RESPONSE TO INITIAL QUALIFICATION OPINION LIST OF ISSUES

QUALIFICATION PROCEDURE FOR THE MOLECULE-INDEPENDENT DEVICE BRIDGING APPROACH (MIDBA)

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ADE	adverse device effects
AE	adverse event
AI	autoinjector
[redacted]	
AUC	area under the serum/plasma concentration-time curve
BE	bioequivalence
CoU	Context of Use
Cmax	maximum serum/plasma concentration
DS	disposable syringe
EMA	European Medicines Agency
FDA	US Food and Drug Administration
HHS	handheld syringe
[redacted]	
ISR	injection site reaction
LE	line extension
PK	pharmacokinetic
MAA	marketing authorisation application
mAb	monoclonal antibody
MIDBA	molecule-independent device bridging approach
NSD	needle safety device
OBDS	on-body delivery system
[redacted]	
PK	pharmacokinetic
PFS	prefilled syringe
SAE	serious adverse event
SC	subcutaneous
[redacted]	
Tmax	time to maximum serum/plasma concentration

Based on the qualification team experts' draft report, the Agency issued a D30 initial qualification opinion list of issues to be addressed by the Applicant in writing and during the discussion meeting (Doc Ref: EMADOC-360526170-2157788).

INITIAL QUALIFICATION OPINION LIST OF ISSUES

In the following, the Applicant presents all comments and queries from the Agency.

First, the Applicant answers the numbered questions from the List of Issues.

Additionally, for each Context of Use (CoU), the Applicant answers the Agency's additional comments from the “Scientific discussion”.

OVERARCHING QUESTION APPLICABLE TO ALL CONTEXTS OF USE (CoUs)

Question 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.

Answer:

The answer to Question 1 is structured into

(1) A discussion of the need for a more quantitative approach to establish the appropriateness of the clinical validation set.

(2) A systematic review of pharmacokinetic (PK) and local tolerability results from various PK comparability studies with mAbs to extend the clinical validation set.

(3) Criteria for assessing mAb eligibility based on PK characteristics, physicochemical properties of mAb formulations, and device characteristics (“design space”).

This more conceptual section will cover any device type [redacted] and will be referenced in the responses to the Agency’s dedicated questions on the different CoUs.

(1) Discussion of the need for a more quantitative approach to establish the appropriateness of the clinical validation set

As a basis for discussing the need for a more quantitative approach to establish the appropriateness of the clinical validation set, the Applicant has created an overview of the prerequisites for the application of MIDBA. The focus is on achieving PK comparability between manual and automated SC injections, along with an acceptable local tolerability profile with the automated device platform. This framework aims to identify the parameters that require a more quantitative approach.

(1a) Achieving PK comparability between manual and automated injection

Table 1 summarizes the parameters that, in the opinion of the Applicant, need to be controlled to achieve comparable PK between manual and automated SC injection. Specifically, the deliverable volume, the formulation (i.e., excipients and concentrations), the nature of the mAb in scope (i.e., molecule type and weight), the mAb's absorption rate from the SC tissue into the systemic circulation, the exposed needle length and associated injection depth, and the injection site have been identified as attributes that may impact the rate and extent of absorption following manual versus automated administration.

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 or OBDS.
[3]Including the production process and control.
[4]Supported with additional literature data for a more quantitative approach.

In the following section, these prerequisites for the application of MIDBA to mAbs, aimed at achieving comparable PK between manual and automated injection, are described along with how they are addressed by MIDBA. For more details, please refer to the briefing package.

Parameters controlled within MIDBA framework

Formulation & deliverable volume

In order 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 2021, ICHQ5E 2005, EMA 2007).

Monoclonal antibody

The mAb used for both manual and automated injection must originate from the same cell line and the same production process while adhering to the required characterization and control of relevant glycosylation structures and biological activity. 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 to the Agency and supported with appropriate evidence according to relevant guidance (EMA 2003, EMA 2005, EMA 2007).

Injection site

Considering the observed injection-site-dependent PK for a number of mAbs (Zou et al. 2021), the Applicant proposes that, for mAbs applying the MIDBA, 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 device platform. This will be specified in the product information of the mAb-device combination product.

Parameters supported with additional literature data for more quantitative approach

Exposed needle length

A systematic survey of biological products approved by FDA's Center for Drug Evaluation and Research (Hu et al. 2020) including 17 biologics license applications (BLAs) with both PFS and AI presentations for SC administration revealed that most PK comparability studies met bioequivalence (BE) criteria. Among the 17 BLAs, nine are mAbs, four are fusion proteins, and the remaining four are cytokines or their PEGylated analogs. Beside 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.

More specifically, data from 17 BLAs were analyzed, with AI presentations categorized based on maximum injection depth into three groups: (1) maximum injection depth of 8 mm (all ≥ 5.5 mm), (2) injection depth exactly 8 mm, and (3) injection depth greater than 8 mm. No PK-non-BE studies were observed in the first category (0/5), while 1 out of 2 BLAs in the second category and 3 out of 4 BLAs in the third category showed PK-non-BE outcomes. This observed trend suggests that the AI injection depth may influence PK comparability outcome. Notably, all PK-non-BE observations were based on Cmax rather than AUC. It was also acknowledged that only two BLAs were based on powered studies, with one demonstrating PK-BE and the other failing to do so. Among the remaining four BLAs using unpowered studies, three showed PK-non-BE results. The authors hypothesized that the higher number of failed BE studies in group 3 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 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.

Similar observations were made by other investigators. Gibney et al. (2010) measured skin thickness, the distance to the muscle fascia, and subcutaneous adipose tissue thickness in male and female adults with diabetes across three BMI subgroups (<25, 25–29.9, and ≥30 kg/m²). The results suggest that, with a 90° insertion angle, a minimum injection depth of 4 to 5 mm is required for subcutaneous administration across the population. Additionally, a needle length of less than 8 mm would help prevent accidental intramuscular (IM) injection, particularly in the limbs of males and individuals with a BMI < 25 kg/m². Hirsch et al. (2014) studied the risk of IM injection during SC insulin therapy and the effect of needle length on injection safety. The study measured skin and SC fat thickness using ultrasound at various injection sites in 341 diabetic adults with a BMI ranging from 19 to 65 kg/m². Results showed that the distance (D) from the skin surface to muscle fascia varied significantly by body site, BMI, and gender (each $P<0.001$), with higher D in individuals with higher BMI and in women. Median D ranged from 10.9 mm at the thigh to 16.9 mm at the buttock. The risk of IM injection with an 8 mm needle was 25% at the thigh and 9.7% at the abdomen, compared to 1.6% and 0.1%, respectively, with a 4 mm needle. A 45° insertion angle reduced, but did not eliminate, IM risk with longer needles.

Based on the above findings, the Applicant will develop the AI platform with a mean exposed needle length of between 4 and 8 mm, namely 6 mm for the YpsoMate platform.

Absorption rate

Monoclonal antibody therapeutics falling within the scope of using an AI platform qualified via MIDBA are generally characterized by slow absorption rates following SC injection. This slow absorption rate 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., Tmax 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.

Considering the need of a more quantitative approach to establish the appropriateness of the clinical validation set, the Applicant has reviewed the results from additional PK comparability studies to increase the confidence in the MIDBA approach in general (see validation sets, Table 3). The described parameters that are considered as prerequisites for the application of MIDBA to mAbs in order to achieve comparable PK between manual and automated injection are either the same (formulation, injection volume, molecule, injection sites) or can be adjusted based on evidence from the literature (needle length). The Applicant agrees that in the previous briefing packages the eligibility of an individual mAb for the application of MIDBA was described based on common sense, while a definite range of PK parameters that reflect the absorption into the systemic circulation was not specifically proposed.

(1b) Achieving an acceptable local tolerability profile with manual and automated injection

In this section, the Applicant is addressing the Agency's request for discussing the need for a more quantitative approach to establish the appropriateness of the clinical validation set with respect to local tolerability.

General considerations

Several factors have been reported to possibly impact the local tolerability of subcutaneous injections. Based on a recent review article by Zhi et al. (2025) that describes risk parameters affecting injection site reactions (ISRs) for SC administered biologics, the applicant differentiates between parameters that remain unchanged between manual and automated administration and are therefore not expected to impact the applicability of the MIDBA approach, and parameters that differ between manual and automated injection with a device.

Parameters that remain unchanged between manual and automated administration include the underlying disease, the injection site, the molecule type, as well as the mAb and its formulation, including the degree of humanization, the glycosylation profile, and the type of cells used in drug production. The underlying disease and the permitted injection sites are specified in the product information and the relevant EMA guidelines are followed to ensure an adequate control strategy for the formulation, including the active biologic agent and the composition of the dosing solution. In case of deviations, relevant measures are implemented to ensure adequate bridging (EMA 2015, EMA 2021, ICH Q5E 2005, EMA 2007). Moreover, injection-site- dependent local tolerability data following manual administration will have been generated as part of the clinical development program.

The following section discusses the parameters that may differ between manual and automated administration. These include the injection methodology (e.g., deliverable volume, injection force/time, exposed needle length and associated injection depth, and needle gauge) and the degree of professional supervision of the injection procedure, i.e., patient training and interaction and communication with healthcare providers. The applicant has addressed the need for a more quantitative approach by the conduct of an additional literature search and has specifically assessed and summarized the local tolerability profiles in the proposed validation sets with PK comparability studies for additional mAbs.

Table 2 lists the prerequisites for the application of MIDBA to mAbs in order to achieve a comparable local tolerability profile between manual and automated injection. These are described in more detail based on a dedicated literature research in the following.

Table 2 Prerequisites for the application of MIDBA to mAbs in order to achieve a comparable local tolerability profile between manual and automated injection.

Parameter	Prerequisite	How addressed
Underlying disease	The same for manual and automated[2] administration	Specified in product information
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	
Injection site	The same for manual and automated[2] administration	Specified in product information

Injection methodology (incl. Injection force/time, needle length and gauge)[4]	Local tolerability studied in pivotal clinical studies in the target population following manual injection Manual versus automated injection data from local tolerability study from the first molecule utilizing the platform (either PK comparability study in healthy subjects or clinical study in target population) Needle length between 4 and 8 mm for automated device	Control strategy
Professional supervision[4]	Proper training of self-administration	Training materials

[1]Including quality and quantity of excipients.
[2]Autoinjector or OBDS.
[3]Including the production process and control.
[4]Supported with additional data for more quantitative approach.

Parameters that may differ between manual and automated administration and assessment of impact on applicability of MIDBA approach

Injection force/time

Several studies have evaluated the impact of injection time on injection site reactions (ISRs) and pain sensations. In a study by Jain et al. (2017), the PK and tolerability of tralokinumab 300 mg were assessed when administered by different SC injection methods and rates. This Phase 1 trial involved 60 healthy adults randomized to receive two 1-mL injections over 10 seconds, or one 2-mL injection over 10 seconds (12 mL/min), 1 minute (2 mL/min), or 12 minutes (0.167 mL/min). The results showed no differences in the PK profiles between the groups. In terms of tolerability, injection-site pain intensity was lowest with the 0.167 mL/min rate (mean 5.1 mm on a 100 mm visual analogue scale (VAS)) and highest with the 12 mL/min rate (mean 41 mm on VAS). Pruritus intensity was low across all participants. Local reactions included erythema (58.3%) and hematoma/bleeding (18.3%), with all treatment-emergent adverse events being mild. Overall, tralokinumab 300 mg was well tolerated, regardless of the injection rate, with comparable pharmacokinetics observed across all delivery methods.

In a study with gantenerumab by Portron et al. 2020, 50 healthy volunteers aged 40-80 years were randomized to receive a 300-mg SC gantenerumab injection into the abdomen and two placebo injections (one into the abdomen and one into the thigh) over 5 or 15 seconds. The PK profiles were similar for both injection times. Tolerability findings indicated that immediately after the SC gantenerumab injection, pain was slightly higher for the 5-second group compared to the 15-second group, but the difference was not statistically significant (VAS mean difference on 100 mm VAS score: 7.492 mm; 95% CI: -4.439 to 19.423 mm). Pain subsided within 5 minutes post-dosing. Pain VAS scores were numerically higher after thigh injections compared to abdomen

injections for both speeds. No serious adverse events (AEs) were reported, and all AEs were mild in intensity and resolved without sequelae at follow-up, with redness being the most common injection site reaction (36% in the 5-second group, 32% in the 15-second group).

Heise et al. (2014) evaluated the pain associated with SC injections in the abdomen and thigh in relation to different injection speeds and volumes. In a single-centre, one-visit, double-blinded randomized controlled trial, 82 adults with type 1 or type 2 diabetes receiving daily insulin or GLP-1 agonists were enrolled. Participants received 17 saline injections (12 in the abdomen, 5 in the thigh) at varying speeds (150, 300, and 450 µL/s) and volumes (400, 800, 1200, and 1600 µL), plus two needle insertions with no injection. Pain was measured using a 100-mm VAS and a yes/no scale for pain acceptability. It was found that injection speed did not influence pain levels (p=0.833). Conversely, larger volumes significantly increased pain [VAS least square mean differences: 1600 vs. 400 µl, 7.2 mm (CI: 4.6-9.7; p<0.0001); 1600 vs. 800 µL, 7.2 mm (4.4-10.0; p<0.0001); 1200 vs. 400 µL, 3.5 mm (0.4-6.6; p=0.025); and 1200 vs. 800 µl, 3.6 mm (0.4-6.7; p=0.027)]. More pain was reported for thigh injections compared to abdomen injections [9.0 mm (6.7-11.3; p<0.0001)].

