Module 1: Example of Assessment Table: Addition of Fixed Dosing to Approved mg/kg Label Regimen

Expert Working Group: ICH M15 General Principles for Model-Informed Drug Development

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Module Overview

- Prereading Recommendations
- Purpose of This Example
- Example Notes
- Illustrative Example
- References and Resources

Please note: This example is provided in both a Word document format and a PowerPoint slide format for clarity and to accommodate different uses (e.g., training presentations); the content in both versions is identical.

Prereading Recommendations

- Before starting this module, it is recommended that learners are familiar with the ICH M15 Guideline, including the following:
  - Key concepts for the assessment of Model-Informed Drug Development (MIDD) evidence (see ICH M15 Guideline Section 2).
  - The structure and content of the table for assessment of MIDD evidence (hereafter “assessment table”) (see ICH M15 Guideline Section 2 and Appendix 1).
  - The elements of model evaluation and related general recommendations (see ICH M15 Guideline Section 3)
  - General recommendations for documentation of MIDD planning and evidence reporting and submissions related to the assessment table (see ICH M15 Guideline Section 4.3)

Purpose of This Example

- This simplified illustrative example using a single modelling and simulation (M&S) method demonstrates the concepts, type of content, and level of detail in a completed assessment table.
- This is an example of how the assessment table might be completed by a drug developer to support submission to regulatory authorities along with appropriate model analysis plans (MAPs), model analysis reports (MARs), and other regulatory documentation.
- The example is not intended to limit the M&S methods, approaches, or types of questions of interest. Its purpose is to explain the concepts and illustrate the thought process involved in completing the table.
- The MIDD strategy and results illustrated in this example should not be interpreted as representing regulatory standards, positions, or expectations and do not imply that any specific methodology or interpretation would be accepted by regulators.
- Ratings are provided only to illustrate a potential scenario. For all items rated low, medium, or high, appropriate justification is expected and essential to support the assessment.
- Background information, item definitions, instructions, or additional notes are included solely for context and should not be included in a submission table.

Example Notes

The following bullets summarise high-level points of consideration for this example. These points are expanded upon in the subsequent slides.

- Question of Interest: Could a fixed-dose regimen provide similar efficacy and safety to the approved mg/kg dosing and therefore be an alternative dosing option in the drug label?
- Development Strategy: Post-approval of the mg/kg dosing.
- M&S Method Being Evaluated in this Example: Population pharmacokinetics (popPK).
- Model Risk: Medium.
- Model Impact: High.

Additional Notes:

1. In this simplified illustrative example, popPK is the single M&S method used to generate MIDD evidence. It is recognised that other modelling approaches, such as modelled exposure-response relationships, may also be used or needed to address this question of interest.
2. Model risk should be interpreted in the context of answering a specific question of interest and is not to be perceived as a risk intrinsic to MIDD or M&S.

Example of Assessment Table: Addition of Fixed Dosing to Approved mg/kg Label Regimen

Regulatory Background [1]

- Indication: Treatment of chronic disease in adults.
- Approved Dosing Regimen: Intravenous administration at 4 mg/kg every 4 weeks.
- Justification for an Alternative Dosing Regimen: The development team is proposing a MIDD strategy to support regulatory approval of a fixed-dose regimen (defined as a single dose across all body weight range or body weight-tiered dose regimen[2]) that provides efficacy and safety comparable to the approved mg/kg dosing.

  This approach is motivated by clinical practice, which indicates that a fixed-dose regimen could be more practical for intravenous administration than the current mg/kg–based dosing and may also reduce the risk of dose calculation errors.
- Current Regulatory Standards: Typically, a clinical study is required to include a new dosing regimen on the label. However, regulators are open to alternative approaches that leverage existing data.
- Current Regulatory Status: In this case, MIDD evidence has already been generated, so the table is for the submission stage rather than the planning stage. To date, there has been no interaction between the drug developer and regulators regarding the MIDD strategy for this question of interest.

