

BRIEFING PACKAGE

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

Company Name: Roche Registration GmbH

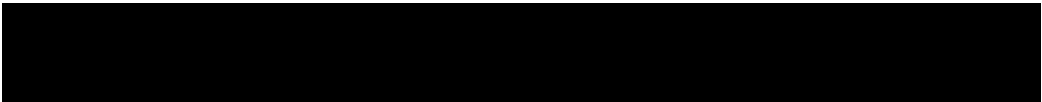
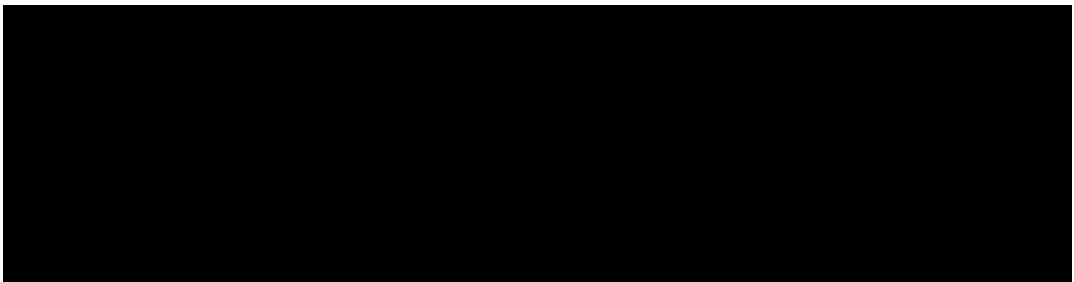
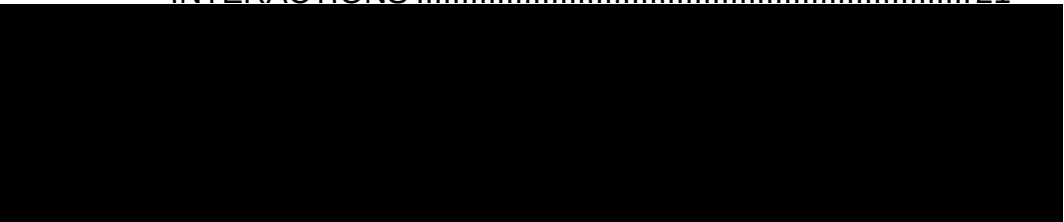
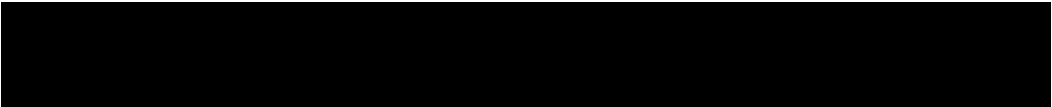
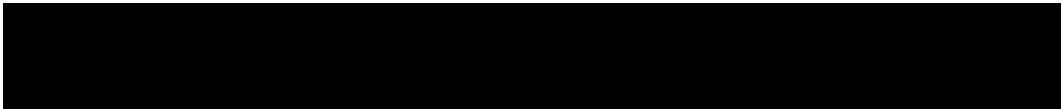
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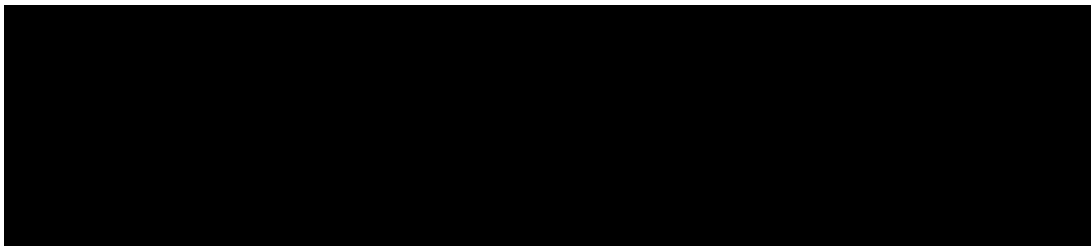
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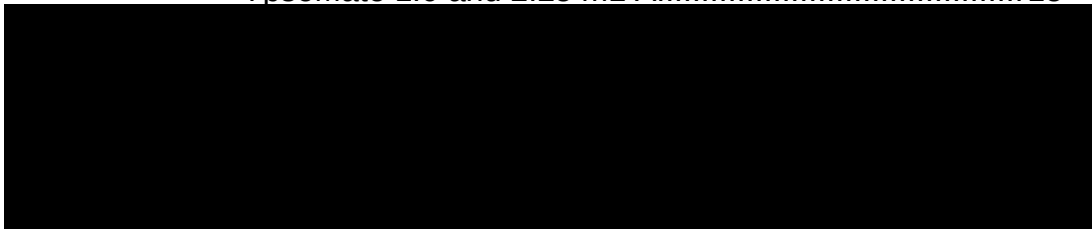
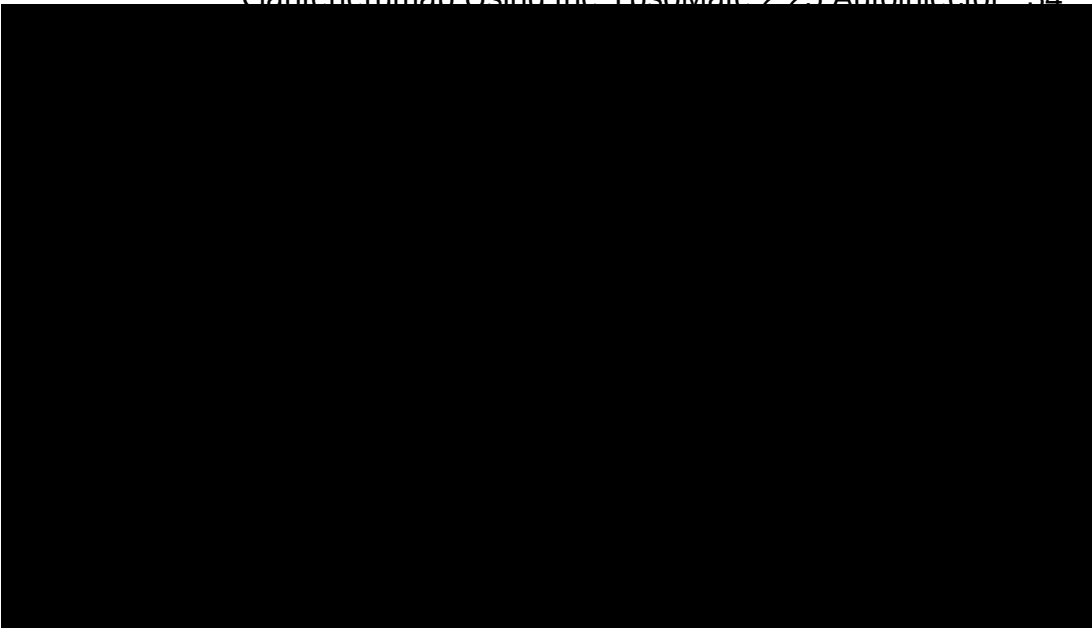


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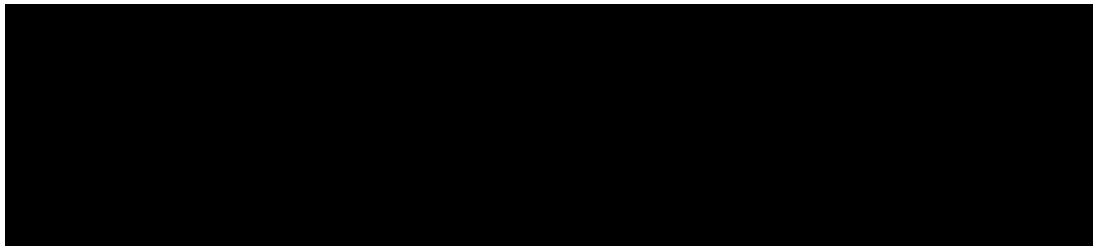
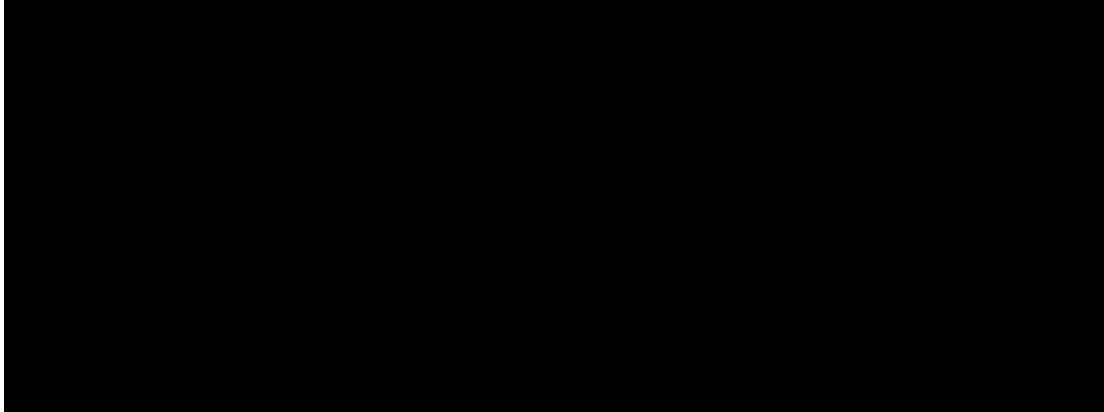


