection time has not yet been defined.

In relation to the absorption rate, the parameter *injection time* was also discussed in relation to local tolerability at the injection site (see below). From a PK perspective, in view of the slow absorption of mAbs after SC injection as discussed above, a difference in seconds when it comes to injection time is hardly expected to affect PK parameters. The Applicant has confirmed that for the YpsoMate AI, the specification demands the solution to be administered within 15 seconds or less. The Applicant points out that for an HHS/PFS, the injection time is not tested because it is user dependent. The injection time is also rarely recorded in clinical studies, but it will inevitably be variable for manual injections due to individual user preferences and capabilities. Hence, from a PK point of view, the slight differences in injection time between manual and automated injection are not deemed relevant for a SC injected mAb. However, as already stated, thresholds for clinically relevant differences are not established.

Support from an expanded validation set

To further support the MIDBA concept from a quantitative perspective, the Applicant expanded their previous overview of PK comparability studies with additional studies for in-house and external mAbs. This validation set comprised three subsets:

- Validation set 1, including studies with mAbs that are commercially available from other manufacturers with the YpsoMate AI platform,1.0 and 2.25 mL (n=11). However, PK comparability data were not available to the Applicant.
- Validation set 2 including studies with mAbs from the Applicant's pipeline (n=4).
- Validation set 3 combining validation sets 1 and 2 and including additional studies with additional mAbs outside of the Applicant's portfolio (n=34).

Based on the described validation sets, the Applicant concluded that PK comparability could be established without a clinically relevant impairment of the local tolerability for the concerned mAbs. Time to reach maximum serum concentration (Tmax) was selected as the most relevant PK parameter for eligibility of a mAb for the application of the MIDBA.

In the comparison of SC administration of the same mAb formulation via PFS or AI, one potential source of absorption differences may be related to the SC fluid depot. Differences in shape of the fluid depot could result in differences in drug transport from such depot to the lymphatic vasculature and, thus, in different residence times in the SC tissue. Impact of residence time differences between PFS and AI would be reflected on differences in Tmax values.

For the mAbs in the validation set, comparable average and ranges of Tmax values were described for automated and manual injection. This supports similar absorption rates for AI and PFS. There was a wide range of individual Tmax values, however, suggesting marked inter-subject variability in the absorption process. The precise root cause of the marked inter-subject variability is unknown and may include physiology differences at the SC administration site. It is expected that such inter-individual variability is more pronounced compared to any potential differences from the different injection procedures within the MIDBA concept. This conclusion is supported by the observation that in the evaluated PK comparability studies, the median Tmax values from PFS/HHS and AI were identical or very similar despite the high ranges of individual Tmax values for both administration methods.

For parameters related to *mAb formulation physicochemical and device characteristics*, the Applicant described the physicochemical parameters of mAb formulations from their portfolio (i.e. validation set 2). In the BE studies comparing manual versus automated administration, various AI and OBDS devices were used. The Active Pharmaceutical Ingredient (API) concentration in the SC formulations ranged between 120 and 180 mg/mL. The pH of the dosing solutions varied from 5.5 to 6, osmolality from 259 to 372 mOsm/Kg, and viscosity from 4.6 to 8.7 cP. The isoelectric point (pI) of the molecules ranged from 8.98 to 9.5. Due to the relatively small number of mAbs, the Applicant acknowledged that this validation set remains descriptive and is considered too small to form a comprehensive framework. This view is endorsed, and it can be concluded that based on these data, no specific physicochemical and/or device characteristics have been possible to identify as critical parameters for acceptance of the MIDBA concept.

Overall, when it comes to parameters to define a certain "design space" for applicability of the MIDBA as an alternative to conducting a comparative PK study, the Applicant has compiled data from several studies comparing PFS/HHS and an AI, in addition to the data obtained for omalizumab and gantenerumab, regarded as reference mAbs.

While the approach may still be regarded as mainly descriptive, certain boundaries have been defined, such as the exposed needle length, which is proposed to be in the range 4-8 mm (to obtain an injection depth for an AI that is similar to that with a manual injection via PFS/HHS and avoid IM

injection) and a slow absorption. For the latter, a specified T_{max} range has not been proposed, other than that T_{max} should be "in a range of days". A median T_{max} in the range of 3-8 days was observed both for manual and automated injection in the presented validation dataset.

No specific physicochemical characteristics have been identified and put forward as critical parameters for acceptance of the MIDBA concept acknowledging however that mainly descriptive data have been provided for those parameters. This can be accepted for the proposed Context of Use (CoU), covering only monoclonal antibodies with similar physicochemical properties as at least one reference product and with slow absorption.

Safety and local tolerability aspects

Introducing an AI device under the conditions described above as an alternative to manual injection via PFS or HHS is not expected to impact the systemic safety profile of the mAb, as long as PK comparability/equivalence can be assumed.

Data on the local tolerability profile of a mAb following manual SC administration using PFS or HHS will always be available 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 must be the same. Thus, with similar depth and speed of injection for AI vs. PFS/HHS, this should result in minimum differences in local tolerability, as long as the formulation, injected volume and injection site(s) remain the same. The angle and depth of injection is, in principle, expected to be more variable with manual injections compared with injections using an AI device.

The Applicant provided comparative data on tolerability between manual and automated injections from bioequivalence (BE) studies involving the reference monoclonal antibodies omalizumab and gantenerumab. Additionally, they shared findings from user preference, usability, and satisfaction studies conducted with mAbs from Validation sets 2 and 3, which compared manual injection methods with autoinjector or pen devices.

The CHMP agrees that in the context described above, clinically relevant differences in the local tolerability between AI and manual injection are not expected. However, due to the inherent challenges in defining the drivers of local tolerability, the omission of dedicated local tolerability assessments based on MIDBA should be supported by a separate, case-specific, justification.

Other considerations

The MIDBA permits the omission of molecule-specific PK comparability assessments for new mAbs between HHS or PFS and AI; however, it does not exempt the medicinal product using an autoinjector device from fulfilling all other standard requirements for marketing authorization as stipulated in the relevant regulatory guidance and governing regulation.

Annexes to be published: (redacted for Context of Use (CoU)2-5 and commercially confidential information)

1. Briefing document
2. List of issues
3. Written responses to list of issues
4. Discussion meeting presentation
5. Overview of comments received on Draft Qualification Opinion