[1] This content is provided to contextualise the example. In practice, this source information and the table should be included in the most appropriate section(s) of the respective regulatory documentation (e.g., regulatory interaction background materials, Common Technical Document sections) in line with the question of interest. Refer to the Guideline for additional information. For simplicity, the specific disease indication and the drug's mechanism of action are not defined.

[2] For simplicity, the selection of the recommended dosing regimen is not discussed in this example.

Clinical Background (1) [1]

- Clinical Development Program:
  - Only mg/kg doses were evaluated during clinical development.
  - Phase I: Healthy volunteers with rich pharmacokinetic (PK) sampling following single doses 4 mg/kg and up to 12 mg/kg.
  - Phase II: Dose-ranging study (1, 2, 4, and 8 mg/kg every 4 weeks [Q4W]) with sparse PK sampling over 16 weeks.
  - Phase III: Two confirmatory studies with 4 mg/kg Q4W with sparse PK sampling for 16 weeks.
- Pharmacokinetics:
  - PopPK model developed using PK data from Phase I–III.
  - Linear PK across the tested dose range.
  - Body weight was the only significant covariate.

[1] This content is provided to contextualise the example. In practice, this source information and the table should be included in the most appropriate section(s) of the respective regulatory documentation (e.g., regulatory interaction background materials, Common Technical Document sections) in line with the question of interest. Refer to the Guideline for additional information. For simplicity, the specific disease indication and the drug's mechanism of action are not defined.

Clinical Background (2) [1]

- Clinical Dose/Exposure-Efficacy Evidence:
  - In Phase II study, the observed efficacy begins to flatten at 2 mg/kg and reaches a plateau at 4 mg/kg.
  - In Phase II, steady-state area under the concentration-time curve (AUC_{ss}) was identified as the PK parameter most strongly associated with efficacy, and a AUC_{ss} target range was identified within which the response difference is not considered clinically meaningful.
  - In Phase II, increasing doses resulted in a higher proportion of patients achieving this target AUC_{ss} range, with approximately 70% of the patients achieving it at a 1 mg/kg dose, 95% at 2 mg/kg, and 100% at 4 mg/kg.
  - Based on these findings, the 4 mg/kg dose was selected for Phase III and its efficacy, as well as the AUC_{ss} range, was subsequently confirmed in Phase III.

[1] This content is provided to contextualise the example. In practice, this source information and the table should be included in the most appropriate section(s) of the respective regulatory documentation (e.g., regulatory interaction background materials, Common Technical Document sections) in line with the question of interest. Refer to the Guideline for additional information. For simplicity, the specific disease indication and the drug's mechanism of action are not defined.

Clinical Background (3) [1]

- Clinical Dose/Exposure-Safety Evidence:
  - No serious adverse events (AEs) were observed during clinical development.
  - The most common AE (~10%) was mild, transient infusion-related reactions (e.g., fever, chills). These events were correlated with steady-state maximum concentration ($C_{max,ss}$). Increasing doses were associated with higher $C_{max,ss}$ and a higher incidence of infusion-related reactions, with 5% of patients experiencing them at 4 mg/kg and 10% at 8 mg/kg.
  - The $C_{max,ss}$ target range associated with an acceptable safety profile (defined as <10% incidence of infusion-related reactions) was based on the exposure achieved at the 4 mg/kg dose in Phase II and III.

[1] This content is provided to contextualise the example. In practice, this source information and the table should be included in the most appropriate section(s) of the respective regulatory documentation (e.g., regulatory interaction background materials, Common Technical Document sections) in line with the question of interest. Refer to the Guideline for additional information. For simplicity, the specific disease indication and the drug's mechanism of action are not defined.

Example Table Orientation

- The following slides present an illustrative example highlighting one way the assessment table could be completed in this scenario.
- The first slides show the completed table in its entirety, and subsequent slides present each row of the table individually.
- Blue ribbons present item definitions and instructions, as described in Section 2 and Appendix 1 of the ICH M15 Guideline, and blue clouds provide additional notes to clarify why the indicated table entry text was chosen.
- The information in the blue ribbons and clouds is included for your information only and should not be included in the version of the assessment table provided to regulatory authorities.