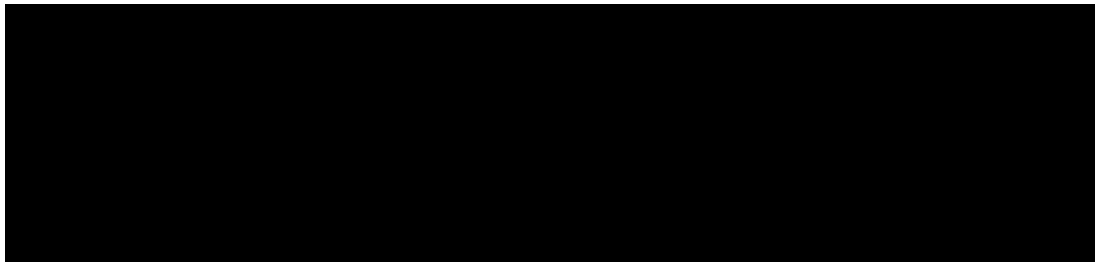
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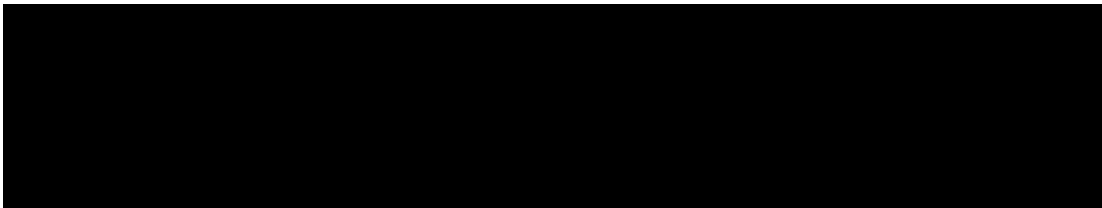
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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
ADE	adverse device effects
AE	adverse event
AI	autoinjector
AUC	area under the serum/plasma concentration-time curve
BE	bioequivalence
CHMP	Committee for Medicinal Products for Human Use
CoU	Context of Use
C _{max}	maximum serum/plasma concentration
C _{trough}	trough serum/plasma concentration
DS	disposable syringe
EMA	European Medicines Agency
FDA	US Food and Drug Administration
HHS	handheld syringe
iP	isoelectric point
LE	line extension
PK	pharmacokinetic
MAA	marketing authorisation application
mAb	monoclonal antibody
M&S	modelling and simulation
MIDBA	molecule-independent device bridging approach
NSD	needle safety device
OBDS	on-body delivery system
PBBM	physiologically based biopharmaceutics models
PBPK	physiologically based PK
PK	pharmacokinetic
popPK	population PK
PFS	prefilled syringe
QoNM	Qualification of Novel Methodology
SAE	serious adverse event
SC	subcutaneous

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[REDACTED]

$T_{\max}$

time to maximum serum/plasma concentration

TERMINOLOGY AND DEFINITIONS

Terminology	Definition
Eligible monoclonal antibodies (mAbs) [REDACTED]	mAb [REDACTED] products that meet the formulation and pharmacokinetic criteria for applying the molecule-independent device bridging approach (MIDBA).
[REDACTED]	[REDACTED]
Reference mAbs	mAb products from the Sponsor's pipeline with available bioequivalence (BE) data supporting the bridge from manual injection with a prefilled syringe (PFS) or HHS to the YpsoMate autoinjector (AI) platform. In this qualification package, the Sponsor presents BE data for omalizumab and gantenerumab as reference mAbs.
Supporting external mAbs	Other mAb products outside of the Sponsor's pipeline approved in combination with the YpsoMate AI platform supporting the bridge from manual injection with a PFS/HHS to an autoinjector.

1. **EXECUTIVE SUMMARY AND OVERVIEW**

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

Selection of a SC injection device platform necessitates knowledge of the final dose and injection volume, which typically becomes available just prior to the start of Phase III. Due to the required molecule-specific technical device development, using a more standardized and convenient AI in the Phase III program may therefore not be feasible. Consequently, pivotal clinical studies are frequently conducted using PFS or HHS (Figure 1). Subsequently, pharmacokinetic (PK) comparability studies may be conducted to demonstrate clinical comparability for administration of the same molecule across two SC injection procedures, that is, to allow presentations to transition from HHS or PFS to AI. To facilitate access to a convenient SC delivery system, the Sponsor is applying the YpsoMate AI platform for the administration of different mAbs across the portfolio.

The underlying prerequisites for applying the MIDBA are that:

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

Technical design verification and validation, including a summative human factors study, would still be conducted for each individual mAb medicinal product. As the main Context of Use (CoU), the Sponsor intends to apply the MIDBA as a novel methodology to generating clinical evidence for the YpsoMate AI platform for use with mAbs. The proposed methodology was already discussed with the Agency for selected molecules within the Sponsor's pipeline [REDACTED]. The concept was substantiated based on the comments received.

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[REDACTED]

[REDACTED]

Sources of data supporting the QoNM Procedure for the YposoMate AI [REDACTED] include PK comparability data generated for the reference mAbs omalizumab and gantenerumab, tabulated overviews of the formulation, device, and PK characteristics of the reference mAbs, and of the mAbs previously discussed with the Agency, an overview of approved products with the YposMate AI, [REDACTED]

[REDACTED]

[REDACTED]

Accounting for the Agency's comments during the preparatory meeting for the QoNM Procedure on September 11th, 2024, the Sponsor has enriched the package with the following:

1. A description of the formulation physicochemical space and PK characteristics for mAbs with PK comparability data between manual and automated injection with the YposoMate AI based on publicly available information.
2. A description of the formulation physicochemical space and PK characteristics for mAbs from the Sponsors pipeline with PK comparability data between manual and automated injection both with AI and OBDS devices.
3. A literature review and feasibility assessment on existing modelling and simulation (M&S) efforts to help define the formulation and PK space for MIDBA.

[REDACTED]

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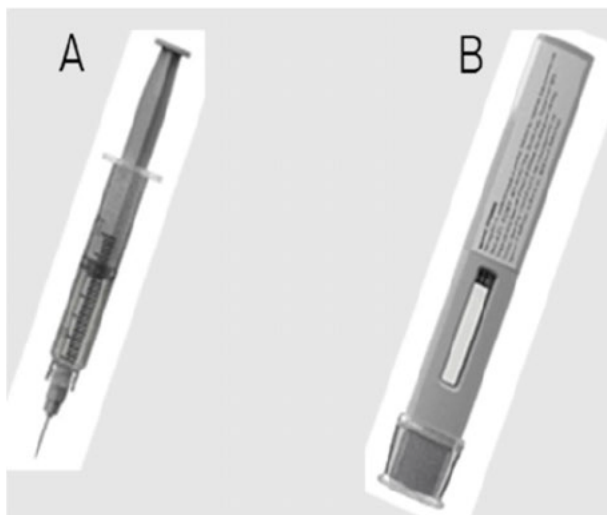
[REDACTED]

Overall, the Sponsor concludes that the MIDBA can be applied for mAbs [REDACTED] when transitioning from the HHS or PFS used in the pivotal Phase III clinical trials to the intended Ypsomate AI platform [REDACTED]

[REDACTED]

[REDACTED]

Figure 1 Overview of Subcutaneous Injection Delivery Devices



A. Example of Handheld syringe (HHS) used with vial; B. Ypsomate 2.25 Autoinjector (AI) [REDACTED]

[REDACTED]

In this briefing package, the Sponsor describes an overall plan for qualifying MIDBA in different CoU scenarios (Section 3), the available data to support qualification (Section 6.1, [REDACTED] and Section 6.3), and any identified gaps or limitations to MIDBA (Section 6.4).