While not involving an active molecule, the Applicant would like to highlight two additional studies that systematically examined the impact of injection speed on injection volumes of the local tolerability of a SC injection (Zijlstra et al. 2018, Berteau et al. 2015). Zijilstra et al. investigated injection volumes from 125 to 2250 µL in 80 participants with type 1 or type 2 diabetes (Zijlstra et al. 2018). Participants were given 24 SC saline injections using a 27-gauge ultra-thin-wall needle. The use of saline solution in this study allows for a comparison of the injection conditions while excluding confounding factors, such as the active biologic and additional formulation ingredients. The injections were administered in random order to either the abdomen (n=19) or the thigh (n=5), with various predefined speed-volume combinations. Pain sensation was assessed using a 100 mm VAS. The results showed that the mean pain scores for all speed-volume combinations were low (<20 mm on VAS), indicating zero to mild pain levels. Pain sensation was statistically higher with the 2250 µL injection volume by 4.3 mm compared to the 800 µL volume and 6.4 mm compared to needle-only insertions (p<0.0001). Compared to equivalent injections in the abdomen, thigh injections were consistently rated as more painful (2.1 mm, p=0.0013). The speed of injection did not influence pain sensation. The authors concluded that patient acceptance of the injection pain was high, ranging from 93.7% to 98.7%. In conclusion, while larger injection volumes and thigh injections were rated as slightly more painful, the absolute pain levels were minimal, and the high acceptance rates suggest that the clinical impact of these findings is marginal. Injection speed did not affect pain perception.

Berteau et al. 2015 evaluated the impact of fluid injection viscosity on SC injection pain tolerance in a single-centre, comparative, randomized, crossover, Phase 1 study involving 24 healthy adults. Participants received six injections of either a 2- or 3-mL placebo solution with three viscosities (1, 8–10, and 15–20 cP) at two flow rates (0.02 and 0.3 mL/s) using 50 mL syringes and 27-gauge, 6 mm needles. Pain was assessed through a 100 mm VAS and the fluid location was confirmed by 2D ultrasound. Results showed that viscosity significantly impacted perceived pain (p=0.0003), with less pain at higher viscosities (VAS=12.6 mm for high versus VAS=22.1 mm for low viscosity; p=0.0002). Injection volume (2 or 3 mL) and flow rate (slow or fast) did not affect pain (p=0.89 and p=0.79, respectively). In 92% of cases, the fluid was confined to SC tissue. Solutions up to 3 mL and 15–20 cP were well tolerated, with high viscosity being the most tolerable.

Needle length

As described above (Hu et al. 2020, Gibney et al. 2010, Hirsch et al. 2014), accidental IM injections may occur with needle lengths of longer than 8 mm. To ensure SC injection and avoid IM injection in a broader population, the mean needle length of the AI platform will be between 4 and 8 mm. Literature data on the impact of needle length on pain experience and ISRs remain inconclusive (Omoigui et al. 2006, Arendt-Nielsen et al. 2006, Hofman et al. 2007). This is likely related to the fact that, besides the needle size, factors such as the composition of the formulation, the overall injection method, and the preferences and experience of the individual operator play a confounding role.

Needle gauge

Today, for SC injections, needle sizes of between 25- to 31-gauge are generally applied (Tinkey et al. 2020), with increasingly smaller needles (up to approximately 33-gauge) being applied predominantly in the insulin space (Gill and Prausnitz 2007). SC injections within this range are generally well tolerated, with a general user preference for smaller needle gauges.

The impact of needle gauge on injection site pain and tolerability was for example studied in an open-label, randomized, crossover trial involving insulin-treated participants with type 1 or 2 diabetes study. Thirty-one-gauge x 6 mm needles were compared with 29-gauge x 12.7 mm needles. Participants alternated between using each needle type for 12 weeks at the same injection site. In the 56 participants who completed the study, there were no significant differences in glycemic control, pain scores, leakage, or overall treatment satisfaction. Despite this, patients reported greater satisfaction with the shorter needle (p<0.001) and 51% experienced bruising with the longer needle compared to 34% with the shorter needle (p=NS). Eighty-nine percent of patients preferred the shorter needle (p<0.001) (Schwartz et al. 2004).

Arendt-Nielsen et al. (2006) studied the impact of outer needle diameter on pain experienced during controlled needle insertion. The study utilized an automated needle injection system to standardize insertion parameters including velocity, insertion angle, and injection depth. The frequency of pain was observed and recorded for various needle sizes (23-gauge, 27-gauge, 30-gauge, 32-gauge), alongside pain intensity (measured by VAS) and bleeding occurrence. Results showed a significant positive correlation between outer needle diameter and the frequency of insertion pain. Pain was reported in 63% of insertions with 23-gauge needles, 53% with 27-gauge needles, and 31% with 32-gauge needles ($p<0.0001$). The thickest needle (23-gauge) was most associated with bleeding. Insertions with bleeding were approximately 1.3 times more painful than those without bleeding ($p=0.004$).

Professional supervision of injection procedure

Effective communication between individuals and their physicians is crucial for supporting and optimizing the treatment experience as well as ensuring adherence to prescribed treatments. Such dialogue not only enhances the therapeutic relationship but also empowers individuals to openly discuss any issues or concerns related to their individualized support programs (Pharmaceutical Society of Australia).

Additionally, providing adequate training is essential, particularly for self-administration with an automated injection device in the home setting. Proper training ensures that individuals are confident and capable of managing their treatments effectively (Hunter 2008). It should be noted that if manual injection is performed under healthcare provider supervision, while the automated device is solely used for self-administration at-home, the resulting lack of direct contact may impact local tolerability. This is especially important as during manual injection, the operator is typically instructed to select the most appropriate injection site, communicate with the recipient, and consider the individual's comfort during the procedure. This level of personalized care is not available when patients self-administer in a home setting; a factor that may negatively impact the perceived convenience of the dosing regimen.

A number of review articles including summaries of the current knowledge on how formulation and device parameters may impact tolerability of SC injection are available in the literature and provided for completeness (Usach et al. 2019, Bruin et al. 2020, St Clair-Jones et al. 2020, Kim et al. 2023, Schneider et al. 2023, Davis et al. 2024, Zhi et al. 2025). Overall, while some studies reveal an impact of injection speed, needle gauge and needle length on the local tolerability of an injected solution, the differences between manual and automated injection are typically not considered clinically relevant. Aspects such as the composition of the dosing solution or the injection site used in the respective tolerability studies complicate a definite conclusion as confounding factors, so that these studies are of limited value to establish suitable device parameter

characteristics. In the context of the MIDBA it is important to emphasize that the formulation and the active molecule remain the same independent of the injection methodology.

Clinical relevance of local tolerability profile

Automated injection devices are designed to facilitate SC injections and promote self-administration in decentralized care settings. To ensure compliance with parenteral dosing outside of a controlled healthcare environment, it is essential for users to feel at ease with the injection method. This includes ease-of-use coupled with an acceptable local tolerability profile. To gain further insights into the acceptance of autoinjector devices, the Applicant reviewed user preference, usability, and satisfaction studies conducted [redacted], comparing manual injections with autoinjector or pen devices.

When evaluating the comparative local tolerability profiles of both injection methods, it was noted that the studies used a variety of assessment tools, requiring a separate narrative description as provided below:

- In a study assessing pain, tolerability, and preference for self-administering adalimumab in 52 participants with rheumatoid arthritis (RA), 76.9% found the autoinjection pen less painful than the syringe, 7.7% preferred the syringe, and 15.4% had no preference (Kivitz et al. 2006).
- In a study that assessed switching adalimumab from a PFS to an autoinjection pen in 55 participants (29 RA, 17 psoriatic arthritis, 9 ankylosing spondylitis), pain at the injection site was significantly reduced with the pen. VAS scores (10 point) were 3.52 (2.26) for the syringe versus 2.02 (2.16) for the pen ($p<0.001$) (Borrás-Blasco et al. 2010).
- In a study on SC self-injection of bimekizumab with PFS and AI devices in 214 participants with psoriatic arthritis, the VAS (0-100) scores were 11.0 (14.1) for the PFS and 11.4 (17.4) for the AI. It was concluded that both devices provide safe and effective self-injection options that cater for patient preferences (Kivitz et al. 2023).
- In a study on switching guselkumab from a PFS to a prefilled pen (PFP) in 40 participants with psoriasis and psoriatic arthritis, self-injection pain scores (10 cm) were PFS (pre-switch) 4.3±1.8, PFP (2 months post-switch) 2.3±2.1, and PFP (6 months post-switch) 2.1±1.9. Overall, the PFP showed higher satisfaction and was less painful compared to the PFS (Borrás-Blasco et al. 2024).
- In a Phase 3 study on the usability and patient preference of the sarilumab pen in 217 patients with moderate-to-severe rheumatoid arthritis, safety and efficacy appeared generally similar between the pen and syringe groups, consistent with other sarilumab trials. There were no clinically meaningful differences in adverse

events, serious adverse events, or adverse events leading to discontinuation between the pen and syringe groups (Kivitz et al. 2018).

- In a randomized crossover study with 91 participants with moderate-to-severe ulcerative colitis, preference for delivering golimumab was assessed between a PFS and an AI device. Extremely easy or easy to use ratings were 94.5% for the AI and 73.6% for the PFS. Moderate discomfort or worse was reported by 5.5% for the AI and 20.9% for the PFS. Severe discomfort or discomfort preventing future self-injection was 0% for the AI and 8.8% for the PFS. Most patients preferred the AI over the PFS for self-administering golimumab (Vermeire et al. 2018).
- In a study comparing the usability and patient experiences of an AI with a PFS in participants with migraine self-administering galcanezumab, 179 patients used both devices at least once. Most patients (91% to 97%) reported positive responses on the Subcutaneous Administration Assessment Questionnaire for the AI. There were 23 injection-site-related adverse events with the first self-injection: 7 with the PFS and 16 with the AI (p=0.061). The most common adverse event was injection-site pain for both devices. No significant differences in injection-site-related adverse events were observed between the devices (Stauffer et al. 2018).
- In a belimumab study, participant experiences with an AI for SC administration in treating systemic lupus erythematosus were assessed. Patients switched from IV or PFS belimumab to eight weekly self-administered AI doses. Seventeen of 21 participants (81%) who took part in follow-up interviews reported positive AI experiences. Injection discomfort was the main disadvantage (5 participants [24%]) (Dashiell-Aje et al. 2018).
- In a study assessing usability and acceptance of SC alirocumab via PFP and PFS, physicians believed 66% (PFP) and 58% (PFS) of their patients would self-inject after instruction, up from 22% and 16% at pre-exposure, respectively (both p<0.05). Specialists had higher estimates than primary care physicians: PFP 72% vs. 61%, PFS 63% vs. 53% (all p<0.05). After instruction, 72% (pen) and 63% (syringe) of patients were very willing to self-inject, with increases of 26% and 11%, respectively. Prior experience with injectable medications made patients more willing to use the pen, but differences disappeared after instruction (Roth et al. 2015).

Overall, in various preference, usability, and satisfaction studies, the majority of participants preferred using an autoinjector over a syringe. This preference was typically accompanied by improved pain sensation at the injection site. While the number of preference studies with a direct comparison of manual versus automated injection was comparatively small, the Applicant's review revealed that, irrespective of the mAb and indication, users generally favored automated injections over manual ones especially when considering the option for self-administration outside of a controlled healthcare environment. The above findings from individual preference and patient satisfaction studies align with numerous review articles in the field that describe a general

preference for autoinjector or pen devices as compared to manual injection with a syringe (Kivitz et al. 2006, Tucker 2025, Borrás-Blasco et al. 2010, Roth et al. 2015, Kivitz et al. 2018, Vermeire et al. 2018, Roy et al. 2021, Tornero Molina et al. 2021, Borrás-Blasco et al. 2024, Fleischmann et al. 2022, García-Moguel et al. 2022, Schneider et al. 2023).

(2) Systematic review of PK and local tolerability results from various PK comparability studies with mAbs to extend the clinical validation set.

Validation sets for more quantitative approach

To address the Agency's request to discuss the need for a more quantitative approach, the Applicant expanded their previous overview of PK comparability studies with additional studies for in-house and external mAbs. Table 3 summarizes the three clinical validation sets that have been created. [redacted]

- *Validation set 1* includes studies with mAbs that are commercially available from other manufacturers with the YpsoMate AI platform (1.0 and 2.25 mL).
- *Validation set 2* includes studies with mAbs from the Applicant's pipeline.
- *Validation set 3* combines validation sets 1 and 2 and includes studies with additional mAbs outside of the Applicant's portfolio.

The following parameters are included in the validation sets:

- *Information from PK comparability studies*: demonstration of PK comparability/BE, Tmax (to reflect absorption rate), comparative local tolerability profile manual versus automated administration, and injection volume.
- *Additional information from the literature*: molecular type, molecular weight, concentration of the formulation, SC bioavailability, and formulation ingredients.

It is noted that the methodologies for the local tolerability assessments differ across the PK comparability studies. Also, studies from the literature typically do not specify the device types, the needle length or needle gauge, nor differences in the injection speed manual versus automated administration. The majority of studies, but not all of them, were powered to statistically demonstrate BE. Due to these methodological differences, the Applicant applied a predominantly descriptive approach when comparing local tolerability findings from these trials. While it is proposed that the design and reporting of PK comparability studies should be further harmonized in the future, the Applicant is confident that relevant results could be drawn from their analyses.

Table 3 Clinical validations sets based on PK comparability studies between manual and automated subcutaneous mAb administration.

VS	Data sources (PK comparability studies)	No. mAbs	Relevant information
1	mAbs approved with YpsoMate AI[1]	11	- Comparative Tmax[2,3] - Comparative local tolerability[2,3] - Molecule type / weight[2,3] - Injection volume[2,3] - Formulation ingredients[2,3,4]
2	mAbs in the Applicant's portfolio[5]	4	- Comparative Tmax[3] - Comparative local tolerability[3] - Molecule type / weight[3] - Injection volume[3] - Formulation ingredients[3,4]
3	Combined validation set: 1 and 2 plus additional mAbs outside of the Applicant's portfolio[1,5]	34	- Comparative Tmax[2,3] - Comparative local tolerability[2,3] - Molecule type / weight[2,3] - Injection volume[2,3] - Formulation ingredients[2,3,4]

For mAbs outside of the Applicant's pipeline, the Applicant cannot comment on the exact injection procedure of the respective mAb formulations applied in the PK comparability studies.
[1]Includes one of the proposed model mAb, gantenerumab. [redacted]
[2]Based on available literature and label information. The majority of the underlying publicly available study manuscripts do not specify the AI platform used. As these mAbs are not part of the Applicant's pipeline, the Applicant cannot comment on the exact injection procedure of the respective mAb formulations.
[3]Roche internal files.
[4]Formulation ingredients were retrieved from label information.
[5]Studies used different AI and OBDS types.