Full Example Assessment Table (1) [3]

Page 1

Item	Entry
Key Assessment Elements	
Question of Interest	Could a fixed-dose regimen provide similar efficacy and safety to the approved mg/kg dosing and therefore be an alternative dosing option in the drug label?

Context of Use	**Description of the Model and Data Used**
	• PopPK model previously developed using rich PK data from Phase I studies and sparse PK samples from Phase II and Phase III studies (<<reference to PopPK Report>>).
	  ○ All studies used mg/kg dosing.
	  ○ Body weight was identified as the only relevant covariate influencing clearance and volume of distribution (consistent with allometric principles).
	  ○ PK dataset fully covered the expected body-weight range in the target population.
	Role and Scope of the Model
	• Simulation of steady-state exposure metrics (AUC_{ss} and $C_{max,ss}$) following either a mg/kg dosing regimen or a fixed-dose regimen across a body-weight range representative of the target population.
	• Comparison of simulated PK exposures with Phase III exposure values associated with the desired efficacy and acceptable safety profiles, as determined during the clinical development program (described below), to quantify the impact of switching from mg/kg dosing to fixed dosing and to support the selection of a fixed-dose suitable for labelling without requiring additional clinical studies.
	Additional Data or Evidence Informing the Question of Interest
	The Phase II dose-ranging study and the 2 successful Phase III studies (<<reference CSRs>>) provide clinical evidence that:
	• AUC_{ss} is the PK parameter most strongly associated with efficacy, and the AUC_{ss} target range associated with Phase III efficacy was identified.
	• No serious AEs were observed across the evaluated PK exposure range during drug development, only mild AEs were reported.
	• $C_{max,ss}$ is the PK parameter associated with the occurrence of these mild AEs, and the $C_{max,ss}$ exposure range associated with acceptable safety profile in Phase III has been identified.
	• Efficacy and safety data beyond target dose and exposure were collected, and the evidence is described in detail in the initial submission (<<reference pervious submission>>).

Model Influence	**Medium** The adequacy of the proposed fixed dose is based on the clinical efficacy and safety over a wide range of doses/exposures, as specified in the context of use, and the population PK model-based simulations. Because both pieces of evidence contribute significantly to answering the question of interest, the overall influence of the model on decision-making is considered medium.

Page 2

Item	Entry

Consequence of Wrong Decision	**Medium**
	A wrong decision in this scenario would be selecting a fixed dose that would either underexpose or overexpose patients.
	• **Efficacy:**
	  ○ In Phase II, at exposures 50% of the Phase III exposure, 95% of patients remained within the target efficacy range.
	  ○ Therefore, underexposures of ≤50% are not expected to lead to a loss of efficacy. Underexposures >50% may result in loss of efficacy, but this magnitude of error is considered unlikely with a change from mg/kg to fixed dosing.
	  ○ From an efficacy standpoint, the consequence of wrong decision is considered to be low.
	• **Safety:**
	  ○ In Phase II, exposures were explored up to 100% higher than those observed in Phase III with no serious AEs observed. Therefore, overexposure is unlikely to result in safety concerns. However, limited Phase II data at the higher exposure ranges leave some residual uncertainty regarding potential, infrequent serious AEs.
	  ○ Therefore, it cannot be excluded that overexposure might lead to clinically important safety consequences. However, the specific risks are unknown and considered unlikely, as no serious AEs were observed across the evaluated PK exposure range during drug development; only mild AEs were reported.
	  ○ From a safety standpoint, the consequence of wrong decision is considered to be medium.
	Overall assessment: Considering both the likelihood and potential severity of negative effects of a wrong decision, for efficacy and safety, its overall consequence is rated as medium.

Model Risk	**Medium** The model risk is considered medium as both the model influence and consequence of wrong decision are medium.
Model Impact	**High** The regulatory standard for adding a fixed-dose regimen as an alternative to the approved mg/kg dosing is a clinical study that would answer the question of interest. Given that the proposed MIDD strategy does not involve conducting a clinical study, the model impact is rated as high.