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An overview of the meeting questions is provided below, and the supporting company positions are provided in Section 7.

Meeting Questions

The Sponsor intends to apply the MIDBA as an alternative methodology to conducting dedicated clinical PK comparability studies between manual and automated subcutaneous injection drug delivery device platforms for eligible monoclonal antibodies

[REDACTED] The Sponsor proposes applying the novel MIDBA methodology across a number of different context of use (CoU) scenarios, each supported by a distinct scientific evidence base. This approach should enable a tailored discussion on the regulatory qualification of this novel methodology for each CoU.

Q1: In CoU scenario 1, the integral mAb drug-YpsoMate 1.0 mL and 2.25 mL AI device combination product presentation to be submitted with the marketing authorisation application (MAA) contains the same injection volume of a mAb formulation as that used in the pivotal clinical studies (manual injection using a PFS or HHS). The total dose volume is administered with one injection both with the AI and the PFS or HHS.

Does the Agency agree that for this CoU, the MIDBA can be applied for clinical qualification of the YpsoMate AI platform, so that eligible mAbs can refer to available PK comparability data previously generated with reference mAbs?

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2. STATEMENT OF THE NEED FOR AND IMPACT OF THE PROPOSED NOVEL METHODOLOGIES IN CLINICAL DRUG DEVELOPMENT

[REDACTED]

Ensuring the timely availability of automated injection devices, such as Als [REDACTED], is crucial for facilitating at-home and self-administration of biotherapeutics. However, developing an AI [REDACTED] for use in the Phase III program may not be practical due to the molecule-specific technical development requirements. Subsequently, pharmacokinetic comparability studies may be considered to demonstrate comparable performance between the PFS or manually filled HHS used in Phase III and the automated device (Hu et al. 2020; US FDA 2019). In view of the more consistent injection with an automated device, in the opinion of the Sponsor, for mAbs utilizing device platforms that were previously validated with another mAb, referencing to these data rather than conducting an additional dedicated pharmacokinetic comparability study should be justified (Lambert 2020).

The underlying prerequisites are that (1) the AI [REDACTED] contain the same formulation (i.e., including the same excipients at the same concentration) as used for manual injection, (2) the injection volume is either the same as in the pivotal Phase III study or bracketed by the range of volumes established for manual injection in the pivotal Phase III study for the respective mAb, and (3) the AI injection sites were previously

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qualified with manual injection. Deviations from this approach would be assessed on a case-by-case basis.

Eligible mAbs would be characterized by slow absorption from the SC tissue into the systemic circulation ([Ryman and Meibohm 2017](#)). The rationale is that the pharmacokinetic profiles of SC administration using different devices, such as PFS, HHS, AI, [REDACTED] are expected to be similar. This is because the rate-limiting factor for absorption into the systemic circulation is the release from the interstitial space via lymph flow, rather than the specific injection method.

For mAbs, the intended use of the MIDBA in clinical development is to replace the need for conducting a dedicated PK comparability study for eligible new mAbs using a SC injection device (AI [REDACTED]) with prior PK comparability data for another mAb.

The novel methodology is intended to be applied across indications and patient populations and is expected to contribute to an earlier injection device availability allowing for at-home and self-administration in a decentralized care setting.

Depending on the outcome of the qualification procedure, relevant information as summarized in [Table 1](#), [REDACTED] will be provided to the Agency at the time of the MAA or line extension (LE) for the integral drug-device combination product, [REDACTED]

Additional evidence on technical design verification and validation, including a summative human factors study will be generated and provided in the MAA. These assessments will be conducted for each individual medicinal product (with integral [REDACTED] device).

The proposed MIDBA impacts the nature of the clinical evidence submitted to register the drug-device combination products, as it may replace molecule-specific clinical data review and approval with a qualification of selected device platforms.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

3. CONTEXT OF USE SCENARIOS FOR MIDBA

The MIDBA would be applied in situations where the device platform was not used in the pivotal clinical studies and SC injection was performed manually via either a PFS or a vial and HHS [REDACTED]. The prerequisites are that (1) the device platform contains the same formulation (i.e., including the same excipients at the same concentrations) as used for manual injection, (2) the injection volume is either the same as in the pivotal Phase III study or bracketed by the range of volumes established for manual injection in the pivotal Phase III study for the respective molecule, and (3) the injection sites were previously qualified with manual injection via HHS/PFS.

The device platform is foreseen to be used by professional healthcare providers, lay caregivers and patients, depending on the safety and tolerability of the product and the preference and abilities of the patient and caregiver population. Supporting evidence on usability of the device is derived in dedicated human factors studies conducted for each eligible molecule in a population reflecting the capabilities of the target user population.

[REDACTED]

[REDACTED]

The Sponsor intends to apply the MIDBA as an alternative methodology to generating clinical evidence for the YpsoMate AI platform for use with [REDACTED] mAbs [REDACTED]. Scenarios include bridging from one manual injection (via HHS or PFS) to one injection of the same injection volume with the YpsoMate AI platform [REDACTED].

[REDACTED]

Table 1 describes [REDACTED] the proposed supporting evidence available with the MAA to qualify the YpsoMate AI with MIDBA. [REDACTED]

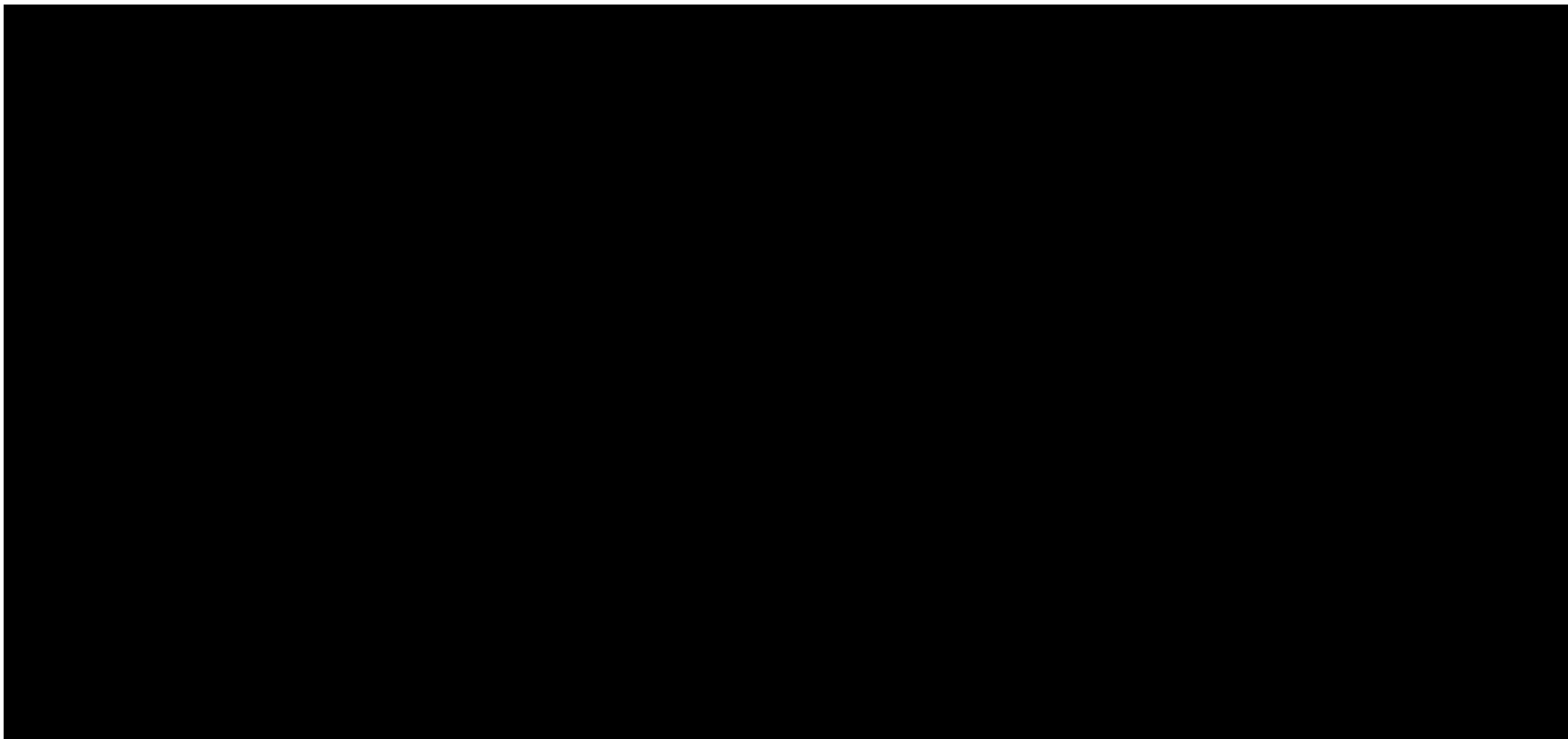
[REDACTED]