Summary PK comparability and local tolerability outcomes from validation set 1 (mAbs approved with the YpsoMate AI platform)

The Applicant has identified 11 PK comparability studies between manual and automated injection conducted with mAbs approved for delivery with the YpsoMate AI platform [redacted]. One study tested PK comparability and tolerability, but did not provide Tmax data and another one provided Tmax data but no ISR data.

PK comparability was demonstrated in all studies. In the study [redacted], BE was established, but comparative Tmax values were not provided.

The percentage difference in ISRs was small with a slight tendency towards a higher incidence of ISRs with the AI. In no case were these differences considered clinically

relevant. [redacted]

[redacted]

It is of note that validation set 1 comprises 11 PK comparability studies between manual and automated administration of mAbs that are approved for use with the YpsoMate AI. While the use of the YpsoMate AI appears to be very likely in the mentioned studies, it is not transparent to the Applicant whether the studies have been conducted with the YposMate AI, as the majority of publications do not report details of the AI configuration.

Summary of PK comparability and local tolerability outcomes from validation set 2 (mAbs from the Applicant's pipeline)

Validation set 2 comprises 4 in-house PK comparability studies between manual and automated administration [redacted] In these studies, different AI and OBDS devices were used. [redacted]

PK comparability was demonstrated in all studies in VS2.

The incidence of ISRs was slightly higher with the automated device platforms as compared to manual injection, with the findings not considered clinically relevant. Across studies the majority of ISRs were of mild intensity and resolved without treatment and sequelae. The overall favorable local tolerability profile for both injection methodologies is reflected in statements such as “no new safety concerns were identified”, “no remarkable differences in safety and tolerability results were observed between” the two devices, “all injection site reactions resolved without treatment and sequelae”, and “no apparent differences related to the injection method were observed”.

Summary of PK comparability and local tolerability from validation set 3 (combination of validation sets 1 and 2 and plus mAbs from other manufacturers)

Validation set 3 combines validation sets 1 and 2 and includes information from additional mAbs outside of the Applicant’s portfolio with PK comparability studies between manual injection and an AI or OBDS platform other than the YpsoMate AI [redacted].

The Applicant has identified additional 19 PK comparability studies conducted with mAbs, of which 15 have collected Tmax or local tolerability data. There was no general trend for a better local tolerability profile for either administration method. In no case were any differences considered clinically relevant.

[redacted]

[redacted]

In total, validation set 3 that combines all identified PK comparability studies consists of 34 studies. The Applicant concludes that from the comprehensive PK comparability and local tolerability database available for a variety of different SC injection devices, there is no evidence that automated injection would result in clinically meaningful differences to manual injection by means of an HHS or PFS. Moreover, to the knowledge of the Applicant, in the event that a mAb is approved with a manual and an automated administration method, the nominal dose and dosing regimen is the same for the same dosing frequency. Acknowledging that this information may not be readily retrievable in the literature, the Applicant did not find information on an AI device that was not launched due to local tolerability findings.

(3) Criteria for assessing mAb eligibility based on PK characteristics, physicochemical properties of mAb formulations, and device characteristics ("design space").

Based on the described validation sets, the Applicant has prepared a "design space" within which PK comparability was established without a clinically relevant impairment of the local tolerability of the mAb. The Applicant wants to emphasize that within the context of the MIDBA, the mAb and the physicochemical properties of the formulation will be the same for manual and automated administration of the respective mAb. Therefore, that "design space" is developed to improve confidence in the overall approach. It is, however, expected that molecules with values outside of the "design space" might be applicable for the MIDBA on a case-by-case basis.

Rationale for selecting time to reach maximum serum concentration (Tmax) as most relevant PK parameter for eligibility of a mAb for the application of the MIDBA

The quantitative comparison of SC absorption of biotherapeutics from HHS/PFS and AI requires a consideration of SC absorption process and potential differences due to the use of PFS versus AI. An SC administration deposits the mAb drug solution in the interstitial space of the SC tissue. The shape of such a fluid depot at an injection volume of, e.g., 2 mL is provided by Pettis et al. (Pettis et al. 2023). The absorption of the administered mAb occurs predominantly via the lymphatic system (Supersaxo et al. 1990, Datta-Mannan et al. 2012). Owing to their size, direct absorption of mAbs into blood capillaries is likely precluded (Sánchez-Félix et al. 2020).

Subcutaneously administered mAbs move through the interstitial space of the SC tissue via fluid flow-driven convection or non-convective diffusion to reach the lymphatic vasculature. Because of the restricted diffusion, it is believed that convection is the

primary mode of transport from the injection site to the lymphatic capillaries. This restricted movement through the hypodermis, along with the path necessary for antibodies to reach the lymphatic vasculature from SC tissue, results in a slow release into the lymphatic vascular compartment and time to peak concentration (Tmax) in the circulation of ~2–8 days, which is characteristic of SC-administered mAbs (Davis et al. 2024).

In the comparison of SC administration of the same mAb formulation via PFS or AI, the only potential source of absorption differences may occur from the shape of the resulting SC fluid depot. Shape differences 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. Relevant residence time differences between PFS and AI would be visible from differences in Tmax values.

Time to reach maximum serum concentration (Tmax), molecular weight, dosing volume, concentration of formulation, bioavailability, and molecular type

Median Tmax values, molecular weights, dosing volumes, and the concentration of the formulations of the mAbs in the comparative PK studies per validation set are compared in Table 4. Median Tmax and range per validation set are also illustrated in Figure 1. Comparative Tmax values for each study are depicted in Figure 2a for validation set 1, Figure 2b for validation set 2 and Figure 2c for validation set 3.

In addition to Tmax, the Applicant also collected the SC bioavailability, if available (Figure 3a for validation set 1, Figure 3b for validation set 2 and Figure 3c for validation set 3), and molecule type (Figure 4a for validation set 1, Figure 4b for validation set 2 and Figure 4c for validation set 3) of the different mAbs as supporting evidence.

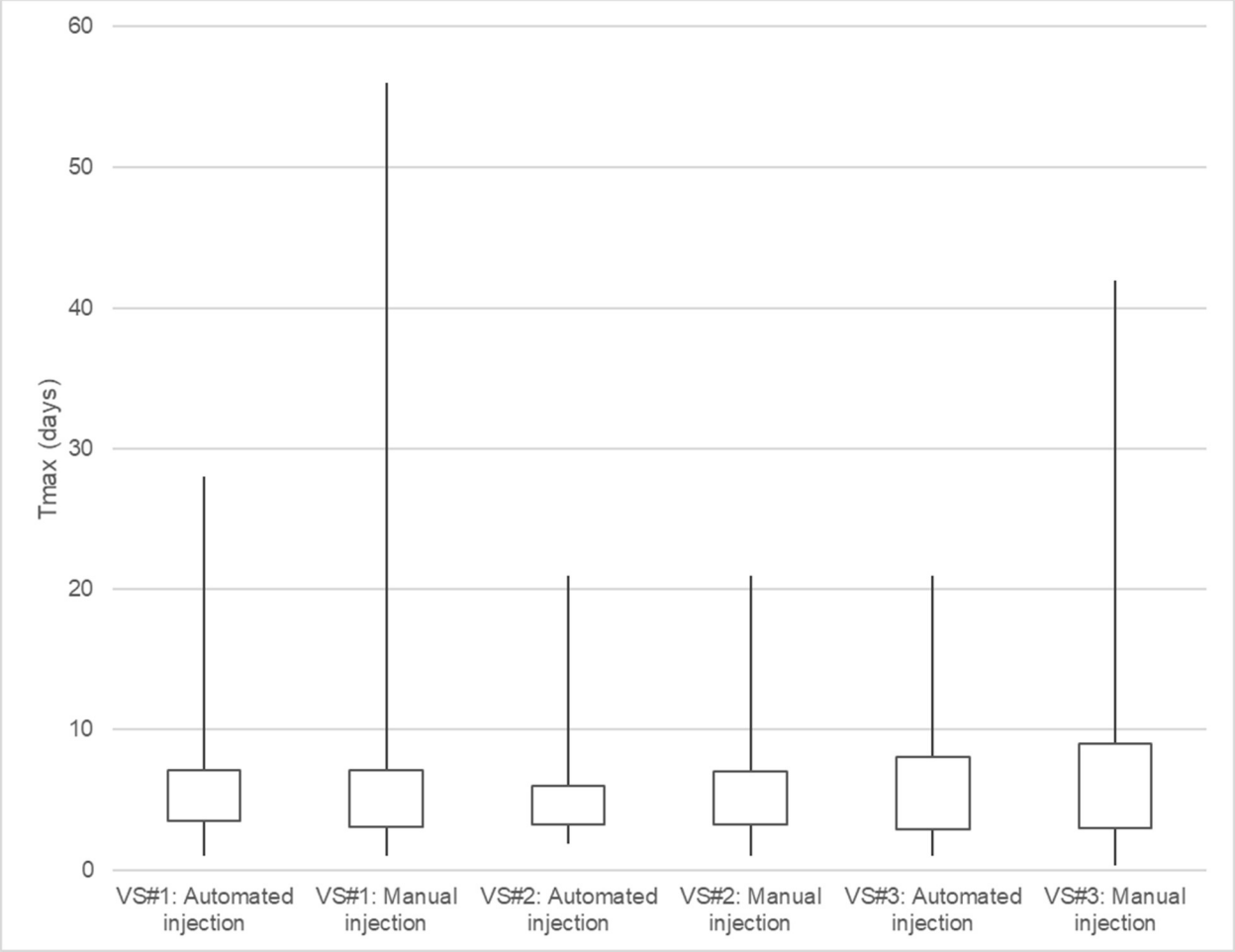
Table 4 Clinical validation sets based on PK comparability studies between manual and automated subcutaneous mAb administration - MIDBA "design space" regarding Tmax (median and range); molecular weight, dosing volumes, and concentration of the formulations.

Validation set	Injection methodology/molecular weight	Range
1	Automated injection	Tmax (median): 3.5–7.1 days Tmax (range): 1.0–28.0 days
	Manual injection	Tmax (median): 3.1–7.1 days Tmax (range): 1.0–56.0 days
	Molecular weight	*144–149 kDa*
	Dosing volume	*0.4–2.0 mL*
	Concentration of formulation	*30–180 mg/mL*
2	Automated injection	Tmax (median): 3.2–6.0 days Tmax (range): 1.9–21.0 days
	Manual injection	Tmax (median): 3.2–7.0 days Tmax (range): 1.0–21.0 days
	Molecular weight	*144–148 kDa*
	Dosing volume	*0.7–10.0 mL*[1]
	Concentration of formulation	*120–180 mg/mL*
3	Automated injection	Tmax (median): 2.9–8.0 days Tmax (range): 1.0–21.0 days
	Manual injection	Tmax (median): 3.0–9.0 days Tmax (range): 0.3–42 days
	Molecular weight	*Molecular weight: 90.8*[2]*-150 kDa*
	Dosing volume	*0.4–10.0 mL*[1]
	Concentration of formulation	*30–200 mg/mL*

[1]Volumes go up to 2mL, except for [redacted] (5 mL) and [redacted] (10 mL).

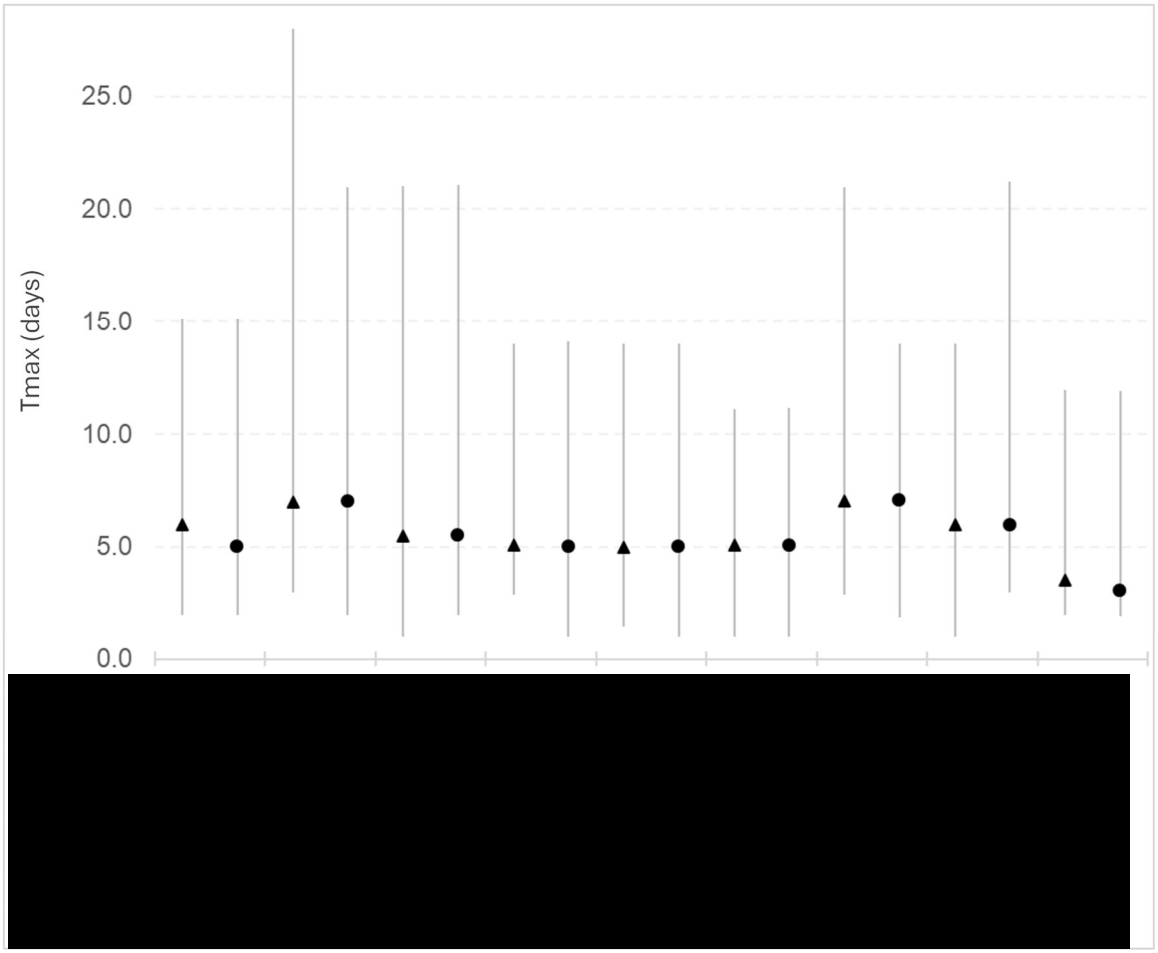
[redacted]

Figure 1 Clinical validation sets based on PK comparability studies between manual and automated SC administration - Tmax median and limit ranges per validation set and injection methodology.