[3] The 4 pages of Figure 1 show the completed table in its entirety, and subsequent pages present each row of the table individually.

Full Example Assessment Table (2) [3]

Page 3

Item	Entry
Additional Considerations for Interaction with Regulators and to Inform Decision-making	
Technical Criteria	**Rationale** • Weight was the only relevant covariate in the popPK model. • The transition from mg/kg dosing to fixed dosing was expected to have the greatest influence for the patients at the highest and lowest ends of the body-weight distribution. • Accordingly, key technical criteria for model evaluation and model outcomes were designed to assess AUC_{ss} and $C_{max,ss}$ across the full body-weight range representative of the target population, with particular attention to the highest and lowest body-weight values. This was implemented in the simulations by using body-weight categories and by ensuring adequate representation of the body-weight distribution. **Technical Criteria for Model Evaluation** • To pass the evaluation, the model was evaluated across body-weight categories and other relevant factors to ensure accurate description and prediction of PK profiles across the full range of body weights in the target population, including but not limited to goodness-of-fit plots and visual predictive checks. Refer to the MAP for additional criteria and full detail on the model evaluation. ○ The model was required not to underpredict or overpredict exposures across the body-weight range, and both central tendency and variability were required to be well captured. ○ The appropriate characterization and level of uncertainty to allow for simulations were required to be demonstrated. **Technical Criteria for Model Outcomes Evaluation** • Simulated body weights were required to be representative of the distribution in the target population. In particular, there was sufficient representation at the highest and lowest aspects of the distribution. • Model outcomes were evaluated by assessing whether simulated AUC_{ss} for fixed dosing remained sufficiently close to the Phase III AUC_{ss} target range and whether simulated $C_{max,ss}$ remained sufficiently close to the Phase III $C_{max,ss}$ target range, applying the following limits: ○ Across the population body-weight range with particular attention to the **high** body-weight values, the lower percentile (Xth) of the simulated AUC_{ss} for fixed dosing was required to be no more than Y% **below** the AUC_{ss} target range. ○ Across the population body-weight range with particular attention to the **low** body-weight values, the upper percentile (Jth) of the simulated $C_{max,ss}$ for fixed dosing was required to be no more than K% **above** the $C_{max,ss}$ target range. ○ Refer to the MAP for additional criteria and full details on the model outcome evaluation.

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Item	Entry
Appropriateness of Proposed MIDD	Given that efficacy and safety are well characterized over a wide range of doses for the mg/kg dose and given the clinical exposure-response evidence, demonstration of PK matching between fixed and body-weight dosing would support their interchangeability. For this purpose, the proposed popPK model, once determined to satisfactorily meet the model evaluation and technical criteria (see technical criteria row above), may be considered as robust as a dedicated PK comparability study. Given the medium model risk, technical criteria for model evaluation were defined to ensure that the model accurately describes the central tendency and variability of PK across body-weight categories, supported by the results, including but not limited to goodness-of-fit diagnostics and visual predictive checks. Technical criteria for model outcomes were defined to ensure that simulated exposures for the fixed-dose regimen are representative of the target population and remain sufficiently close to the AUC_{ss} and $C_{max,ss}$ target established using data from mg/kg dosing, with particular attention to extremes of body weight. While the model impact is considered high (i.e., in the absence of a clinical study [e.g., a dedicated PK comparability study] that would typically be expected by regulators), the proposed MIDD approach was anticipated, if adequately implemented, to provide a scientifically sufficient level of evidence to support regulatory decision-making, based on the establishment of the model ability to predict exposures across the target population.
Evaluation of Model(s) and Model Outcomes	The comprehensive model evaluation confirmed that the model adequately describes the observed data with acceptable performance and robustness. Additionally, the population PK model satisfied the predefined technical criteria for both model performance and model-based outcome simulations. No issues were identified that limit its utility for the intended purpose. **Evaluation of Model(s)** Across the full body-weight range, results including but not limited to goodness-of-fit diagnostics and body weight–stratified visual predictive checks showed that observed PK profiles were well described. There was no evidence of systematic bias across the body-weight range, and both central tendency and variability in concentrations were adequately predicted. This confirms that the model provides reliable predictions over the intended body weight spectrum (see MAP for full details). **Evaluation of Model Outcomes** The simulated body-weight distribution closely matched that of the target population, including sufficient representation at the extremes. Under the fixed dosing regimen, simulated AUC_{ss} and $C_{max,ss}$ remained close to the Phase III exposure target ranges across body weights, as per the predefined percentile and margin criteria (see technical criteria item above and MAP for full details). Overall, these findings demonstrate that the model is robust and that the resulting exposure simulations under fixed dosing are consistent with the Phase III targets across the full body-weight range.
Outcome of the MIDD Evidence Assessment	Based on an overall assessment across the elements described above, the MIDD activities have confirmed that the model outcomes constitute MIDD evidence specific to the question of interest and support a fixed-dose regimen as an alternative to weight-based (mg/kg) dosing in the drug label. This conclusion integrates the medium model risk and high model impact, acknowledging that a dose regimen change in the label would traditionally require clinical data. This outcome is supported by clinical efficacy and safety data over a wide range of doses, the clinical exposure-response evidence, meeting the technical criteria that confirmed the robustness of the popPK model, and the close alignment of simulated exposures (AUC_{ss} and $C_{max,ss}$) with the target exposure.