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Table 1 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 / Question 1 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.	PK comparability data (i.e., HHS/PFS versus YpsoMate AI) previously generated for omalizumab^c and gantenerumab. Safety and local tolerability with the YpsoMate 2.25 AI from the PK comparability studies with omalizumab^c and gantenerumab. Assessment of eligible mAb's PK characteristics space based on proposed reference mAbs and mAb-YpsoMate 1.0 mL and 2.25 mL AI device 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;
antibody; [REDACTED]
SC=subcutaneous; [REDACTED]

LE=line extension; MAA=marketing authorisation application; mAb=monoclonal
PFS=prefilled syringe; PD=pharmacodynamics; PK=pharmacokinetics;

^a1 to 1 bridge: The PFS or HHS for manual injection delivers the same injection volume as the AI.

^cPublicly available data.

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4. MEETING OBJECTIVES

The purpose of this meeting is to seek feedback from the Agency on the qualification of MIDBA as an alternative methodology for clinical bridging from manual to automated SC administration to support registration of:

- Integral mAb drug-YpsoMate 1.0 mL and 2.25 mL AI device combination products

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5. REGULATORY STATUS AND PREVIOUS INTERACTIONS

The Sponsor has previously received Health Authority feedback on the general MIDBA concept and its specific application for pipeline molecules. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6. METHODOLOGY, RESULTS, AND SUPPORTIVE DATA FOR QUALIFICATION

A description of the overall approach to the novel methodology is provided in the Company Positions underlying the different questions to the Agency (Section 7).

6.1 **COMPARATIVE PK AND PHYSICOCHEMICAL DATA FOR OMALIZUMAB AND GANTENERUMAB**

The MIDBA aims to refer to data generated previously by the reference mAbs omalizumab (using publicly available data [REDACTED]) and gantenerumab in BE studies (note: data are not [REDACTED])

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published [REDACTED]
comparing manual injection via a PFS or HHS and the YpsoMate 2.25 AI. The supportive data from these mAbs for the qualification of the MIDBA are tabulated below with additional details provided in the respective appendices to this briefing package.

Comparative datasets include:

- technical details on the drug products, HHS, PFS, and automated injection delivery devices ([Table 5](#)).
- the dose volumes administered with the PFS/HHS and YpsoMate 2.25 AI in the BE studies with omalizumab and gantenerumab ([Table 6](#)).
- the pharmacokinetic parameters for omalizumab and gantenerumab ([Table 7](#)).
- the results of the BE studies omalizumab and gantenerumab ([Table 8](#)).

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Table 5 Comparison of Drug Products and Manual/Automated Injection Delivery Devices for Omalizumab and Gantenerumab.

Attribute	Omalizumab	Gantenerumab
#1 Physical properties of liquid		
Formulation	<u>PFS-NSD^a</u> 150 mg/mL omalizumab 42.1 mg/mL L-Arginine Hydrochloride 2.3 mg/mL L-Histidine HCL 1.4 mg/mL L-Histidine 0.4 mg/mL Polysorbate 20 pH 6.0	<u>Autoinjector</u> 144 mg/mL gantenerumab L-Histidine L-Histidine HCL Monohydrate alpha-Trehalose dihydrate L-Methionine Poloxamer 188 pH 5.5 <u>PFS-NSD / vial formulation</u> 150.0 mg/mL gantenerumab L-Histidine L-Histidine HCL Monohydrate alpha-Trehalose dihydrate Poloxamer 188
pI	7.3 ^b	
Dose and injection volume	75 mg/0.5 mL, 150 mg/1 mL, 300 mg/2 mL	255 mg/1.77 mL
Viscosity	Appr. 14 cP at 20°C ^c	7.7 cP at 20°C (formulation used in AI)
Osmolality		275-375 mOsmol/kg
#2 Device properties (manual injection)		
Manual Device	PFS-NSD	Vial and disposable syringe for manual injection

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Attribute	Omalizumab	Gantenerumab
Device Image		
Syringe	Becton Dickinson Neopak 2.25 mL (glass syringe)	Disposable syringe for manual injection
NSD	BD Ultrasafe with extended finger flange (EFF).	Not applicable
Filter	Without Filter	Without filter
Needle Extension / Exposed Needle Length (mm)	12.7 (1/2 inch staked-in-needle)	12.7 (maximal length 1/2 inch)
Injection time (s)	User determined	User determined
#3 Device properties (automated injection)		
Device	YpsoMate 2.25	YpsoMate 2.25

Attribute	Omalizumab	Gantenerumab
Device Image		
Plunger Rod length	Length adjusted to 2.0 mL dose	Length adjusted to 1.77 mL dose
Needle Extension / Exposed Needle Length (mm)	Approximately 6	6.0±2.0
Injection time (s)	2.0 mL: up to 15 ^d	1.77 mL: ~ 6.5

pI= isoelectric point; q.s = quantum satis (as much as may suffice); Poloxamer 188 = polyoxyethylene (160) polyoxypropylene (30) glycol.

^a [XOLAIR® PFS \(150 mg\) Safety Data Sheet](#)

^b [Wang et al. 2022 \(Table 3\)](#)

^c [Tsumura et al. 2022 \(estimate from publication\)](#)

^d [XOLAIR® \(omalizumab\) US prescribing information](#)

Table 6 Volumes Administered with the PFS/HHS and YpsoMate 2.25 AI in the Bioequivalence Studies for Omalizumab and Gantenerumab.

Omalizumab		Gantenerumab	
PFS	AI	HHS	AI
2 mL 2 x 1 mL	2 mL	1.7 mL	1.77 ^a mL

^a The higher fill-volume in the gantenerumab AI as compared to the HHS did derive 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. No additions had to be made to the drug product in the glass vial (i.e., no methionine required), which resulted in the volume difference.

Table 7 Summary of Plasma Pharmacokinetic Parameters for Omalizumab and Gantenerumab.

Compound		Omalizumab ^a	Gantenerumab ^b
MAB type		Humanized IgG1 mAb	Humanized IgG1 mAb
Dose, regimen, device		single dose of 300 mg (2 x 150 mg) SC, PFS-NSD	single dose of 255 mg SC, HHS
Bioavailability (F)		62%	55% (150 mg) ^c
T_{max} (h)	N Median (min;max)	63 166.3 (reported as 6.9 days) (12, 338) (reported as 0.5, 14 days)	131 122 (24.0, 268)
C_{max} (µg/mL)	N Mean CV, %	63 40.5 22.0	131 17.0 48.4
AUC_{inf} (µg*h/mL)	N Mean CV, %	57 38500 27.5	129 12294 39.7
Vz/F (L)	N Mean CV, %	57 6.8 25.8	129 19.3 38.0
terminal t_{1/2} (h)	N Mean CV, %	57 581 (reported as 24.2 days) 21.6	129 577 20.7
CL/F (mL/h)	N Mean CV, %	57 8.37 (reported as 0.00837 L/h) 27.4	129 23.9 (reported as 0.0239 L/h) 37.9

CV=coefficient of variation; HHS=handheld syringe; Max=maximum; Min=minimum; N=total number of participants; NSD=needle safety device; PFS=pre-filled syringe

^a [Sangana et al. 2024](#)



Table 8 Trial Designs, Endpoints and Results from the Bioequivalence Studies for Omalizumab and Gantenerumab Using the YpsoMate 2.25 Autoinjector.