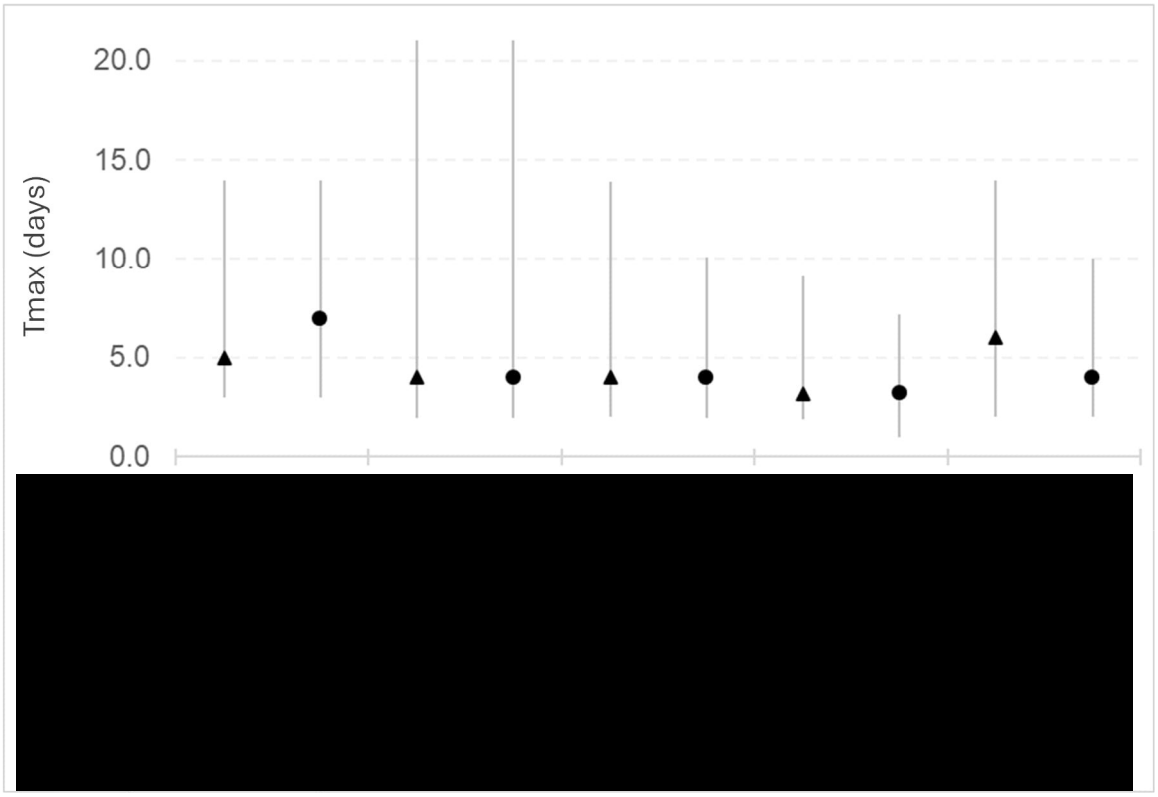
The lower and upper horizontal lines of the boxes indicate the range of the medians, and the vertical lines represent the minimum and maximum range around the median.
VS: validation set.

Figure 2a Tmax median values and ranges for each study, validation set 1 (mAbs approved with YpsoMate AI)



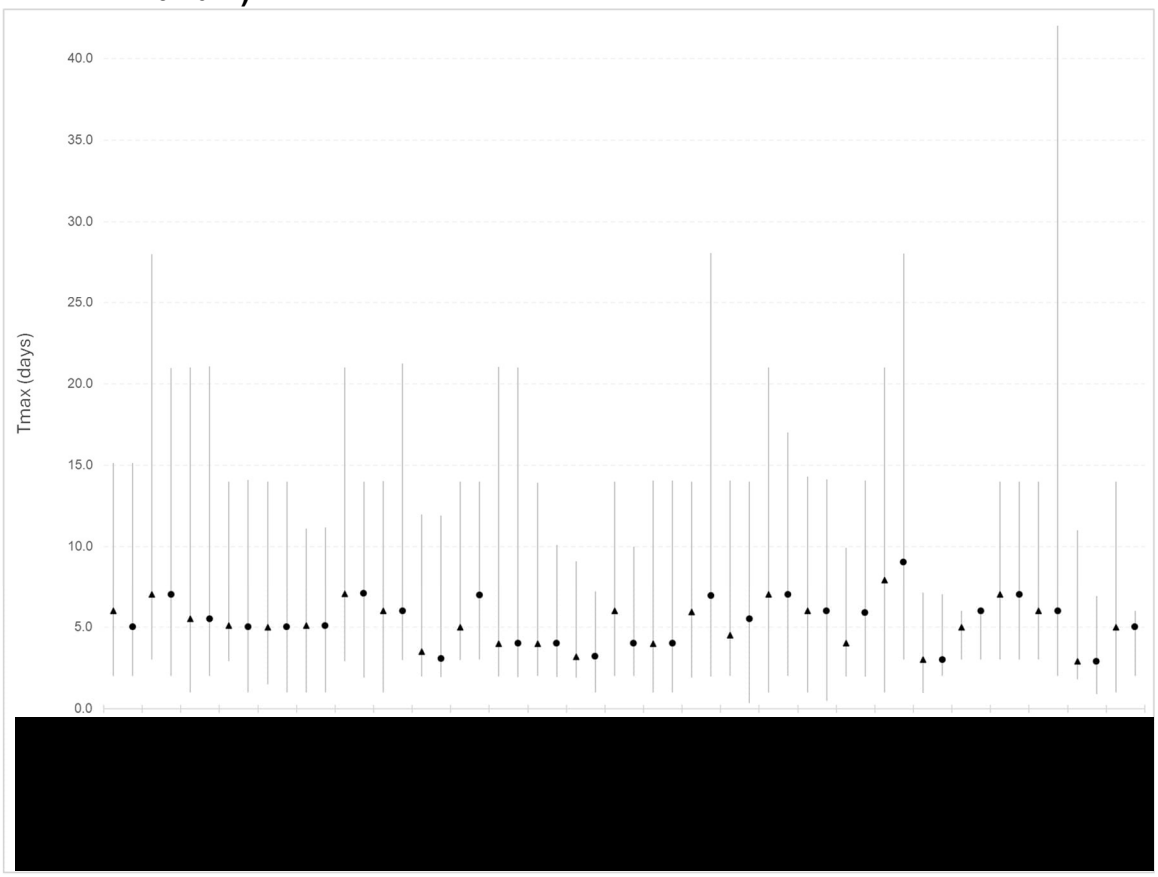
▲ Tmax median - Automated injection; ● Tmax median - Manual injection; – Tmax limit ranges

Figure 2b Tmax median values and ranges for each study, validation set 2 (mAbs from the Applicant's pipeline).



▲ Tmax median - Automated injection; ● Tmax median - Manual injection; – Tmax limit ranges

Figure 2c Tmax median values and ranges for each study, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2)



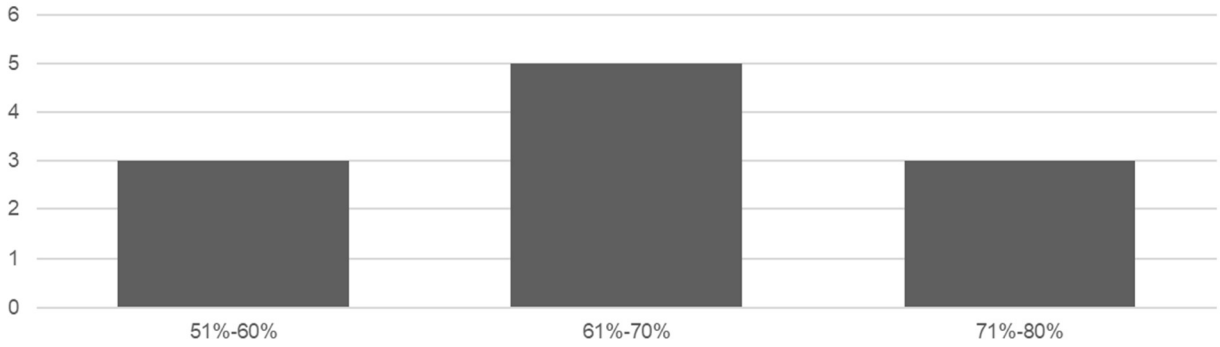
▲ Tmax median - Automated injection; ● Tmax median - Manual injection; – Tmax limit ranges

The results of this comparison demonstrate comparable Tmax values for automated versus manual injection of the same mAb. Also, the observed Tmax ranges were very comparable in most cases. This observation would be consistent with a similar absorption from both AI and PFS. The wide range of individual Tmax values, however, suggests 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 (Figure 1).

Overall, this meta-analysis of Tmax values together with the observed PK comparability for both Cmax and AUC in most cases underscores that the absorption from the SC

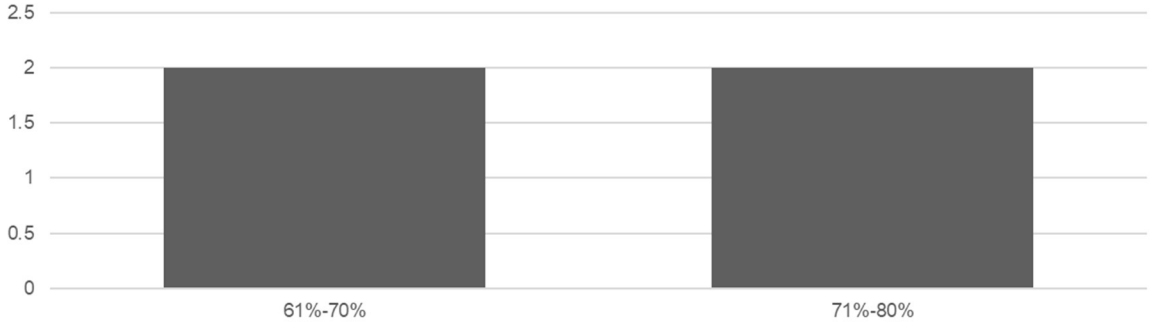
depot formed following either AI- or PFS-injection is similar and leads to comparable exposures in the systemic circulation.

Figure 3a Bioavailability, validation set 1 (mAbs approved with YpsoMate AI)



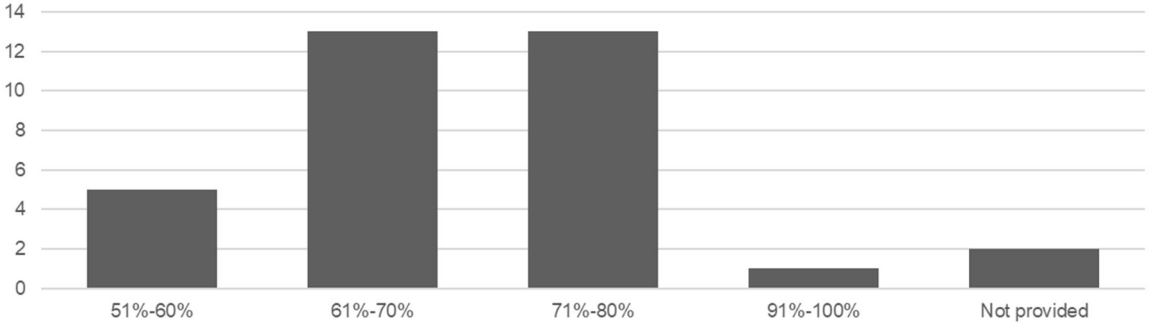
Bars indicate the number of mAbs categorized within bioavailability ranges of 51%-60%, 61%-70%, and 71%-80%.

Figure 3b Bioavailability, validation set 2 (mAbs from the Applicant's pipeline)



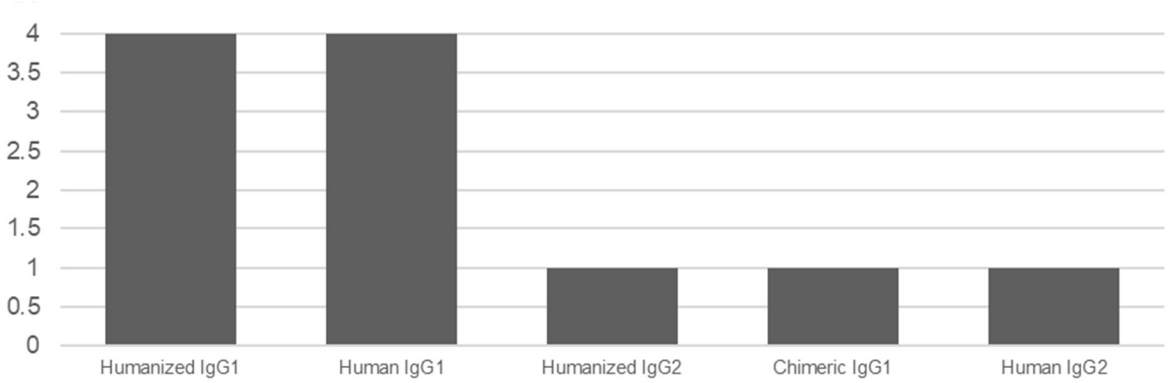
Bars indicate the number of mAbs categorized within bioavailability ranges of 61%-70% and 71%-80%.

