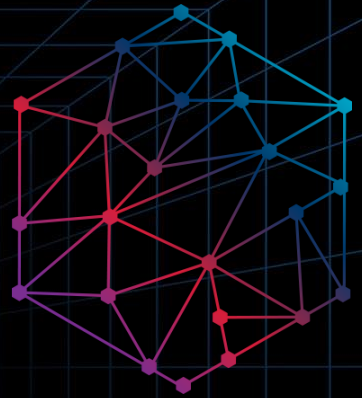
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Pharmacometrics in Phase 3 – Data Integration and Analysis to Support Dose and Labeling for the NDA

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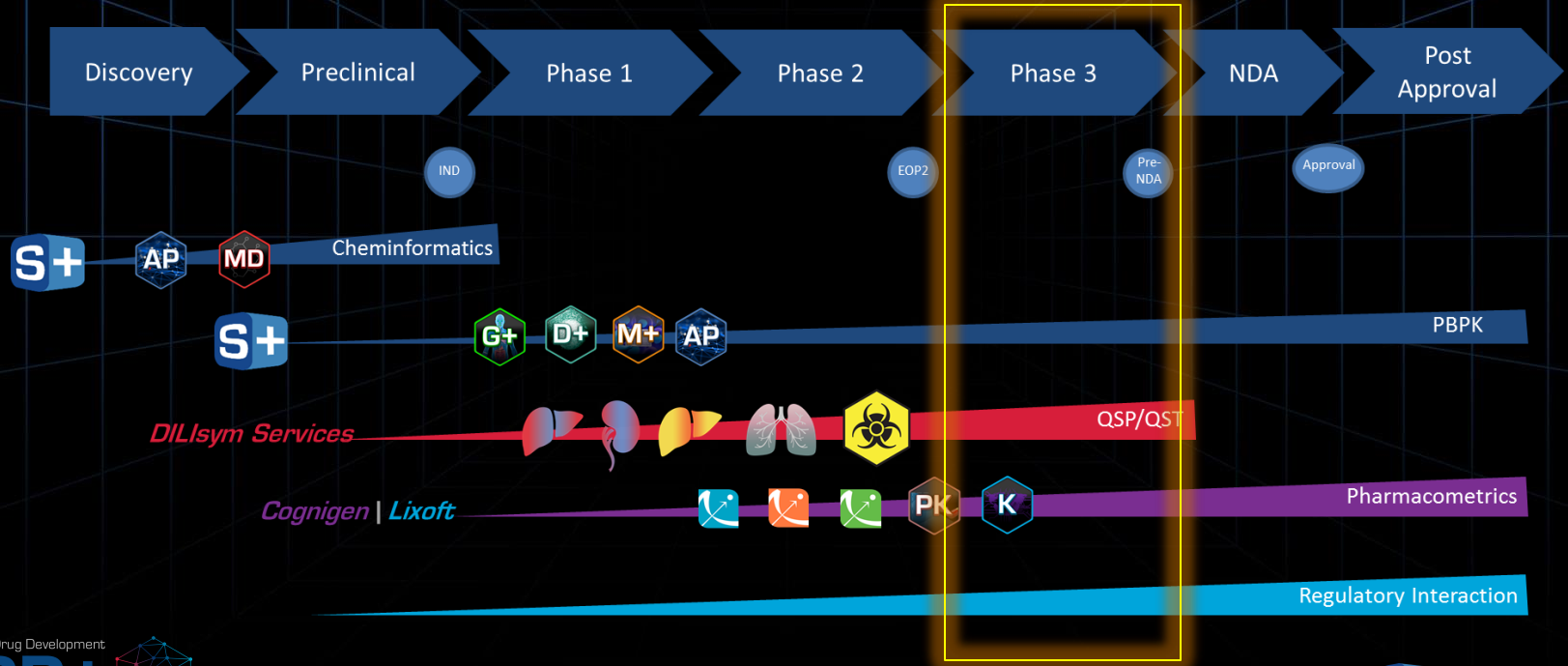
Phases of Drug Development



Characteristics of Phase 3?

- Phase 3 studies typically involve 300 to 3,000 participants from patient populations for which the medicine is eventually intended to be used.
- Participants are assigned to receive either the medication being evaluated or a control group that receives either the current standard of care treatment or a placebo.
- Phase 3 studies are designed to:
  - demonstrate whether or not a drug candidate offers a treatment benefit to a specific population
  - provide more detailed safety data, and
  - serve as the basis for product labeling
- Only 33% of drugs make it to Phase 3

End of Phase 3

- When one or more Phase 3 trials are complete, results examined and decide whether the drug has demonstrated effectiveness and an acceptable safety profile in treating a disease.
  - If so, a New Drug Application (NDA) can be submitted, which contains all of the data and information gathered at every stage of the process through the results of the Phase 3 clinical trial(s).