Molecule (Brand name)	Clinical trial title	Design clinical device bridging study	Endpoints	Results clinical bridging study
Omalizumab (Xolair) ^a	An open-label, randomized, single-dose, 3-parallel-group, bioequivalence study of omalizumab administered by a proposed prefilled syringe system in an autoinjector configuration and with a needle safety device configuration, both compared against the registered prefilled syringe product in healthy participants	Participants: 193 HMFS Injection sites: Abdomen, thigh, and arm Randomization (1:1:1): Arm 1: PFS-NSD (2x150 mg/1 mL) Arm 2: PFS-NSD (300 mg/2 mL) Arm 3: AI (300 mg/2 mL)	AUC _{0-t} , AUC _{0-∞} , C _{max}	BE established for all comparisons
Gantenerumab ^b	A multi-center, randomized, open-label, single-dose, parallel group study	Participants: 266 HMFS Injection site: Abdomen Randomization (1:1): Arm 1: HHS (255 mg/1.7 mL) Arm 2: AI (255 mg/1.77 mL)	AUC _{0-∞} , C _{max}	BE established for all comparisons:

AI=autoinjector; AUC_{0-t}=serum concentration-time curve to the last detectable value; AUC_{0-∞}=serum concentration-time curve extrapolated to infinity; BE=bioequivalence; C_{max}=maximum concentration; HHS=handheld syringe; HMFS=healthy male and female subjects; NSD=needle safety device; PFS=prefilled syringe.

^a [Sangana et al. 2024](#)

[REDACTED]

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6.3 OTHER DATA TO SUPPORT QUALIFICATION OF MIDBA

6.3.1 Additional Publicly Available Pharmacokinetic and Formulation Data with the YpsoMate AI

The YpsoMate platform (1.0 and 2.25 mL) is commercially available for the administration of additional molecules from other manufacturers [REDACTED]. For a number of these molecules, PK comparability has been established between manual injection via HHS or PFS and an autoinjector [REDACTED].

[REDACTED]

[REDACTED] The majority of the underlying publicly available study manuscripts do not specify the AI platform used. As these mAbs are not part of the Sponsor's pipeline, the Sponsor cannot comment on the exact injection procedure of the respective mAb formulations. However, it is expected that the injection depths and times, the physicochemical properties of the mAbs, as well as specifics of the formulations (i.e., drug concentration, viscosity) vary between the different products.

[REDACTED]

[REDACTED]

Overall, this available evidence further supports that changing from manual injections by means of HHS or PFS to an AI platform results in comparable pharmacokinetics and an acceptable tolerability profile.

[REDACTED]

6.3.2 Pharmacokinetic and Formulation Data with Additional AI and OBDS Platforms – Inhouse data

The Sponsor has previously established PK comparability/BE for a number of mAbs in their pipeline when comparing manual injection with automated injection by means of an AI or OBDS platform. Here, injection volumes for AI-based injections range between 0.5 and 1.77 mL and OBDS-based injections range from 5 to 10 mL.



[REDACTED]

Although a variety of AI and OBDS types were used in these PK comparability studies, the Sponsor believes that this collective data set can support expanding the MIDBA framework to additional delivery platforms.

6.4 IDENTIFIED GAPS AND LIMITATIONS

[REDACTED]

For mAbs, the YpsoMate AI platform has been approved with a number of products that are also available for manual injection via PFS. Moreover, an acceptable tolerability profile has been demonstrated across a range of injection volumes. PK comparability/bioequivalence was demonstrated for the mAbs gantenerumab [REDACTED] [REDACTED] and omalizumab ([Sangana et al. 2024](#)). For the latter, even comparing two times 1 mL via manual injection with one time 2 mL with the YpsoMate AI platform met BE criteria. From the Sponsor's perspective, no gaps and limitations have been identified and the applicability of MIDBA to eligible mAbs can be justified.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]
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[REDACTED]
[REDACTED]
[REDACTED]

7. **MEETING QUESTIONS WITH SUPPORTING COMPANY POSITION**

The Sponsor intends to apply the MIDBA as an alternative methodology to conducting dedicated clinical PK comparability studies between manual and automated subcutaneous injection drug delivery device platforms for eligible monoclonal antibodies

[REDACTED]

7.1 QUESTION 1

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

Does the Agency agree that for this CoU, the MIDBA can be applied for clinical qualification of the YpsoMate AI platform, so that eligible mAbs can refer to available PK comparability data previously generated with reference mAbs?

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Company Position:

In CoU scenario 1, the YpsoMate AI platform contains the same injection volume of a mAb formulation as that used in the pivotal clinical studies (manual injection using a PFS or HHS). The total dose volume is administered with one injection both with the AI and the PFS or HHS. The supporting evidence underlying the MIDBA approach in scenario 1 is summarized in [Table 1](#).

The MIDBA is proposed to be used as a new clinical bridging approach to the YpsoMate AI in case the use of the device has not been an integral part of pivotal clinical trials for eligible mAbs. Currently, the underlying bridging program would typically include the demonstration of PK comparability ([Hu et al. 2020](#)) between the injection by means of an HHS or PFS used in the pivotal trial with the newly introduced AI platform.

For mAb-products to be eligible for application of the MIDBA, the underlying prerequisites are that

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

The proposal to apply the proposed MIDBA as a new methodology for the clinical bridge from manual injection to the YpsoMate AI platform for new mAbs is based on:

1. PK comparability data (i.e., HHS/PFS versus YpsoMate AI) previously generated for omalizumab and gantenerumab.
2. Assessment of eligible mAb's PK characteristics space based on proposed reference mAbs and mAb-YpsoMate 1.0 mL and 2.25 mL AI device combination products in the public domain.
3. General assessment of eligible mAb's formulation physicochemical space for MIDBA.
4. Safety and local tolerability from the eligible mAb's clinical development program and from the PK comparability studies with omalizumab and gantenerumab with the YpsoMate 2.25 AI.
5. Subcutaneous injection sites qualified with manual injection via HHS/PFS in pivotal clinical trials for eligible mAb.
6. Analytical comparability and formulation characterization, design verification and validation, including a summative human factors study for the YpsoMate AI, being

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successfully completed in a population that reflects the intended use population for the eligible mAb.

Overall, the Sponsor provides supporting evidence that differences in SC injection methodologies (i.e., via HHS or PFS versus the AI platform) are not expected to have a clinically relevant impact on pharmacokinetics, efficacy, safety, or local injection reactions of eligible new mAbs.

1. PK comparability data (i.e., HHS/PFS versus YpsoMate AI) previously generated for omalizumab and gantenerumab

Dose accuracy and PK comparability between manual injection via PFS or HHS and the YpsoMate 2.25 AI platform has been previously demonstrated in BE studies with omalizumab and gantenerumab ([Table 8](#)). With the MIDBA, the Sponsor proposes to leverage these data aiming to demonstrate the interchangeability of manual and automated SC dose administration methods. New mAbs that were administered via PFS or HHS in the pivotal Phase III study would reference the outcome of the BE studies with omalizumab and gantenerumab, rather than conducting a dedicated PK comparability study for the eligible mAb.

The slow absorption from the SC tissue is reflected in T_{max} , and both reference mAbs exhibit a late median T_{max} at approximately 5 days and 7 days for gantenerumab and omalizumab, respectively. The relevance of PK processes of distribution and elimination - marked by PK parameters, such as volume of distribution (V_z/F), clearance (CL/F) and terminal half-life ($t_{1/2}$) - are considered negligible for the assessment of PK comparability after administration by either HHS/PFS or AI across mAbs, since these processes are not considered to be impacted by the SC administration device, considering a slow SC absorption process.

Like the reference mAbs, omalizumab and gantenerumab, ([Drugs.com](#); [REDACTED]), mAbs eligible for using the YpsoMate AI platform qualified via the MIDBA are characterized by a slow absorption from the SC tissue into the systemic circulation ([Ryman and Meibohm 2017](#), [Lobo et al. 2004](#)). The underlying rationale for assuming that the PK profiles for SC administration using HHS or PFS and AI devices will be similar is that in such situations, the release from the interstitial space via lymph flow (i.e., the rate and extent of drug absorption post SC injection into the systemic circulation), rather than the particularities of the SC injection method, is expected to be the rate limiting factor for absorption into the systemic circulation.