Figure 3c Bioavailability, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2)



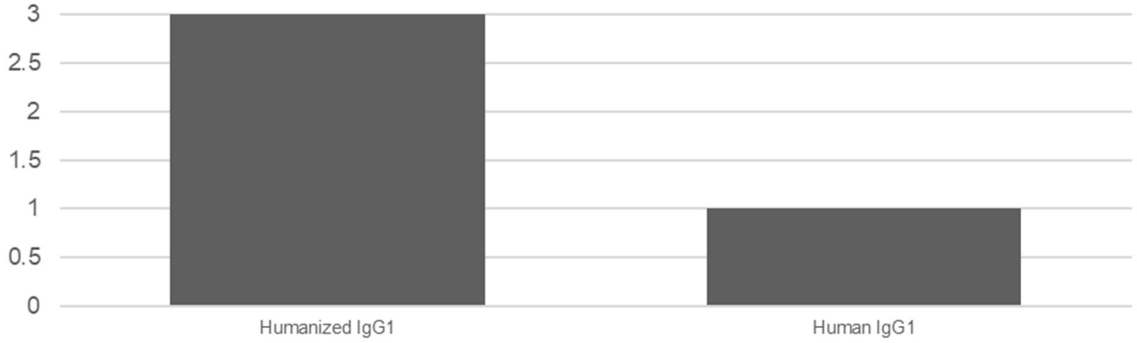
Bars indicate the number of mAbs categorized within bioavailability ranges of 51%-60%, 61%-70%, 71%-80%, 91%-100%, and not available.

Figure 4a Molecule type, validation set 1 (mAbs approved with YpsoMate AI)



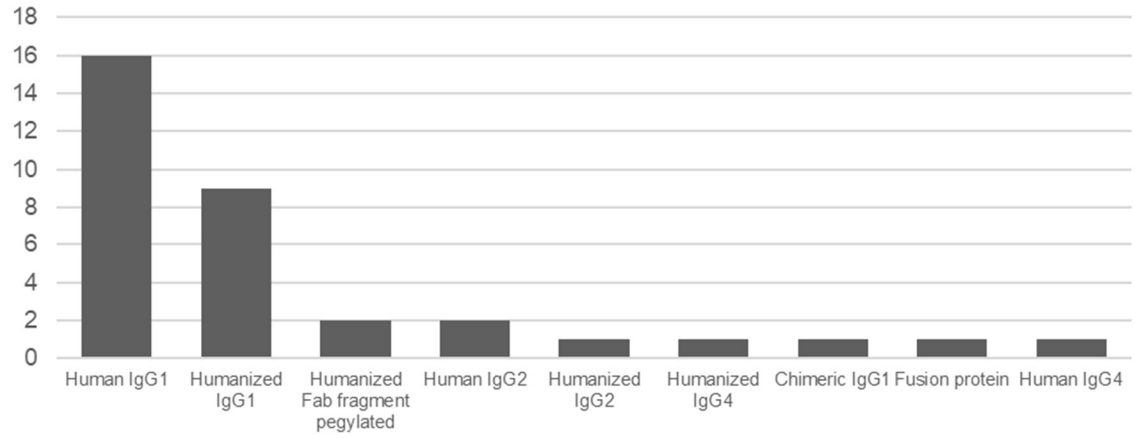
Bars indicate the number of molecules within the different mAb types.

Figure 4b Molecule type, validation set 2 (mAbs from the Applicant's pipeline)



Bars indicate the number of molecules within the different mAb types.

Figure 4c Molecule type, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2)



Bars indicate the number of molecules within the different molecule types.

mAb formulation physicochemical and device characteristics

Formulation physicochemical characteristics

The physicochemical parameters of mAb formulations from the Applicant's portfolio (validation set 2) [redacted]. A descriptive summary is provided in the following. In the BE studies comparing manual versus automated administration, various AI and OBDS devices were used. [redacted]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, this validation set remains descriptive and is considered too small to form a comprehensive framework.

[redacted]Reliable details on the physicochemical properties of mAb-based formulations from other manufacturers are not available to the Applicant.

The formulation excipients for validation set 1, validation set 2, and validation set 3 are listed in Figure 5a, Figure 5b, and Figure 5c, respectively. For mAbs outside of the Applicants pipeline, this information was retrieved from the label information.

Figure 5a . Formulation excipients, validation set 1 (mAbs approved with YpsoMate AI)

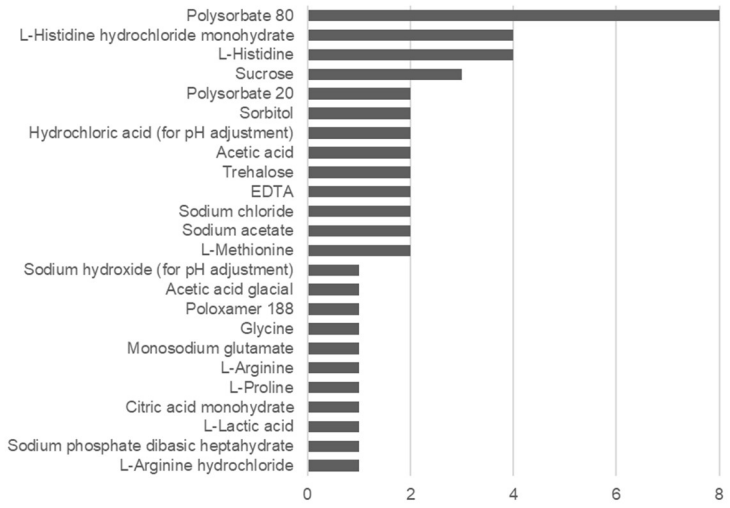


Figure 5b Formulation excipients, validation set 2 (mAbs from the Applicant's pipeline)

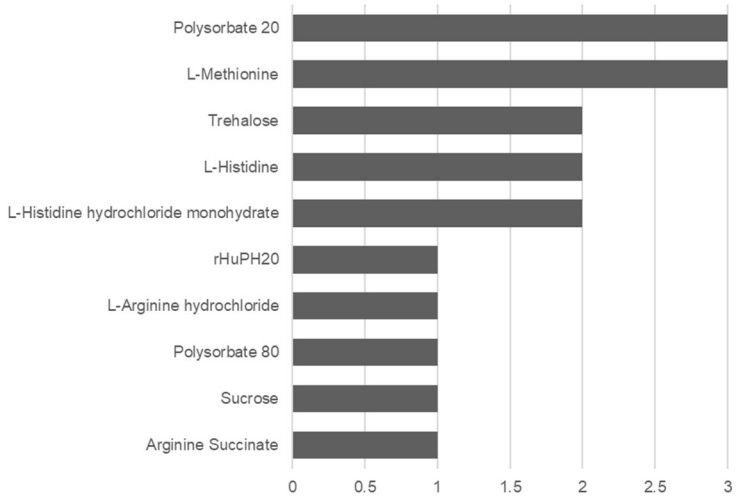
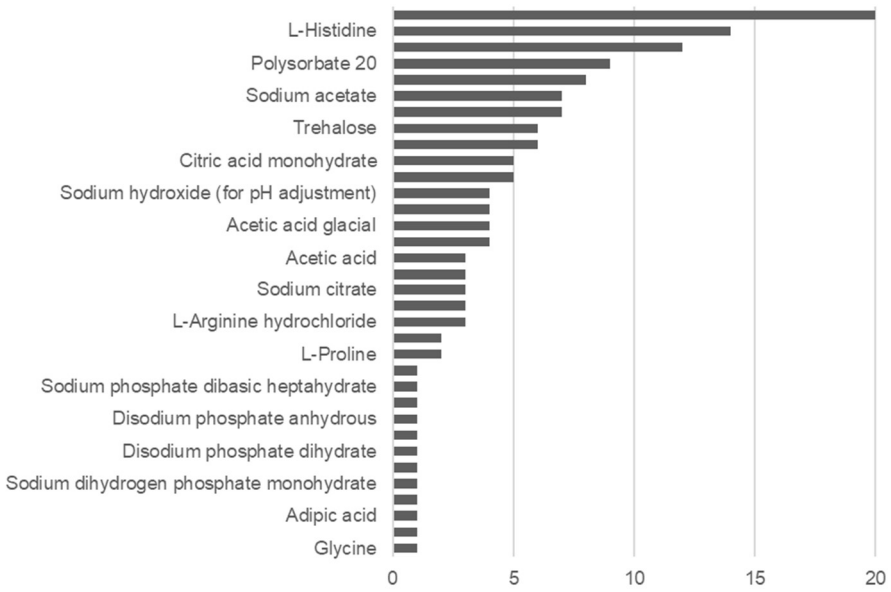


Figure 5c Formulation excipients, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2)



Device characteristics

Across the three validation sets, mAbs with demonstrated PK comparability between manual and automated injection are approved in a variety of device platforms [redacted]

As described above, the device parameters that need to be controlled in order to ensure an accurate injection of the required dose, and, thus, comparable PK between manual and automated dosing, comprise the exposed needle length and the deliverable volume. Target values are also provided for injection time, as this parameter may impact local tolerability and is part of the control strategy of the AI to ensure its proper function.

The specifications for the YpsoMate autoinjectors and the prefilled syringes used in Roche are listed in Table 5 . More details on the control strategy and the specifications of the in-house model mAbs gantenerumab [redacted] are provided in Appendix 2.

Table 5 Specifications for the YpsoMate autoinjectors and the prefilled syringes

Attribute	Autoinjector specifications	prefilled syringe specifications
Deliverable Volume	Label Claim – USP	Label Claim - USP
Injection Time	15 seconds or less	User dependent (typically from a few seconds to under a minute)
Exposed Needle Length	6 mm +/- 2 mm (injection taking place perpendicularly to the skin)	12.7 mm +/- 1mm (injection taking place at an angle to the skin)

Accuracy and reproducibility of these parameters is assessed by applying principles of design verification and validation. The Applicant implements a rigorous control strategy based on available regulatory guidelines to meet the intended clinical performance (EMA 2021, EMA 2025, EU MDR (Regulation (EU) 2017/745) 2017).

In summary, based on the general MIDBA concept, where the active molecule and formulation are consistent between manual and automated administration, coupled with the "design space" outlined above, the Applicant is confident that MIDBA can be applied without the need for additional PK comparability studies, particularly for AI platforms delivering volumes up to 2 mL.

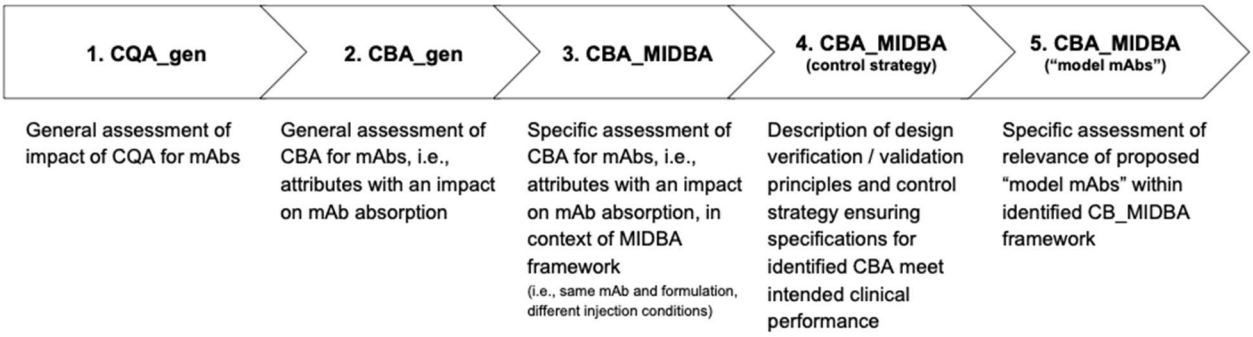
Other questions under “Scientific discussion”

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.

A detailed discussion of CQA and CBA is provided in Appendix 2. [redacted]

Overall, to identify the CQAs and CBAs relevant for the application of MIDBA in the clinical bridging from manual to automated administration for mAbs, the Applicant follows a stepwise approach (Figure 6).

Figure 6 Stepwise assessment of Critical Quality Attributes (CQA) and Critical Bioavailability Attributes (CBA) relevant for the MIDBA approach.



In Step 1, CQAs with possible impacts on the molecule's mechanisms of action (MoAs), mechanisms of toxicity (MoTs), general safety, or pharmacokinetic properties (Alt et al. 2016) are being identified.

In Step 2, the Applicant describes CBAs, which are a subset of the CQAs with the potential to affect the bioavailability of a SC administered mAb via its absorption profile. Steps 1 and 2 involve a general assessment of CQAs and CBAs, outside the context of MIDBA. These parameters are referred to as "general CQAs" (CQA_gen) and "general CBAs" (CBA_gen) in the following.