[3] The 4 pages of Figure 1 show the completed table in its entirety, and subsequent pages present each row of the table individually.

Question of Interest

Definition: The question that MIDD is intended to answer.

Instruction: Explicitly state the question of interest. This should reflect and inform multidisciplinary assessments and regulatory decision-making.

Additional Notes: In this case, the question of interest is broader than the intended use of the model.

Item	Entry
Question of Interest	Could a fixed-dose regimen provide similar efficacy and safety to the approved mg/kg dosing and therefore be an alternative dosing option in the drug label?

Context of Use (1)

Definition: The role and scope of the model(s) used to answer the question of interest.

Instruction: Provide a concise, clear, and explicit description of the model, its role and scope, and the data used to build the model. In addition, discuss any additional data or evidence that will inform the answer to the question of interest.

Item	Entry
Context of Use	**Description of the Model and Data Used** • PopPK model previously developed using rich PK data from Phase I studies and sparse PK samples from Phase II and Phase III studies (<<reference to PopPK Report[4]>>). ○ All studies used mg/kg dosing. ○ Body weight was identified as the only relevant covariate influencing clearance and volume of distribution (consistent with allometric principles). ○ PK dataset fully covered the expected body-weight range in the target population.

[4] For this example, a summary of this information is provided in the background information. In a real-world setting, this would be provided in additional materials such as the PopPK Report and CSRs.

Context of Use (2)

Item	Entry
Context of Use	**Role and Scope of the Model** • Simulation of steady-state exposure metrics (AUC_{ss} and $C_{max,ss}$) following either a mg/kg dosing regimen or a fixed-dose regimen across a body-weight range representative of the target population. • Comparison of simulated PK exposures with Phase III exposure values associated with the desired efficacy and acceptable safety profiles, as determined during the clinical development program (described below), to quantify the impact of switching from mg/kg dosing to fixed dosing and to support the selection of a fixed-dose suitable for labelling without requiring additional clinical studies. **Additional Data or Evidence Informing the Question of Interest** The Phase II dose-ranging study and the 2 successful Phase III studies (<<reference clinical study reports [CSRs][4]>>) provide clinical evidence that: • AUC_{ss} is the PK parameter most strongly associated with efficacy, and the AUC_{ss} target range[5] associated with Phase III efficacy was identified. • No serious AEs were observed across the evaluated PK exposure range during drug development, only mild AEs were reported. • $C_{max,ss}$ is the PK parameter associated with the occurrence of these mild AEs, and the $C_{max,ss}$ exposure range[5] associated with acceptable safety profile in Phase III has been identified. • Efficacy and safety data beyond target dose and exposure were collected, and the evidence is described in detail in the initial submission (<<reference previous submission>>).

[4] For this example, a summary of this information is provided in the background information. In a real-world setting, this would be provided in additional materials such as the PopPK Report and CSRs.