This hypothesis is supported by the findings from a survey of biological products approved by FDA's Center for Drug Evaluation and Research ([Hu et al. 2020](#)). Seventeen biologics license applications (BLAs) with both PFS and AI presentations for

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SC administration were systematically reviewed on the device parameters and the PK comparability studies bridging the two presentations. Among the 17 BLAs with both AI and PFS, nine are mAbs, four are fusion proteins, and the remaining four are cytokines or their PEGylated analogs. The assessment revealed that most PK comparability studies met BE criteria. The injection site for either AI or PFS and the injection depth of the AI were suggested as potential factors influencing the outcome of the PK comparability study.

These potential influencing factors are accounted for with the MIDBA approach. Only injection sites previously qualified with manual injection via HHS/PFS are allowed for injection with the AI. Moreover, major differences in injection depth between HHS/PFS and AI are reduced by applying different injection angles. HHS/PFS are typically applied on pinched skin with a 45° to 90° angle from the skin surface and the YpsoMate AI is designed to inject at 90° from the skin surface without pinching. This difference in injection technique is accounted for with different exposed needle lengths for the HHS/PFS versus the AI. Namely, the exposed needle length for the YpsoMate AI is approximately 5.5 to 6 mm versus approximately 12 mm for the PFS/HHS to ensure injection into the SC, despite these differences in exposed needle lengths for the HHS/PPF versus the AI, PK comparability (BE criteria) was demonstrated for both omalizumab and gantenerumab ([Table 8](#)).

The slow absorption rate of mAbs into the systemic circulation is also reflected in the lack of impact of injection rate on the PK profile of different experimental mAbs. Previously, the Sponsor assessed the impact of injection time on the PK profile of gantenerumab using a manual injection apparatus mimicking an AI in a study in healthy volunteers (██████). Volumes of 2 mL (300 mg) of gantenerumab have been injected in 5 and 15 seconds (sec), reflecting injection flow rates of 0.4 and 0.133 mL/sec, respectively. Comparable PK (C_{max} , T_{max} , AUC, $t_{1/2}$) has been demonstrated (see [Table 19](#)) ([Portron et al. 2020](#)).

Table 19 Plasma PK Parameters for 300-mg SC Gantenerumab Injections.

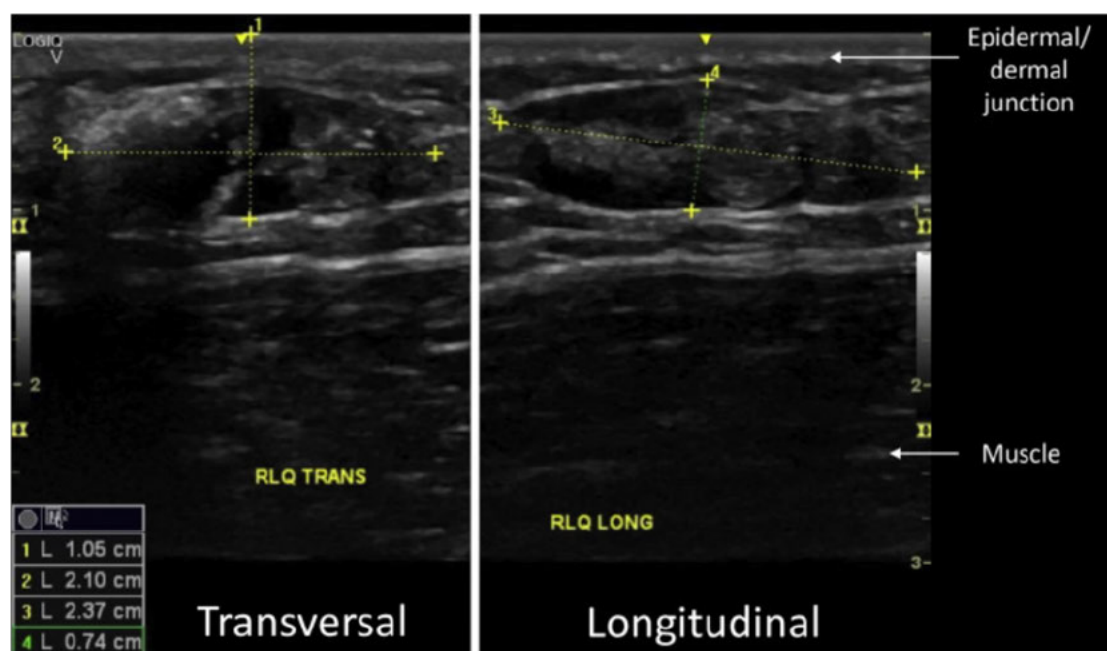
PK Parameter ^a	5-sec injection (n = 23)	15-sec injection (n = 23)
T _{max} median (minimum–maximum), day	4.96 (2.98–11.0)	4.96 (2.98–20.0)
C _{max} mean (% coefficient of variation), µg/mL	13.5 (40.2)	14.5 (40.3)
AUC _{0-inf} mean (% coefficient of variation), µg·day/mL	375 (34.5)	409 (25.8)
t _{1/2} mean (% coefficient of variation), day	21.9 (22.1)	21.2 (22.2)

^a Portron et al. 2020

AUC_{0-inf}=area under the plasma concentration–time curve between time zero (before dose) and extrapolated to infinity; C_{max}=maximum observed plasma concentration; inf=infinity; max=maximum; PK=pharmacokinetics; sec=seconds; SC=subcutaneous; t_{1/2}=terminal half-life; T_{max}=time to C_{max}.

In the same study, the Sponsor also assessed the SC fluid depot formation via 2-dimensional ultrasound echography ([Figure 2](#)). Measurements revealed exclusively SC localization of fluid depot, with a mean (SD) fluid depot depth of 0.83 (0.24) and 1.03 (0.47) cm after 5- and 15-sec injections of gantenerumab into the abdomen, respectively. The mean (SD) fluid depot depth after placebo injection into the thigh was 0.75 (0.14) cm for the 5-sec and 0.80 (0.17) cm for the 15-sec injection speed groups. Mean (SD) depot sizes were also comparable immediately after 5-sec (area, 4.19 [2.29] cm²; volume, 2.53 [1.80] cm³) and 15-sec (area, 4.28 [1.96] cm²; volume, 3.04 [2.17] cm³) SC injections of gantenerumab to the abdomen. Similar results were observed with 5-sec (area mean [SD], 4.34 [1.95] cm²; volume mean [SD], 2.19 [1.10] cm³) and 15-sec (area mean [SD], 5.29 [1.91] cm²; volume mean [SD], 2.91 [1.44] cm³) SC injections of placebo to the thigh.

Figure 2 Representative echography image of gantenerumab administration in the abdomen.



Subcutaneous localization of fluid depot in the right lower quadrant of the abdomen on 2-dimensional ultrasound echography. 1 indicates subcutaneous injection depth; 2, width of the depot; 3, length of the depot; and 4, depth of the depot. RLQ=right lower quadrant of abdomen.

The observation that the injection speed did not impact the PK profile of a mAb is further supported by studies with secukinumab ([Bruin et al. 2020](#)) and tralokinumab ([Jain et al. 2017](#)) that demonstrated no significant impact on PK profiles when compared across different injection flow rates.

Bruin et al. ([Bruin et al. 2020](#)) describe the SC administration of secukinumab in a Phase I study in healthy volunteers and in a Phase III study using a variety of delivery systems in participants with psoriasis. Namely, in healthy volunteers (n=20 per arm), six different administration conditions were assessed to inject 2 mL of a 150 mg/mL solution of secukinumab. The authors compared different AI, PFS, and pump systems. In addition to the device type, injection conditions differed in needle size, needle length, and injection duration (10 and 90 sec, and 5 min). Despite the marked differences in injection speed and injection device types, it was concluded that the six dosing procedures resulted in “very comparable serum concentration-time profiles”. Similar observations were made in the study in psoriasis. Here, secukinumab was administered using a PFS with either two 1-mL injections (n=71) or with one 2-mL injection (n=72) resulting in comparable mean serum concentration-time profiles.