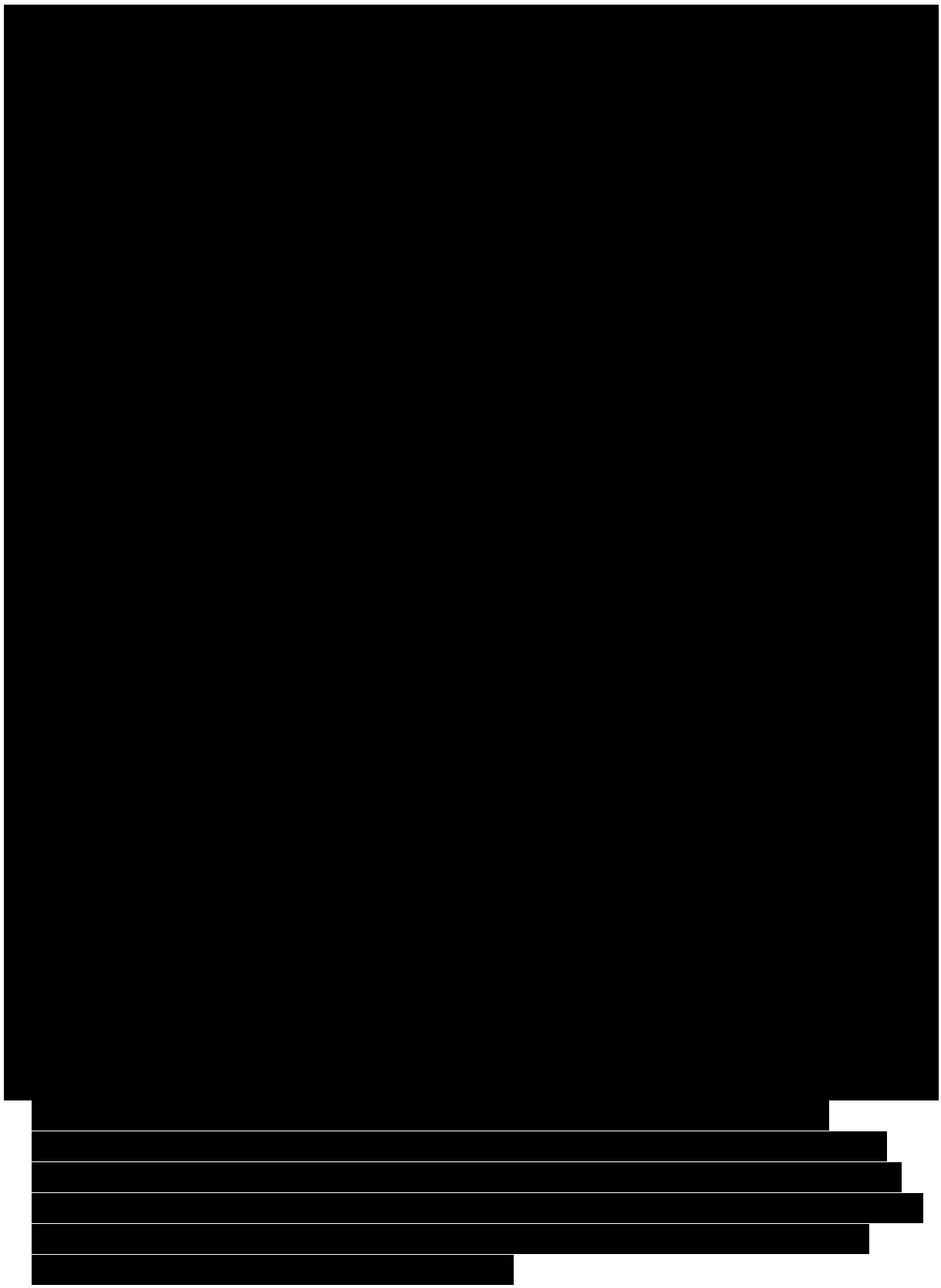
In Step 3, the CBA evaluation is conducted specifically within the MIDBA framework. Here, the same mAb and formulation are used for both manual administration and administration using an automated device platform at the same injection sites (CBA_MIDBA). The impact of CBA_MIDBA on the absorption profile of a mAb is thoroughly assessed under these conditions.

In Step 4, the principles of design verification and validation as per ISO 13485 together with the Applicants control strategy are referenced to ensure that the specifications for identified QBA_MIDBA meet the intended clinical performance.

In Step 5, the relevance of proposed "model mAbs" such as gantenerumab [redacted] is assessed within the described CBA_MIDBA framework.

[redacted]

[redacted]



[redacted]

[redacted]

CoU1

Question 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.

Answer:

The Applicant proposes to limit the application of MIDBA to mAbs and other biologics that exhibit slow absorption into the systemic circulation, as characterized by Tmax values in the order of days (Table 4). In response to the Agency’s general question, the Applicant has expanded their argumentation beyond the two “model mAbs” by reviewing additional PK comparability studies with both in-house and external mAbs. This has enabled them to generate a "design space" within which MIDBA should be feasible. This approach should increase confidence in the applicability of MIDBA. However, future molecule-device combination products with one or more parameters outside this design space might also be eligible for MIDBA, especially, if deviations involve the composition of a formulation that remains unchanged between manual and automated administration.

Three validation sets have been generated as a basis for the “design space”. Validation set 1 includes mAbs that are commercially available from other manufacturers with the YpsoMate AI platform (1.0 and 2.25 mL) for which PK comparability has been tested between manual injection via HHS or PFS and an AI platform. Validation set 2 includes mAbs from the Applicant’s pipeline for which PK comparability has been established

between manual injection and an AI or OBDS platform. Validation set 3 combines validation sets 1 and 2 and adds information from other mAbs outside of the Applicant's portfolio for which PK comparability has been established between manual and automated injection.

Please refer to the related "design space" in the answer to the more general question above and to Appendix 1 for the summary of the PK comparability studies sorted by validation set.

Question 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.

Answer:

The Applicant agrees that especially for gantenerumab the rate of ISRs is 40.7% for the AI and, thus, somewhat higher than for the HHS with 27.5%. For completeness the Applicant provides a more detailed description of the underlying findings in the following: "The most frequently reported injection reaction TEAEs by preferred term were injection site erythema (64 [24.1%] participants), injection site pain (46 [17.3%] participants), injection site pruritus (12 [4.5%] participants), injection site swelling (11 [4.1%] participants), and injection site paresthesia (3 [1.1%] participants). All of the injection reaction TEAEs were judged by the Investigator as related to the study drug injection, with the majority of mild severity, and the majority deemed resolved within 1 day of study drug administration without sequalae. One injection reaction TEAE (injection site discoloration) of moderate severity was noted with a participant who received gantenerumab 255 mg AI that was deemed related to the study drug injection and recovered/resolved with sequelae."

In the gantenerumab BE study, the operators were instructed to administer the dosing solution within approximately 10 seconds with the HHS and within less than 15 seconds with the device (automated injection speed). Acknowledging possible deviations from the manual injection time based on preferences and capabilities of the operator, the nominal injection times are comparable and unlikely to have contributed to the differences in the rates of ISRs. The finding might however be attributed to the slightly higher fill-volume in the gantenerumab AI (1.77 mL) as compared to the HHS (1.70 ml). This difference derived from using the WEST polymer PFS in the AI. A methionine stock solution had to

be added to the drug substance solution prior to PFS filling to protect the polymer PFS from oxidation caused by air diffusion. This small methionine addition during drug product manufacturing slightly decreased the gantenerumab concentration in the final drug product, resulting in a higher administration volume for the AI. The Applicant believes that gantenerumab remains a relevant “model mAb”. Especially as BE was achieved despite the difference in the formulation, this finding further underscores the hypothesis that the slow absorption of mAbs from the SC tissue into the systemic circulation rather than the injection conditions is the main factor for determining Tmax.

The Applicant did not find information on the injection instructions in the BE study with omalizumab. It is conceivable that the observed somewhat higher rate of ISRs for the AI versus PFS for omalizumab (24% vs. 14%) is attributed to either a faster injection rate or a comparatively strong push of the AI to the skin surface. This would be in line with what was suggested by the authors of the manuscript for the PK comparability study with an adalimumab biosimilar (Ramael et al. 2018). Here, the incidence of ISRs was 57.1% with an AI versus 38.9% with a PFS following injection into the abdomen and 32.1% with an AI versus 24.7% with a PFS following injection into the thigh. The authors speculated that the numerically greater proportion of ISRs in the AI group compared to the PFS group might be due to greater pressure applied with the AI against the skin, as users may press it firmly during injection. In contrast, PFS administration tends to be more cautious. Additionally, in their study, the AI had a fixed 3-second injection time, whereas the PFS did allow for variable injection speeds, enabling subjects to slow down if they experience pain, potentially resulting in fewer ISRs.

Notably, the majority of injection site reactions in the omalizumab BE study were mild in severity (there were no serious or severe cases), and all resolved without treatment (Sangana et al. 2024). Likewise, in the study with the adalimumab biosimilar (Ramael et al. 2018), all ISRs were mild in intensity, and resolved within hours in the majority of subjects, without the need for corrective treatment.

Dedicated studies in the literature indicate that a change in the injection time did not impact the PK profile of the administered mAbs (Davis et al. 2024). For instance, for dupilumab, administration of a single dose of 300 mg (2 mL) as a 30-second SC bolus or 10-minute SC infusion via a syringe pump to healthy individuals resulted in similar PKs (Li et al. 2020). Additionally, injection time and its relationship to pain has been studied extensively, with most studies concluding that increasing injection speed did not result in clinically relevant differences in pain sensation (Davis et al. 2024).

The observation that the majority of ISRs was of mild intensity and not considered clinically relevant is indirectly confirmed by the Applicant’s comprehensive literature search on PK comparability studies (refer to validation sets described in the answer to the Agency’s general question above). While typically studies do not report the injection

time, it can be expected that a variety of manual injection times have been applied across the trials.

Overall, the Applicant concludes that for the volumes delivered with AI platforms of up to 2 mL, differences in the actual injection speed following more variable manual versus more standardized automated injection are not expected to result in clinically relevant differences in the local tolerability profile of the mAb. This is particularly plausible, as in order to be eligible for the MIDBA, mAb formulations will be the same with both injection methodologies.

Question 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.

Answer:

Ensuring consistent injection times is integral to AI development. The Applicant implements a rigorous control strategy based on available regulatory guidelines to meet the intended clinical performance. The specification for the YpsoMate AI demands the solution to be administered within 15 seconds or less. This comparatively short injection duration aims to avoid premature removal of the injector, especially when administration takes place in a remote setting and without professional supervision. Available insights into injection hold times for the YpsoMate AI used with different mAb-based products range between approximately 7 and 20 seconds dependent on the injection volume and drug product formulation as shown in **Table 13** of the briefing package (also attached to this response document as Table 13 BP)

The Applicant's control strategy for the injection time of the platform consists of Design Verification Testing, and testing at Release and during Stability at Process Performance Qualification (PPQ), to ensure that design requirements are met and that the specifications are maintained throughout the shelf life. (Table 7).

Table 7 Control strategy for the injection time of the autoinjector.

Test Method	Dossier Location for Method Description	Design Verification	Release (PPQ)	Stability (PPQ)	Release (Com.)
Injection Time	3.2.R	✓	✓	✓	

PPQ: Process Performance Qualification.

For PFS the injection time is not tested because it is user-dependent. However, the syringe factors affecting injection time in the hands of the users (Break Loose Force and

Average Injection Force) are subjected to Design Verification Testing, and testing at Release and during Stability at PPQ (Process Performance Qualification), to ensure that design requirements are met and that the specifications are maintained throughout the shelf life (Table 8).

Table 8 Break Loose Force and Average Injection Force for PFS.

Test Method	Dossier Location for Method Description	Design Verification	Release (PPQ)	Stability (PPQ)
Break Loose Force	3.2.R	✓	✓	✓
Average Injection Force	3.2.R	✓	✓	✓

PPQ: Process Performance Qualification.

The Applicant expects that the injection time following manual injection in the pivotal clinical studies varies based on individual healthcare provider preferences and capabilities and that with the AI platform the rate is more standardized and should be within the range of that following manual injection. It is acknowledged that in pivotal Phase 3 studies injection time is usually not recorded for manual injections via HHS or PFS, a factor that challenges a more quantitative assessment. Especially in clinical studies with SC volumes not exceeding 2 mL, healthcare providers are allowed to inject according to individual preferences and capabilities. This is based on established guidelines to HCPs for the SC administration of low volume formulations (Michigan Medicine 2012, Ernstmeyer et al. 2023). Such guidelines include instructions on how to select the injection angle and injection site based on the size of the individual and the amount of adipose tissue, as well as on how to place the syringe in the dominant hand of the operator, while instructions on the injection rate are not provided.

Supporting evidence for the assumption that injection times for the YpsoMate AI remain within the injection time range of the HHS or PFS has been found in two studies from the Applicants pipeline. In the gantenerumab BE study [redacted] the operators were instructed to administer the dosing solution within approximately 10 seconds with the HHS and within less than 15 seconds with the device (automated injection speed). Moreover, in a randomized, double-blind, parallel-group study of safety and the effect on clinical outcome of 0.9 mL tocilizumab SC versus placebo SC in combination with traditional disease modifying anti-rheumatic drugs in participants with moderate to severe active rheumatoid arthritis [redacted] the mean injection time via manual administration recorded by observers for all users of the PFS was 20.3 seconds, with a minimum of 3 seconds and a maximum of 80 seconds. It was concluded that these results showed that users performed the injection at various speeds based upon their capability, comfort,

professional training and preference. This limited dataset supports that hypothesis that the injection time with the AI is more standardized and within the range of injection times achieved with manual injection. Table 9 summarizes the observed manual injection time by user population.

Table 9 From Brevacta CSR - Results for PFS Observer Question 8: How long did it take to inject the medication (seconds)?

User type	Minimum	Mean	Maximum	Standard deviation	Total users
Patient	5	15.8	30	5.8	28
Non-professional caregiver	3	9.3	15	6.0	3
Professional caregiver	15	40.3	80	21.2	8
Overall results	*3*	*20.3*	*80*	*14.7*	*39*

As discussed in the answer to the general question above, dedicated studies did not reveal a general impact of injection time on the local tolerability and pain sensation. Aspects such as the composition of the dosing solution or the injection site used in the respective tolerability studies complicate a definite conclusion as confounding factors (Shi et al. 2021, St. Clair-Jones et al. 2020, Usach et al. 2019). In the context of the MIDBA this finding is especially relevant, as the formulation and the active molecule remain the same independent of the injection methodology.

Additional comments from the Agency on CoU1:

"...it is noted that for one of the model drugs, gantenerumab, the formulations were different. The relevance of this model drug could therefore be questioned, as it seems to prove that the prerequisite is not really needed. "

Answer:

The Applicant acknowledges that local tolerability could be impacted by the difference in the composition of the gantenerumab formulations. From a bioavailability perspective, while the two formulations differ, BE was still achieved following subcutaneous administration. This suggests that gantenerumab remains a valid "model mAb", as even under slightly different formulation conditions (e.g., small methionine addition), its PK profile remains consistent.