[5] The numerical value of the range should be specified if it has been determined.

Model Influence

Definition: The intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence.

Instruction: Describe the model influence; rate it as low, medium, or high; and provide a justification for the rating.

Additional Notes: The rating of model influence depends on the relative contribution of MIDD and non-MIDD evidence to the overall decision. In this case, both MIDD evidence and clinical study data contribute significantly to the decision-making process and, therefore, the model influence is medium.

Item	Entry
Model Influence	**Medium** The adequacy of the proposed fixed dose is based on the clinical efficacy and safety over a wide range of doses/exposures, as specified in the context of use, and the population PK model-based simulations. Because both pieces of evidence contribute significantly to answering the question of interest, the overall influence of the model on decision-making is considered medium.

Consequence of Wrong Decision

Definition: The potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information.

Instruction: Describe the consequence of a wrong decision; rate it as low, medium, or high; and provide a justification for the rating.

Item	Entry
Consequence of Wrong Decision	**Medium** A wrong decision in this scenario would be selecting a fixed dose that would either underexpose or overexpose patients. • **Efficacy:** ○ In Phase II, at exposures 50% of the Phase III exposure, 95% of patients remained within the target efficacy range. ○ Therefore, underexposures of ≤50% are not expected to lead to a loss of efficacy. Underexposures >50% may result in loss of efficacy, but this magnitude of error is considered unlikely with a change from mg/kg to fixed dosing. ○ From an efficacy standpoint, the consequence of wrong decision is considered to be low. • **Safety:** ○ In Phase II, exposures were explored up to 100% higher than those observed in Phase III with no serious AEs observed. Therefore, overexposure is unlikely to result in safety concerns. However, limited Phase II data at the higher exposure ranges leave some residual uncertainty regarding potential, infrequent serious AEs. ○ Therefore, it cannot be excluded that overexposure might lead to clinically important safety consequences. However, the specific risks are unknown and considered unlikely, as no serious AEs were observed across the evaluated PK exposure range during drug development; only mild AEs were reported. ○ From a safety standpoint, the consequence of wrong decision is considered to be medium. **Overall assessment:** Considering both the likelihood and potential severity of negative effects of a wrong decision, for efficacy and safety, its overall consequence is rated as medium.

Model Risk

Definition: The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.

Instruction: The model risk is derived by combining model influence and consequence of wrong decision. Describe the model risk; rate it as low, medium, or high; and provide a justification for the rating.

Additional Notes: Model risk should be interpreted in the context of answering a specific question of interest and is not to be perceived as a risk intrinsic to MIDD or M&S.

Item	Entry
Model Risk	**Medium** The model risk is considered medium as both the model influence and consequence of wrong decision are medium.

Model Impact

Definition: The extent to which the proposed MIDD strategy varies from regulatory standards, or expectations when no regulatory standard is in place, for answering the question of interest.

Instruction: Describe the model impact; rate it as low, medium, or high; and provide a justification for the rating.

Additional Notes: The level of model impact is determined by how much the MIDD-based approach deviates from this regulatory standard (i.e., conducting a clinical study) and is, therefore, rated as high.

Item	Entry
Model Impact	**High** The regulatory standard for adding a fixed-dose regimen as an alternative to the approved mg/kg dosing is a clinical study that would answer the question of interest. Given that the proposed MIDD strategy does not involve conducting a clinical study, the model impact is rated as high.

Technical Criteria (1)

Definition: Key criteria for evaluating the model and model outcomes, and that are needed to inform MIDD evidence acceptance, contributing to the answer to the question of interest.

Instruction: Provide a clear and concise description of, and rationale for, the technical criteria, which are specific to the question of interest.

Additional Notes: Key technical criteria should be presented here; general technical standards are to be discussed in evaluation of model and model outcomes. When the model risk is higher, the technical criteria should be strengthened. In a high model-risk scenario, the margins for X, Y, J, and K would be expected to be set more conservatively and additional technical criteria may be necessary.