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In the Phase I study described by Jain et al. (Jain et al. 2017), 60 healthy volunteers were randomized to receive 300 mg tralokinumab either as two 1-mL SC injections each delivered over 10 seconds or as one 2-mL injection delivered over 10 seconds (12 mL/min), 1 minute (2 mL/min), or 12 minutes (0.167 mL/min). No differences in the PK profile of tralokinumab were observed between cohorts.

Based on the above data, and considering that the injection depth following manual injection with an HHS or PFS by different healthcare professionals varies by each injection as compared to automated injection with the AI platform (Hu et al. 2020), the Sponsor concludes that neither the described differences in the injection time nor in needle length are expected to impact the PK profile for eligible mAbs when administered manually via HHS or PDS versus an AI platform.

2. Assessment of eligible mAb's PK characteristics space based on proposed reference mAbs and mAb-YpsoMate 1.0 mL and 2.25 mL AI device combination products in the public domain

Descriptive framework

The Sponsor also proposes to consider the PK comparability studies conducted by other manufacturers who developed the YpsoMate AI device platform. [REDACTED]

[REDACTED] The majority of those SC mAb formulations can be administered with either a PFS or an AI. Available results from PK comparability/BE studies [REDACTED] support interchangeability between manual and AI injection and a supportive tolerability profile for both injection methodologies has been demonstrated.

It is of note that while the likelihood that these PK comparability studies have been conducted with the YpsoMate AI is high, most of the respective publications do not specify the AI type used in the trial. [REDACTED]

[REDACTED] the mAbs types delivered with the YpsoMate AI include IgG1 and IgG2 isotypes (both kappa and lambda), classified as human, humanized, or chimeric. Injection volumes between 0.4 and 2 mL were evaluated in PK comparability studies using the YpsoMate AI, with active pharmaceutical ingredient (API) concentrations ranging from 30 to 180 mg/mL. Injection hold times ranged from 10 to 15 seconds. Formulation ingredients were diverse, spanning surfactants, buffers, salts, amino acids, and other stabilizers. Bioavailability values varied between 55% and 80%,

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with time to maximum concentration ($T_{\max}$) occurring between 1 and 28 days across mAbs.

The Sponsor proposes that for future applications of the MIDBA to the YpsoMate AI, mAbs with PK characteristics and formulation properties within this studied framework be considered for a waiver of a dedicated PK comparability study with the YpsoMate AI platform. MAb products with parameters outside this range should consult with the Agency to discuss MIDBA applicability on a case-by-case basis.

Modelling and simulation literature assessment

In addition to this descriptive molecule, PK and formulation framework for MIDBA for the YpsoMate AI platform, the Sponsor has been exploring the use of Modelling and Simulation (M&S) to support the formulation and PK space for the MIDBA, as recommended by the Agency during the QoNM procedure preparatory meeting. An in-depth literature search revealed several ongoing attempts to develop mechanistic models aimed at predicting the absorption of mAbs based on molecular, formulation, device and PK parameters. Three M&S approaches are commonly used to study SC absorption of biotherapeutics: (i) PK and population PK (popPK) models, (ii) physiologically based PK (PBPK) models, and (iii) physiologically based biopharmaceutics models (PBBM) ([Dubbelboer and Sjögren 2022](#)). These approaches are characterized by an increasing complexity:

- PK and popPK models are empirical. Absorption from the SC administration site into systemic circulation is usually summarized in a first or zero order rate constant, i.e., such rate constants combine drug spreading and mass transport in the SC interstitial space to the initial lymphatics as well as transport in the lymphatics into systemic circulation.
- PBPK models of SC absorption usually comprise the SC injection site, separated in interstitial, vascular and endosomal space (e.g., [Varkhede and Forrest 2018](#); [Stader et al. 2024](#)). The models describe the mass transfer of drug from SC interstitial space into lymphatics and subsequently into circulation and other tissues. Drug spreading and mass transport within the SC interstitial space to initial lymphatics is not addressed.
- PBBM may provide a mathematical framework on the SC delivery of drugs from the injection into SC interstitial space to lymphatic uptake ([Zheng et al. 2021](#); [Pepin et al. 2023](#); [de Lucio et al. 2024](#); [Rahimi et al. 2024](#)). Drug spreading and mass transport in the interstitial space can be described, including impact of administration mode e.g. by devices as well as impact of drug and formulation properties. PBBM can be linked to PBPK models for the description of drug disposition ([Zheng et al. 2021](#)).

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Commonly used PK and PBPK models do not allow detailed description of the events in the SC interstitial space following administration, such as plume formation, binding events or mass transport to initial lymphatics. Understanding of such events, however, would be needed to explore the formulation and PK space for the MIDBA in a mechanistic approach. PBBM would allow such detailed studies. However, currently available PBBM are exploratory models with limited validation against clinical data. Furthermore, there are knowledge gaps. For instance, data on biomechanical properties of human skin tissue are missing ([Zheng et al. 2021](#)), or there is uncertainty on the actual localization of absorbing initial lymphatics, which has relevant impact on actual modelling results ([de Lucio et al. 2024](#)). As stated by Rahimi and co-workers on their PBBM: "It should be noted, however, that these results are purely computational and based on the known mechanisms that we introduced in this paper. More experiments are needed to fully validate the results"([Rahimi et al. 2024](#)).

Due to the relatively immature nature of PBBM and the missing coverage of events in SC interstitial tissue in PBPK models, the Sponsor proposes to anchoring the MIDBA on the current PK comparability studies as outlined above to bracket the formulation and PK space for the MIDBA. Moreover, the descriptive framework on PK and physicochemical formulation characteristics is proposed to guide the Agency in granting a waiver for a dedicated PK comparability study.

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

3. General assessment of eligible mAbs formulation physicochemical space for MIDBA – YpsoMate AI

In this section, the Sponsor discusses how and whether the formulation physicochemical space could impact comparability between manual injection and injection with an AI platform. Focus is on parameters that might impact the absorption profile of a mAb that in addition would translate in clinically relevant differences in the PK profile and bioavailability.

It is of note that to be eligible for the MIDBA approach, the formulation, including the concentration of all ingredients, needs to be the same with manual and automated injection. Consequently, the Sponsor does not expect differences in the solubility in the subcutaneous tissue nor in the movement to the lymphatic system that might be impacted when comparing the same mAb in formulations with different composition.

From the Sponsor's perspective, formulation parameters that could impact functionality of the injection device comprise viscosity of the dosing solution as well as the overall injection volume. This aspect is accounted for by testing a possible effect of these parameters on device performance in the technical development program of the device platform. In addition, clinical PK comparability data for the YpsoMate AI are available across a range of dosing volumes and viscosities within the operational ranges of the

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device and further support the comparability of this AI platform with manual injection across a range of volumes and viscosities. Other formulations physicochemical parameters such as osmolality, pH, or pI are not expected to impact functionality of the injection device.

4. Safety and local tolerability from the eligible mAb's clinical development program and from the PK comparability studies with omalizumab and gantenerumab with the YpsoMate 2.25 AI

Introducing a novel AI platform as an alternative to manual injection via PFS or HHS is not expected to impact the systemic safety profile of the mAb.

To qualify for the MIDBA, data on the local tolerability profile of a mAb following manual SC administration using PFS or HHS is required from previous clinical trials. This data should encompass injection volumes that cover the range of injection volumes foreseen to be delivered with the YpsoMate AI platform. The database is complemented by the comparative tolerability profile for manual versus automated injection from the BE studies with the reference mAbs omalizumab and gantenerumab.

In the BE trial with omalizumab in healthy adults ([Sangana et al. 2024](#)), administration of 300 mg/2 mL either in the AI platform or in a PFS-NSD was safe and generally well tolerated. There were no deaths or subject discontinuation due to AEs or AEs of special interest reported in the study. One subject experienced an SAE of appendicitis considered unrelated to study drug. Injection site reactions (e.g., induration, pain, erythema, hemorrhage, swelling, discomfort, bruising, hypoesthesia, edema, pruritus) were observed in 24% (16/66) of subjects treated with the autoinjector compared with 14% (9/64) of subjects treated with the prefilled syringe. All AEs were mild or moderate in severity with the exception of one event of appendicitis which was severe and assessed unrelated to study drug. There were no clinically relevant treatment-related trends noted in the vital sign measurements, clinical laboratory parameters, or ECG data in this study.