The Applicant wants to add that there is currently another in-house BE study [redacted] ongoing [redacted]. These data will further complement the overall tolerability database once available.

"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."

Answer:

As discussed above, a detailed discussion of CQA and CBA including an assessment of the relevance of the proposed "model mAbs" gantenerumab [redacted] is provided in Appendix 2.

"...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."

Answer:

See above

[redacted]

Changes and clarifications of the proposed supporting evidence for each Context of Use Scenario

Table 11 [redacted] contain the revised CoU scenarios and the proposed supporting evidence available with the Marketing Authorization Application. [redacted]

Changes and clarifications of the proposed supporting evidence based on the Agency's "List of Issues" are **highlighted in bold blue letters**.

Table 11 Context of use scenarios for applying the MIDBA to the YpsoMate 1.0 and 2.25 mL AI.

Prerequisites: The integral drug-YpsoMate AI device combination product contains the same formulation (i.e., including the same excipients at the same concentrations) and injection volume as that injected manually in the pivotal clinical studies (using a HHS/PFS).

Context of Use	Proposed MIDBA evidence and reference mAbs	Additional Evidence provided for the MAA
Scenario 1 / CoU1 **mAbs / YpsoMate AI 1 to 1 bridge**[a]: The same total dose volume is administered with one injection both with the AI and the HHS/PFS at the same injection site. **Injection volumes up to 2 mL.**	PK comparability data (i.e., HHS/PFS versus YpsoMate AI) previously generated for omalizumab[c], gantenerumab, [redacted] **and for other mAb-AI combination products in the public domain.** Safety and local tolerability with the YpsoMate 2.25 AI from the PK comparability studies with omalizumab[c] and gantenerumab **and from other mAb-AI combination products in the public domain.** Assessment of eligible mAb's PK and local tolerability characteristics space based on proposed reference mAbs and mAb-YpsoMate 1.0 mL and 2.25 mL AI **and other mAb-AI** combination products in the public domain. General assessment of eligible mAb's formulation physicochemical space for MIDBA.	Safety and local tolerability from the eligible mAb's clinical development program. Subcutaneous injection sites qualified with manual injection via HHS/PFS in pivotal clinical trials for eligible mAb. Analytical comparability and formulation characterization, design verification and validation, including a summative human factors study for the YpsoMate AI, being successfully completed in a population that reflects the intended use population for the eligible mAb.

AI=autoinjector; BE=bioequivalence; HHS=handheld syringe; LE=line extension; MAA=marketing authorisation application; mAb=monoclonal antibody; PFS=prefilled syringe; PD=pharmacodynamics; PK=pharmacokinetics; SC=subcutaneous;

[a]1 to 1 bridge: The PFS or HHS for manual injection delivers the same injection volume as the AI.

[c]Publicly available data.

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Appendix 1 Validation Sets with PK Comparability Studies with mAbs

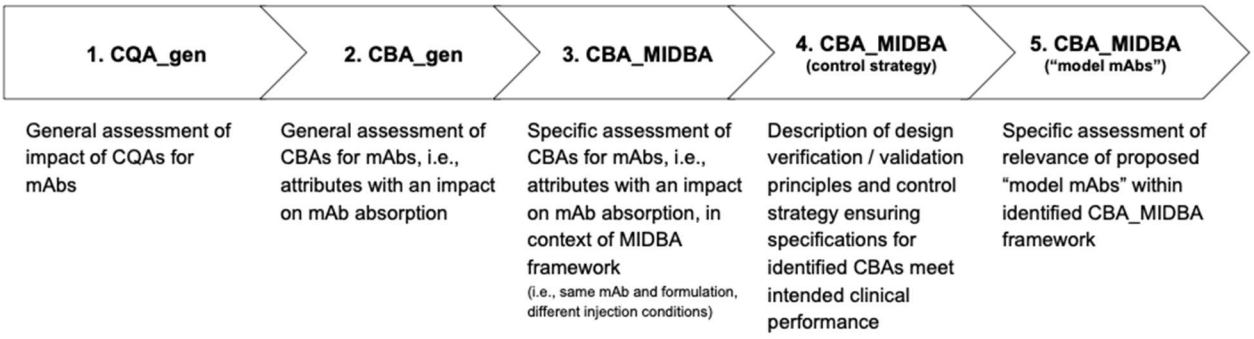
Appendix 1 shows the three clinical validation sets have been created. VS1 includes mAbs that are commercially available from other manufacturers with the YpsoMate AI platform (1.0 and 2.25 mL) for which PK comparability with manual injection via HHS or PFS has been established. Validation set 2 includes mAbs from the Applicant's pipeline for which PK comparability has been established between manual and automated injection. Validation set 3 lists additional information from mAbs outside of the Applicant's portfolio for which PK comparability has been established between manual injection and automated administration to be combined with validation sets 1 and 2.

[redacted]

Appendix 2 Discussion of Critical Quality Attributes (CQAs) and Critical Bioavailability Attributes (CBA) for the Proposed Molecule-Independent Device Bridging Approach (MIDBA)

To identify the Critical Quality Attributes (CQAs) and Critical Bioavailability Attributes (CBAs) relevant for the application of MIDBA in the clinical bridging from manual to automated subcutaneous (SC) administration with a device platform for monoclonal antibodies (mAbs), the Applicant follows a stepwise approach (Appendix 2-Figure 1).

Appendix 2-Figure 1 Stepwise assessment of Critical Quality Attributes (CQA) and Critical Bioavailability Attributes (CBA) relevant for the MIDBA approach.



In Step 1, CQAs with possible impacts on the molecule's mechanisms of action (MoAs), mechanisms of toxicity (MoTs), general safety, or pharmacokinetic (PK) properties (Alt et al. 2016) are being identified.

In Step 2, the Applicant describes CBAs, which are a subset of the CQAs with the potential to affect the bioavailability of a SC administered mAb via its absorption profile. Steps 1 and 2 involve a general assessment of CQAs and CBAs, outside the context of MIDBA. These parameters are referred to as "general CQAs" (CQA_gen) and "general CBAs" (CBA_gen) in the following.

In Step 3, the CBA evaluation is conducted specifically within the MIDBA framework. Here, the same mAb and formulation are used for both manual administration and administration using an automated device platform at the same injection sites (CBA_MIDBA). The impact of CBA_MIDBA on the absorption profile of a mAb is thoroughly assessed under these conditions.

In Step 4, the principles of Design Verification and Validation as per ISO13485 together with the Applicants control strategy are referenced as a basis for ensuring that the specifications for identified QBA_MIDBA meet the intended clinical performance.

In Step 5, the relevance of the proposed "model mAbs" gantenerumab and satralizumab is assessed within the described CBA_MIDBA framework.

Step 1: General assessment of impact of CQA_gen for mAbs

A CQA is described as a physical, chemical, biological, or microbiological property or characteristic that must remain within specific limits, ranges, or distributions to ensure the desired product quality (Reason et al. 2018). ICH guideline Q8 (R2) on pharmaceutical development describes CQA independent of the physicochemical and biological properties of the drug substance or the administration route (EMA 2017).

The list of potential CQA_gen comprises product variants and process-related impurities that may potentially impact the molecule's MoAs and MoTs, general safety, or PK properties (Alt et al. 2016). Additionally, the composition and strength of the respective formulation are considered as obligatory CQA_gen (e.g., protein content, osmolality, pH, buffer, excipients and surfactants). While Alt et al. (2016) primarily focus on intravenous (IV) administration of mAbs, the Applicant in addition assesses aspects related to SC administration. The compilation of the list of potential CQA_gen is complemented with a narrative risk assessment for each potential CQA. Product variants with potential impact on MoAs/bioactivity and PK are discussed below in more detail.

Product variants with potential impact on MoAs/bioactivity include Fc glycosylation variants modifying the Fcγ receptor binding, which may result in changed effector functions of the mAb (Reusch and Tejada 2015). The MoAs/bioactivity may also be modified by post-translational modifications changing the target binding behavior in the complementary-determining regions (CDR) of the respective antibody. CQA_gen with impact on safety include adventitious agents, contaminants and impurities from bacteria and other microbes. Attributes present in clinical materials are generally rated Low Risk in the CQA_gen risk assessment, if the product has a good clinical safety profile (Alt et al. 2016).

The PK properties of a mAb can be influenced by various product variants from post-translational modifications, which may therefore qualify as a CQA_gen. Such product variants may alter the antibody clearance by modifying binding to the neonatal Fc receptor (FcRn) (Alt et al. 2016). Post-translational modifications often also modify the charge of an antibody. As the PK of an antibody may be influenced by its charge with positive charges leading to a more rapid endocytosis and clearance (Liu et al. 2021), charge-modifying variants may be a CQA_gen. This topic was reviewed by Singh et al. (Singh et al. 2016). Basic charge variants in antibodies comprise for example the formation of N-terminal pyroglutamic acid, succinimide formation from aspartic acid and C-terminal proline amidation. Acidic charge variants result from, e.g., deamidation of asparagine, glycation of lysine, mismatched disulfide bonds, trisulfide bond formation, and sialic acid-containing glycosylation variants. N-terminal lysine, however, does not give rise to charge variants, as it is rapidly cleaved in vivo after both IV and SC administration (Ayalew et al. 2022).

The PK/clearance of an antibody may also be influenced by its glycosylation. Antibodies with oligomannose glycans in the Fc glycosylation are more rapidly cleared than those with other Fc

glycans, so that Fc oligomannose is usually a CQA_gen (Reusch and Tejada 2015). Few mAbs also carry Fab glycosylation, which may impact their PK (e.g., more rapid clearance of antibodies with Fab oligomannose glycans). Potential CQA from such Fab glycosylation are discussed in more detail under Step 5 below for the case example gantenerumab.

Formulation composition and properties qualify as obligatory CQA_gen. As with any formulation intended for SC injection, certain characteristics are important to ensure tolerability in terms of pain and irritation at the injection site. These characteristics may include a formulation with a pH ranging from 4 to 9, osmolality of ~300 and ≤600 mOsm/kg, buffer concentrations of phosphate limited to 10 mM, and citrate <7.3 mM. These limits minimize pain, irritation, and potential tissue damage at the injection site (Davis et al. 2024). The viscosity of the dosing solution must be low enough to allow a smooth manual injection with handheld syringe/prefilled syringe (HHS/PFS) or a reliable injection via AI. The ease of injection is also influenced by needle dimensions, particularly its inner diameter. Preferred solution viscosity values for subcutaneous injections, especially when the liquid formulation is filled into PFSs, are below 10 cP (Jiskoot et al. 2022).

A number of the CQA_gen discussed above may also affect the extent and rate of absorption after SC administration. Such general Critical Bioavailability Attributes (CBA_gen) are described in Step 2.

Step 2: General assessment of impact of CBA_gen for mAbs

The Applicant considers CBA_gen as product variants, formulation or administration attributes that are expected to critically impact the bioavailability (absorption rate and extent) of a mAb. In the following, the CBA_gen that could potentially affect the absorption of mAbs from the SC tissue into the systemic circulation are described generally, without taking the MIDBA framework into account.

The assessment of CBA_gen for mAbs after SC administration requires an analysis of the processes involved in the absorption and disposition of mAbs from administration until they reach systemic circulation. An SC administration deposits the mAb drug solution in the interstitial space of the SC tissue. The shape of such a fluid depot at an injection volume of e.g. 2 mL is provided by Pettis et al. (Pettis et al. 2023). The absorption of the administered mAb occurs predominantly via the lymphatic system (Supersaxo et al. 1990, Datta-Mannan et al. 2012), i.e., the injected drug must reach lymphatic capillaries in the SC tissue. Owing to their size, direct absorption of mAbs into blood capillaries via the paracellular route is likely precluded (Sánchez-Félix et al. 2020). Absorption via FcRn-mediated transcytosis through blood capillaries appears to be also of little or no relevance (Richter et al. 2018), which is consistent with the described absorption via the lymphatic system.

Subcutaneously administered mAbs move through the interstitial space of the SC tissue via fluid flow-driven convection or non-convective diffusion to reach the lymph capillaries in the SC tissue. Because of the restricted diffusion of mAbs due to their size (approximately 140 to 150

kDa), it is believed that convection is the primary mode of transport from the injection site to the lymph capillaries. The transport rate through the interstitial space may be reduced by positive charge of the mAb (Mach et al. 2011) or increased by hypertonic formulations (Fettner et al. 2019).

As described above, molecular size influences SC absorption. Molecules smaller than 10 nm are absorbed by blood capillaries (Richter et al. 2012). Optimal molecular size for lymphatic uptake is 10–100 nm (size of IgG mAb estimated at about 11 to 14 nm). Small size differences within the scope of mAb post-translational modifications are not expected to influence SC absorption of mAbs, as they amount to only a small fraction of the total molecular size. Monoclonal Ab dimers and other oligomers, however, are expected to undergo a slower absorption due to increased size (size of mAb dimers estimated at 15-30 nm). However, data on SC absorption of mAb dimers are missing in the literature. Data on SC absorption and disposition of larger oligomers in mice are provided by Filipe et al. (Filipe et al. 2014). In their study, a mAb was aggregated by agitation stress, which resulted in oligomeric particles mostly in the micrometer-range. The aggregated mAb preparation was shown to remain longer at the SC injection site as compared to the non-aggregated mAb. After absorption, the aggregated mAb preparation was cleared more rapidly from circulation compared to the non-aggregated mAb.