Item	Entry
Technical Criteria	<<See next slides>>

Technical Criteria (2) [6,7]

Item	Entry
Technical Criteria	**Rationale** • Weight was the only relevant covariate in the popPK model. • The transition from mg/kg dosing to fixed dosing was expected to have the greatest influence for the patients at the highest and lowest ends of the body-weight distribution. • Accordingly, key technical criteria for model evaluation and model outcomes were designed to assess AUC_{ss} and $C_{max,ss}$ across the full body-weight range representative of the target population, with particular attention to the highest and lowest body-weight values. This was implemented in the simulations by using body-weight categories and by ensuring adequate representation of the body-weight distribution. **Technical Criteria for Model Evaluation** • To pass the evaluation, the model was evaluated across body-weight categories and other relevant factors to ensure accurate description and prediction of PK profiles across the full range of body weights in the target population, including but not limited to goodness-of-fit plots and visual predictive checks. Refer to the MAP for additional criteria and full detail on the model evaluation. ○ The model was required not to underpredict or overpredict exposures across the body-weight range, and both central tendency and variability were required to be well captured. ○ The appropriate characterization and level of uncertainty to allow for simulations were required to be demonstrated.

[6] The technical criteria described here are used for illustrative purposes and not meant to be comprehensive; they are adapted to the simplified nature of this example.

[7] To avoid setting a precedent for other compounds or indications, no numerical thresholds are specified in these criteria. Specific values should be defined on a case-by-case basis based on the clinical exposure–response evidence and context.

Technical Criteria (3) [6,7]

Item	Entry
Technical Criteria	**Technical Criteria for Model Outcomes Evaluation** • Simulated body weights were required to be representative of the distribution in the target population. In particular, there was sufficient representation at the highest and lowest aspects of the distribution. • Model outcomes were evaluated by assessing whether simulated AUC_{ss} for fixed dosing remained sufficiently close to the Phase III AUC_{ss} target range and whether simulated $C_{max,ss}$ remained sufficiently close to the Phase III $C_{max,ss}$ target range, applying the following limits: ○ Across the population body-weight range with particular attention to the **high** body-weight values, the lower percentile (Xth) of the simulated AUC_{ss} for fixed dosing was required to be no more than Y% **below** the AUC_{ss} target range. ○ Across the population body-weight range with particular attention to the low body-weight values, the upper percentile (Jth) of the simulated $C_{max,ss}$ for fixed dosing was required to be no more than K% above the $C_{max,ss}$ target range. ○ Refer to the MAP for additional criteria and full details on the model outcome evaluation.

[6] The technical criteria described here are used for illustrative purposes and not meant to be comprehensive; they are adapted to the simplified nature of this example.
[7] To avoid setting a precedent for other compounds or indications, no numerical thresholds are specified in these criteria. Specific values should be defined on a case-by-case basis based on the clinical exposure–response evidence and context.

Appropriateness of Proposed MIDD (1)

Definition: The rationale for why the proposed MIDD is suitable to answer the question of interest.

Instruction: Provide a brief discussion of why and how the proposed MIDD is considered appropriate for answering the question of interest, taking into account aspects of the key assessment elements and including information on how the technical criteria are suitable to ensure the appropriateness.

Additional Notes: At the planning stage, this would be based on planned MIDD and provide considerations regarding principles as to why it is believed that it would be appropriate to answer the question of interest. This example is at the submission stage, at which time this element should provide a brief discussion based on completed MIDD with critical arguments being provided in the evaluation of model(s) and model outcomes, and outcome of the MIDD evidence assessment.