Similarly, in the BE study with gantenerumab [REDACTED], administration via both the YpsoMate 2.25 AI platform (255 mg/1.77 mL) and HHS (255 mg/1.7 mL) was generally safe and well tolerated in a group of healthy male and female participants. Injection reactions were reported by 40.7% of the participants after a single 255 mg dose of gantenerumab YpsoMate 2.25 AI and by 27.5% of the participants after a single 255 mg dose of gantenerumab HHS. All of the injection reactions were judged as related to study drug injection; the majority were mild in severity and resolved within 1 day of study drug administration without sequelae. No new safety concerns were observed with the AI platform.

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The injection depth following manual injection with an HHS or PFS by different healthcare professionals varies by each injection as compared to automated injection with the AI platform ([Hu et al. 2020](#)). Consequently, any tolerability findings associated with different injection depths would be reflected in the overall local tolerability profile from the supporting clinical trial data studies with HHS injection.

Overall, assuming a favorable safety database for eligible new mAbs and considering the tolerability profile of the YpsoMate 2.25 AI platform for gantenerumab and omalizumab, the Sponsor expects that the overall safety and tolerability profile of eligible mAbs will not be negatively affected with the introduction of the AI platform.

5. Subcutaneous injection sites qualified with manual injection via HHS/PFS in pivotal clinical trials for eligible mAb

Considering the observed injection-site-dependent PK for a number of mAbs ([Zou et al. 2021](#)), the Sponsor proposes that for mAbs applying the MIDBA, only injection sites that are permitted for PFS or HHS injection (abdomen, upper arm or thigh) based on clinical trial data would be eligible for use with the YpsoMate AI platform.

6. 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

The capabilities of the intended user to apply the AI platform are expected to depend on the user population (i.e., healthcare providers, patients) and not on the specific mAb administered. Therefore, the proposed MIDBA will be complemented with the technical development (analytical comparability, formulation characterization) and human factors usability data specific to the eligible mAb-device integral combination product in accordance with its intended use environment.

In future filing dossiers for combination products with YpsoMate AI drug delivery device, the Sponsor proposes to provide a complete design verification and validation technical package, including a summative human factors study, for the mAb combination product's intended use in the representative target patient and user populations. The Sponsor believes the combination of the clinical qualification and the design verification and validation technical package will be adequate to support a future regulatory submission for the integral drug-AI combination products with eligible new mAbs.

[REDACTED]

[REDACTED]

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8. REFERENCES

8.1 LITERATURE REFERENCES

[REDACTED]

Bruin G, Hockey HU, La Stella P, Sigurgeirsson B, Fu R, Patekar M, Charef P, Woessner R, Boutouyrie - Dumont B. Comparison of pharmacokinetics, safety and tolerability of secukinumab administered subcutaneously using different delivery systems in healthy volunteers and in psoriasis patients. British journal of clinical pharmacology. 2020;86(2):338-51.

[REDACTED]

[REDACTED]

de Lucio M, Leng Y, Wang H, Vlachos PP, Gomez H. Modeling drug transport and absorption in subcutaneous injection of monoclonal antibodies: Impact of tissue deformation, devices, and physiology. Int J Pharm. 2024;661:124446.

[REDACTED]

Drugs.Com .“How Long before Xolair Starts Working?” Available from: www.drugs.com/medical-answers/long-before-xolair-starts-working-3545752/#:~:text=The%20dosage%20of%20Xolair%20is,to%208%20days%20after%20administration. Accessed 10 May 2024.

[REDACTED]

Dubbelboer IR, Sjögren E. Physiological based pharmacokinetic and biopharmaceutics modelling of subcutaneously administered compounds - An overview of in silico models. Int J Pharm. 2022;621:121808.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Hu P, Wang J, Florian J, Shatzer K, Stevens AM, Gertz J, Ji P, Huang SM, Zineh I, Wang YM. Systematic review of device parameters and design of studies bridging biologic-device combination products using prefilled syringes and autoinjectors. The AAPS Journal. 2020;22:1-9.

Jain M, Doughty D, Clawson C, Li X, White N, Agoram B, van der Merwe R. Tralokinumab pharmacokinetics and tolerability when administered by different subcutaneous injection methods and rates. International Journal of Clinical Pharmacology and Therapeutics. 2017;55(7):606.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Lambert WJ. Why Do the majority of submissions for bridging from a prefilled syringe to an autoinjector include bioequivalence studies in order to demonstrate comparability?. The AAPS Journal. 2020;22(3):72.

Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. Journal of Pharmaceutical Sciences. 2004;93(11):2645-68.

[REDACTED]

Pepin XJH, Grant I, Wood JM. SubQ-sim: a subcutaneous physiologically based biopharmaceutics Model. Part 1: the injection and system parameters. Pharm Res. 2023;40:2195–2214.

Portron A, Jordan P, Draper K, Muenzer C, Dickerson D, van Iersel T, Hofmann C. A phase I study to assess the effect of speed of injection on pain, tolerability, and pharmacokinetics after high-volume subcutaneous administration of gantenerumab in healthy volunteers. Clinical Therapeutics. 2020;42(1):108-20.

[REDACTED]

Rahimi E, Li C, Zhong X, Shi GH, Ardekani AM. The role of initial lymphatics in the absorption of monoclonal antibodies after subcutaneous injection. Comput Biol Med. 2024;183:109193.

[REDACTED]

[REDACTED]

Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. CPT: pharmacometrics & systems pharmacology. 2017;6(9):576-88.

Sangana R, Xu Y, Shah B, Tian X, Zack J, Shakeri - Nejad K, Kalluri S, Jones I, Ligueros - Saylan M, Taylor AF, Jain DK. Bioequivalence Between a New Omalizumab Prefilled Syringe With an Autoinjector or with a Needle Safety Device Compared with the Current Prefilled Syringe: A Randomized Controlled Trial in Healthy Volunteers. Clinical Pharmacology in Drug Development. 2024 Feb 22.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Stader F, Liu C, Derbalah A, Momiji H, Pan X, Gardner I, Jamei M, Sepp A. A physiologically based pharmacokinetic model relates the subcutaneous bioavailability of monoclonal antibodies to the saturation of FcRn-mediated recycling in injection-site-draining lymph nodes. Antibodies (Basel). 2024;13(3):70.

[REDACTED]

Tsumura K, Hsu W, Mimura M, Horiuchi A, Shiraki K. Lowering the viscosity of a high-concentration antibody solution by protein–polyelectrolyte complex. Journal of bioscience and bioengineering. 2022;133(1):17-24.

Qualification Procedure: Molecule-Independent Device Bridging Approach — Roche Registration GmbH

US Food and Drug Administration. Bridging for drug-device and biologic-device combination products. Guidance for Industry. 2019. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bridging-drug-device-and-biologic-device-combination-products>. Accessed 20 May 2024.

Varkhede N, Forrest ML. Understanding the monoclonal antibody disposition after subcutaneous administration using a minimal physiologically based pharmacokinetic model. J Pharm Pharm Sci. 2018;21(1s):130s-148s.

Wang Y, Zheng C, Zhuang C, Fu Q, Zhang B, Bian Y, Qi N, Zhu J. Characterization and pre-clinical assessment of a proposed biosimilar to its originator omalizumab. European Journal of Pharmaceutical Sciences. 2022;178:106292.

XOLAIR® PFS (150 mg) Safety Data Sheet Version 1.1. Revised 11-08-2022.

XOLAIR® (omalizumab) US Prescribing Information. Revised 2/2024.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Zheng F, Hou P, Corpstein CD, Park K, Li T. Multiscale pharmacokinetic modeling of systemic exposure of subcutaneously injected biotherapeutics. J Control Release. 2021;337:407-416.

Zou P, Wang F, Wang J, Lu Y, Tran D, Seo SK. Impact of injection sites on clinical pharmacokinetics of subcutaneously administered peptides and proteins. Journal of Controlled Release. 2021;336:310-21.

8.2 SPONSOR CLINICAL STUDY REPORTS

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Qualification Procedure: Molecule-Independent Device Bridging Approach — Roche Registration GmbH

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