Product variants can also have an impact on endocytosis and FcRn binding. During transport through the SC interstitial space and through the lymphatics into systemic circulation the administered drug is subject to clearance by hematopoietic cells (e.g. macrophages and dendritic cells) located in these body compartments (Richter et al. 2018). In the used mouse model, the authors demonstrated the pre-systemic clearance by hematopoietic cells to be the predominant cause of incomplete SC bioavailability. The clearance process involves cellular uptake usually by fluid-phase endocytosis followed by either lysosomal degradation or FcRn-mediated salvage of the mAb molecule. Dedicated studies on the impact of product variants on SC bioavailability are largely missing. Nevertheless, it is reasonable to assume based on the described pre-systemic clearance mechanism that product modifications leading to a different FcRn binding behavior or modified cellular endocytosis (e.g., from charge modification) usually qualify as a CBA_gen. It is of note that hematopoietic cells were also shown to be a main site of mAb clearance after IV administration besides endothelial cells (Akilesh et al. 2007, Montoyo et al. 2009). Therefore, compound/mAb specific CQA_gen that affect the general PK of mAb after IV administration (particularly its clearance) are likely to also affect the SC absorption/bioavailability of mAbs and, thus, should be considered as CBA_gen.

The charge of a mAb and accordingly its propensity to undergo endocytosis is also dependent on its amino acid sequence. A measure for the charge on a mAb is its isoelectric point (pI), i.e., the pH at which the mAb has no net electrical charge. If the pH of the surrounding environment is below the antibody's pI, the molecule carries a net positive charge, whereas the antibody will carry a net negative charge when the pH is above the pI. An overview of mAb pI values is

provided by Zou for registered SC administered mAbs and those in clinical development (Zou 2023). Amino-acid sequence-based pI values range from 6 to 9. A weak inverse correlation was observed between SC bioavailability and pI of 96 mAbs (R2=0.0973) (Zou 2023). However, pI values as such are not predictive for SC bioavailability and therefore not to be considered as CBA_gen. For instance, the SC bioavailabilities of mAbs in the pI range of 8.5 to 9.0 range from ca. 30% up to ca. 90% (Zou 2023).

Recombinant human hyaluronidase may be added to a higher volume SC formulation to facilitate spreading of the injected volumed in the interstitial space (Frost 2007). As hyaluronidase has been shown to increase absorption rate of co-administered mAbs (Knowles et al. 2021), this excipient may become a CBA_gen.

Another obligatory CBA_gen is the protein concentration in the formulation. Formulations with mAbs and mAb-based modalities widely differ in protein concentration. Jiskoot et al. provide a range of 0.012 to 200 mg/mL (Jiskoot et al. 2022). Simulations using a physiologically-based PK model suggest that a high drug concentration after injection transiently saturates the FcRn recycling pathway, resulting in a higher fraction of the endosomal mAb being degraded (Stader et al. 2024).

The described mAb- and formulation-related CQA_gen/ CBA_gen are not expected to affect the applicability of the MIDBA, as MIDBA includes administration of the same mAb in the same formulation for both manual and automated injection with a device. Moreover, compound and formulation-related CQA_gen/CBA_gen are an integral part of the quality assessment of the formulations used in MIDBA. These assessments will be included in the filing dossier for each mAb-device combination product to ensure the quality of these attributes and to build in measures to account for potential differences, in accordance with the relevant EMA guidelines (Step 4).

Critical obligatory bioavailability attributes relevant for the MIDBA (CBA_MIDBA) basically comprise the injection conditions and related device features, as described in more detail under Step 3.

Step 3: Specific assessment of impact of CBA_MIDBA for mAbs

In this step, the evaluation proceeds within the MIDBA framework, where the same mAb and formulation are used, but the injection conditions differ between manual and automated injection with a device to better understand their effects on the absorption profile of the mAbs. The relevance of the identified CBA_MIDBA on the absorption profile is assessed under these conditions.

Potential CBA_MIDBA comprise the administration method (manual vs. automated), needle length, needle gauge, injection time, as well as the extractable volume. These parameters will be critically discussed in the following.

The general impact of the SC administration method (manual administration or automated device) has been tested for numerous mAbs. A survey of biological products approved by FDA's Center for Drug Evaluation and Research in 2020 evaluated the outcome of AI/PFS PK comparability studies for 17 products being on file at the agency (Hu et al. 2020). Most PK comparability studies met bioequivalence (BE) criteria. This outcome is consistent with the Applicant's comprehensive literature search, summarizing results from available PK comparability studies comparing manual and automated injection for mAbs approved with the YpsoMate AI platform, in-house products with relevant BE studies for different AI or OBDS platforms, and relevant PK comparability studies with other mAbs reported in the literature. Almost all studies demonstrated BE for both AUC and Cmax.

Needle length was reported to have an impact on SC administration (Gibney et al. 2010, Hirsch et al. 2014). Autoinjector (AI) presentations are administered via a 90° angle and usually the entire extended needle pierces the skin; thus, the extended needle length is the effective injection depth. Four to five mm injection depth ensures complete penetration of the dermis and subsequent injection into SC tissue. At injection depths ≥8 mm the risk of intramuscular administration increases. Consistent with this Hu et al., reported failures in AI/PFS SC bioequivalence studies with needle lengths ≥8 mm (Hu et al. 2020). Therefore, needle lengths ranging from 4 to 8mm should be used in device platforms suitable for application of the MIDBA.

Today, for SC injections, needle sizes of between 25- to 31-gauge are being applied (Tinkey et al. 2020), with increasingly smaller needles (up to approximately 33-gauge) used predominantly in the insulin space (Gill and Prausnitz 2007). Subcutaneous injections within this range are typically well tolerated, with a general user preference for smaller needle gauges. The Applicant was not able to identify an article in which needle size was identified as having an impact on the bioavailability of a mAb. Needle gauge may impact local tolerability at the injection site (refer to main response document), but is not expected to qualify as a CBA_MIDBA.

For AI platforms, the injection time is determined mainly by the force parameters of the AI, needle dimensions and viscosity of the mAb formulation, which are tightly controlled or defined parameters. For manual injection the injection rate will depend on needle dimensions and viscosity as well, but will be variable based on individual healthcare provider/caregiver preferences and capabilities. Dedicated studies in the literature indicate that a change in the injection time did not impact the PK profile of the administered mAbs (Davis et al. 2024). For instance, for dupilumab, administration of a single dose of 300 mg (2 mL) as a 30-second SC bolus or 10-minute SC infusion via a syringe pump to healthy individuals resulted in similar PKs (Li et al. 2020). The variable injection rate from manual injection is therefore not expected to have a relevant impact on SC absorption.

The hypothesis that both needle gauge and injection time are not expected to qualify as CBA_MIDBA, is indirectly confirmed by the Applicant's comprehensive literature search on PK comparability studies in the field (refer to main response document). While typically studies do not report the needle length and gauge, it can be expected that a variety of different

configurations have been used in all studies; still BE was demonstrated for Cmax and AUC in the majority of trials. The needle gauge and injection rate appear to be unlikely to be a CBA.

In case of major deviations between the injection volume that is administered manually with a HHS or PFS and the extractable volume of an AI, BE might no longer be demonstrated in a PK comparability study with a reasonable sample size. Consequently, accuracy and reproducibility of the extractable volume qualifies as CBA_MIDBA and is assessed as part of the overall control strategy as outlined in Step 4 below.

Appendix 2-Table 1 lists the CQA_Gen, CBA_gen, and CBA_MIDBA as identified during this systematic assessment.

Appendix 2-Table 1 CQA_Gen, CBA_gen, and CBA_MIDBA identified during this systematic assessment (+: CQA or CBA, -: non-CQA or non-CBA, +/-: case-by-case)

Attribute Category	Quality Attribute Category*	Examples of Quality Attributes*	CQA_gen	CBA_gen	CBA_MIDBA
Product variants	Size-related variants	High-molecular weight forms	+	+	n.a.
		Low-molecular weight forms	+	+	n.a.
	Charge-related variants: Acidic variants	Deamidation in non-CDRs	+	+	n.a.
		Deamidation in CDRs	+/-**	-	n.a
		Glycation in non-CDRs	+/-**	-	n.a
	Charge-related variants: Basic variants	Aspartic acid isomerization in CDRs	+/-**	-	n.a.
		Aspartic acid isomerization in non-CDRs	+/-**	-	n.a.
		C-terminal lysine	-	-	n.a.
	Oxidation-related variants	Met oxidation in CDR	+/-**	-	n.a.
		Met oxidation at FcRn binding site (homodimer)	+	+	n.a.
	Fc glycosylation	High-mannose glycans	+	+	n.a.
		Fc afucosylation	+/-**	-	n.a.
	Cysteine forms	Free thiol	+	+/-	n.a.
Process-related impurities		Host cell proteins	+**	-	n.a.
		Host cell DNA	+**	-	n.a.
		Leached Protein A	+	+	n.a.
Quality attributes for drug formulation		Protein content, potency, osmolality, pH, appearance, visible particles, subvisible particles, sterility	Obligatory CQAs	-***	n.a.
Quality attributes for SC administration		Exposed needle length, extractable volume	n.a.	n.a	Obligatory CBAs
		Needle gauge, injection time	n.a.	n.a.	-

*: list focused on key potential CQA and not exhaustive; **: no risk for PK; ***: hyaluronidase would qualify as CBA_gen; n.a.: not applicable.

Step 4: Description of design verification/validation and control strategy for CBA_MIDBA

In this step, the Applicant describes the target values for the identified CBA_MIDBA, exposed needle length and deliverable volume, as well as the applied principles of Design Verification and Validation to ensure that the identified CBA_MIDBA are controlled for consistent drug delivery and maintained bioavailability.

Injection time is not considered as a CBA_MIDBA, as it has no impact on the PK profile of the mAb. However, the parameter is part of the control strategy of the AI to ensure its proper function and therefore included in the description below.

The specifications for the YpsoMate AIs and the PFS used in Roche are listed in Appendix 2-Table 2.

Appendix 2-Table 2 Specifications for the YpsoMate AIs and the PFS.

Attribute	AI specifications	PFS specifications
Deliverable Volume	Label Claim - USP	Label Claim - USP
Injection Time	15 seconds or less	User dependent (typically from a few seconds to under a minute)
Exposed Needle Length	6 mm +/- 2 mm (injection taking place perpendicularly to the skin)	12.7 mm ± 1mm (injection taking place at an angle to the skin)

AI: autoinjector; mm: millimeters; PFS: prefilled syringe; USP: United States Pharmacopeia.

The Applicant implements a rigorous control strategy based on available regulatory guidelines to meet the intended clinical performance. The control strategy for the exposed needle length, injection time, and deliverable volume for the AI constitute of Design Verification Testing, and testing at Release and during Stability at Process Performance Qualification (PPQ), to ensure that design requirements are met and that the specifications are maintained throughout the shelf-life. The deliverable volume is tested also at Batch Release (Appendix 2-Table 3).

Appendix 2-Table 3 Control strategy for the exposed needle length, injection time, and deliverable volume for the AI

Test Method	Dossier Location for Method Description	Design Verification Testing	Release (PPQ)	Stability (PPQ)	Release (Commercial)
Deliverable Volume	3.2.R, P.5.2	✓	✓	✓	✓
Injection Time	3.2.R	✓	✓	✓	
Exposed Needle Length	3.2.R	✓	✓	✓	

PPQ: Process Performance Qualification.

For PFSs the exposed needle length is controlled through Material Specification (purchasing controls). The injection time is not tested because it is user-dependent. However, the syringe factors affecting injection time in the hands of the users (Break Loose Force and Average Injection Force) are subjected to Design Verification Testing, and testing at Release and during Stability at PPQ, to ensure that design requirements are met and that the specifications are maintained throughout the shelf life (Appendix 2-Table 4, Appendix 2-Table 5).

Appendix 2-Table 4 Control strategy for the deliverable volume for PFS.

Test Method	Dossier Location for Method Description	Design Verification	Release (PPQ)	Stability (PPQ)	Release (Com.)
Deliverable Volume	3.2.R, P.5.2	✓	✓	✓	✓

PPQ: Process Performance Qualification.

Appendix 2-Table 5 Break Loose Force and Average Injection Force for PFS.

Test Method	Dossier Location for Method Description	Design Verification	Release (PPQ)	Stability (PPQ)
Break Loose Force	3.2.R	✓	✓	✓
Average Injection Force	3.2.R	✓	✓	✓

Control of the CBA_MIDBA is guided by EMA quality guidelines for medicinal products used with medical devices, and applicable standards (EMA 2017, EMA 2021, EMA 2025, EU MDR (Regulation (EU) 2017/745) 2017. To ensure all the critical parameters in the table below are controlled effectively, the Applicant follows design verification and validation principles (ISO 13485), ensuring specifications meet intended clinical performance. Risk management principles (per ISO 14971) are followed to identify potential risks and mitigate them through design verification, validation, and usability studies (Appendix 2-Table 6).

Appendix 2-Table 6 EU MDR, and EMA quality guidelines for medicinal products used with medical devices applied to control CBA_MIDBA.

Parameter	Control	Reference
Exposed Needle Length	Defines design control requirements for needle length per ISO 11608-1 (Needle-based injection systems). - Verified through design validation and human factors studies to ensure consistent injection depth.	- EU MDR (Regulation (EU) 2017/745), Annex I (General Safety and Performance Requirements). - EMA Quality Guideline: "Quality documentation for medicinal products when used with a medical device" requires characterization of needle insertion depth.
Deliverable Volume	Requires extractable volume testing under simulated use conditions to ensure dose accuracy. - Stability testing ensures consistent dose delivery over shelf life.	- EMA Q&A on MDR/IVDR: Device variability must not impact drug efficacy. - EU MDR Annex I requires manufacturers to demonstrate dose delivery consistency.
Injection time	Requires injection speed control within predefined limits. - Usability and patient experience studies evaluate injection speed effects on pain and comfort.	- EMA Quality Guideline: Injection parameters must be evaluated for their influence on pharmacokinetics and tolerability. - EU MDR (Regulation (EU) 2017/745), Annex I (General Safety and Performance Requirements).

Step 5: Assessment of model mAbs based on CQA and CBA within the MIDBA framework

The Applicant has conducted a comprehensive CQA assessment for the “model mAbs” gantenerumab [redacted] The relevance of these proposed "model mAbs" is assessed outside and within the MIDBA framework in the following.

[redacted]

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