Item	Entry
Appropriateness of Proposed MIDD	<<See next slide>>

Appropriateness of Proposed MIDD (2)

Item	Entry
Appropriateness of Proposed MIDD	Given that efficacy and safety are well characterized over a wide range of doses for the mg/kg dose and given the clinical exposure-response evidence, demonstration of PK matching between fixed and body-weight dosing would support their interchangeability. For this purpose, the proposed popPK model, once determined to satisfactorily meet the model evaluation and technical criteria (see technical criteria row above), may be considered as robust as a dedicated PK comparability study. Given the medium model risk, technical criteria for model evaluation were defined to ensure that the model accurately describes the central tendency and variability of PK across body-weight categories, supported by the results, including but not limited to goodness-of-fit diagnostics and visual predictive checks. Technical criteria for model outcomes were defined to ensure that simulated exposures for the fixed-dose regimen are representative of the target population and remain sufficiently close to the AUC_{ss} and $C_{max,ss}$ target established using data from mg/kg dosing, with particular attention to extremes of body weight. While the model impact is considered high (i.e., in the absence of a clinical study [e.g., a dedicated PK comparability study] that would typically be expected by regulators), the proposed MIDD approach was anticipated, if adequately implemented, to provide a scientifically sufficient level of evidence to support regulatory decision-making, based on the establishment of the model ability to predict exposures across the target population.

Evaluation of Model(s) and Model Outcomes (1)

Definition: A brief discussion of the key results and conclusions of the technical evaluation of the model and model outcomes.

Instruction: Provide a concise summary of the technical evaluation of the model and model outcomes and describe how they fulfill the technical criteria.

Additional Notes: In the current example, the model meets all evaluation and model outcome criteria. However, there may be situations where some criteria are not fully met. This would not necessarily invalidate the use of the model. In such cases, the implications of unmet criteria should be carefully assessed, and a clear, scientifically sound justification should be provided to support the model's validity and its use for decision-making.

Item	Entry
Evaluation of the Model(s) and Model Outcomes	<<See next slide>>

Evaluation of Model(s) and Model Outcomes (2)

Item	Entry
Evaluation of the Model(s) and Model Outcomes	The comprehensive model evaluation confirmed that the model adequately describes the observed data with acceptable performance and robustness. Additionally, the population PK model satisfied the predefined technical criteria for both model performance and model-based outcome simulations. No issues were identified that limit its utility for the intended purpose. **Evaluation of Model(s)** Across the full body-weight range, results including but not limited to goodness-of-fit diagnostics and body weight–stratified visual predictive checks showed that observed PK profiles were well described. There was no evidence of systematic bias across the body-weight range, and both central tendency and variability in concentrations were adequately predicted. This confirms that the model provides reliable predictions over the intended body weight spectrum (see MAP for full details). **Evaluation of Model Outcomes** The simulated body-weight distribution closely matched that of the target population, including sufficient representation at the extremes. Under the fixed dosing regimen, simulated AUC_{ss} and $C_{max,ss}$ remained close to the Phase III exposure target ranges across body weights, as per the predefined percentile and margin criteria (see technical criteria item above and MAP for full details).[8] Overall, these findings demonstrate that the model is robust and that the resulting exposure simulations under fixed dosing are consistent with the Phase III targets across the full body-weight range.

[8] In a real-world case, it is encouraged to add numerical values in the comparison with the technical criteria.

Outcome of the MIDD Evidence Assessment

Definition: The multidisciplinary team's assessment and conclusion on whether the model outcomes are considered MIDD evidence.

Instruction: Provide a concise multidisciplinary assessment and conclusion of whether the model outcomes are considered MIDD evidence. This should integrate all of the assessment elements. Also provide a concise summary of the MIDD evidence related to the question of interest.

Item	Entry
Outcome of the MIDD Evidence Assessment	Based on an overall assessment across the elements described above, the MIDD activities have confirmed that the model outcomes constitute MIDD evidence specific to the question of interest and support a fixed-dose regimen as an alternative to weight-based (mg/kg) dosing in the drug label. This conclusion integrates the medium model risk and high model impact, acknowledging that a dose regimen change in the label would traditionally require clinical data. This outcome is supported by clinical efficacy and safety data over a wide range of doses, the clinical exposure-response evidence, meeting the technical criteria that confirmed the robustness of the popPK model, and the close alignment of simulated exposures (AUC_{ss} and $C_{max,ss}$) with the target exposure.

References & Resources

- ICH Guidelines, including M15, are available here: https://www.ich.org/page/ich-guidelines
- For any questions, please contact the ICH Secretariat: admin@ich.org