Role of Pharmacometrics in Phase 3

- Support label statements with respect to PK, efficacy, and safety
- Support dose recommendations and justification

Support From Regulatory Authorities

- Pop PK
  - Original FDA Guidance on Pop PK published in 1999, revised in 2019
  - EMA Guidance on Reporting Pop PK Analyses (2008)
- ER
  - ICH and FDA (2003) guidance for ER relationships
  - PMDA Guideline for Exposure-Response Analysis of Drugs 2020
    - https://www.pmda.go.jp/files/000235605.pdf

Data Integration

- Phase 3 sparse PK data are pooled with Phase 1 and 2 data for population PK analysis to:
  - Confirm PK characteristics in the intended patient population
  - Evaluate covariate effects in the intended patient population
  - Test drug-drug interactions
  - Understand special populations – pediatrics, renal impairment, hepatic impairment

Data Integration

- Phase 3 efficacy and safety data are integral to drug approval:
  - Leverage the Pop PK model to predict individual measures of drug exposure for use in ER modeling
  - Build on early data and knowledge gained in Phase 2
  - Integration of data across studies
  - Relate drug exposure to efficacy and safety responses
  - Evaluate covariate effects for efficacy and safety
  - Determine therapeutic window

Leverage Early Modeling

- Early PK modeling using rich Phase 1 and sparse Phase 2 data can be used as a basis for quickly understanding Phase 3 sparse data
- Modeling could be informed by other quantitative modalities
  - For example: Semi-mechanistic models, PBPK information on DDI or variability in absorption
- Phase 2 ER modeling can be used to gain knowledge of ER relationships in patients and can be extended to Phase 3 data

Simulations

- Simulations can be used to:
  - Predict expected range of exposure measures in patients following different dose regimens, including dose regimens not studied
  - Simulate missed dosing and consequences on ER
  - Predict ER efficacy and safety responses
  - Identify therapeutic window or threshold of safe and effective dose(s)
  - Understand responses in special populations and covariate effects
  - Selection of final label dose(s)

Pmetrics on the Critical Path

- Regulatory agencies now recommend Pop PK and ER modeling to support decision making
- Implications
  - Tight timelines for Pmetrics analyses are the same as for the primary analyses
    - Options: Unblinded Third Party status allows us to meet challenging timelines
  - Need appropriate resources and advanced planning
  - Requires efficient analyses and regulatory submittable documentation

Case Study 1 – Omarigliptin Dose Rationale in Diabetes Patients Including Missed Dosing Instructions

- Goal - characterize the popPK and PD of the once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor omarigliptin in healthy subjects and patients with type 2 diabetes mellitus, and use these models to support the dosing recommendation for patient labelling including patients with renal impairment
- PK and PD were assessed from 9827 omarigliptin Cps collected from 1387 healthy subjects and patients in Phase 1, 2 and 3 studies of single- or multiple-dose weekly administration of omarigliptin at doses ranging from 0.25 to 400 mg.
- Population PK and PD analyses were performed using nonlinear mixed effect modelling in NONMEM.

Jain, et al. Pharmacokinetic–pharmacodynamic (dipeptidyl peptidase-4 inhibition) model to support dose rationale in diabetes patients, including those with renal impairment, for once-weekly administered omarigliptin. Br J Clin Pharm. 2019 Dec.

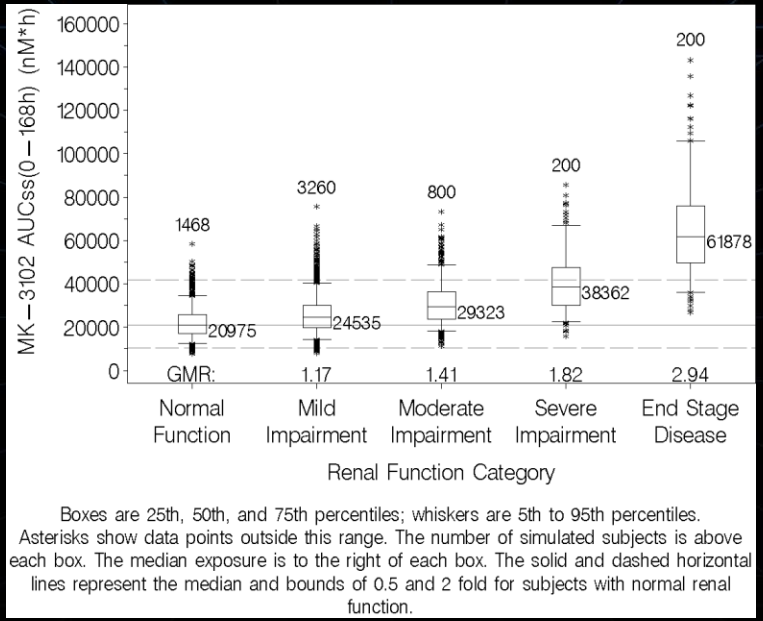
Case Study 1 – Omarigliptin Dose Rationale in Diabetes Patients Including Missed Dosing Instructions

- A semi-mechanistic 2-compartment model with linear unbound clearance and concentration-dependent binding of omarigliptin to the DPP-4 enzyme in both the central and peripheral compartments adequately described omarigliptin PK.
- Key covariates on omarigliptin PK included reduced unbound clearance with renal impairment.
- A direct effect sigmoid maximum inhibitory efficacy model adequately described the relationship between omarigliptin plasma concentrations and DPP-4 inhibition.
- Key covariates for PKPD included: Asian race, patient status, and male sex

Case Study 1 – Omarigliptin Dose Rationale in Diabetes Patients Including Missed Dosing Instructions

- Simulations using these models supported the current Japan label instructions that the approved omarigliptin 25-mg once-weekly dose be halved in patients with severe renal impairment and in those with end-stage renal disease.
- Also, if patients missed a dose, the next dose of omarigliptin should be taken as soon as remembered up to and including the day before the next scheduled dose.
- No other clinically important covariates were identified.

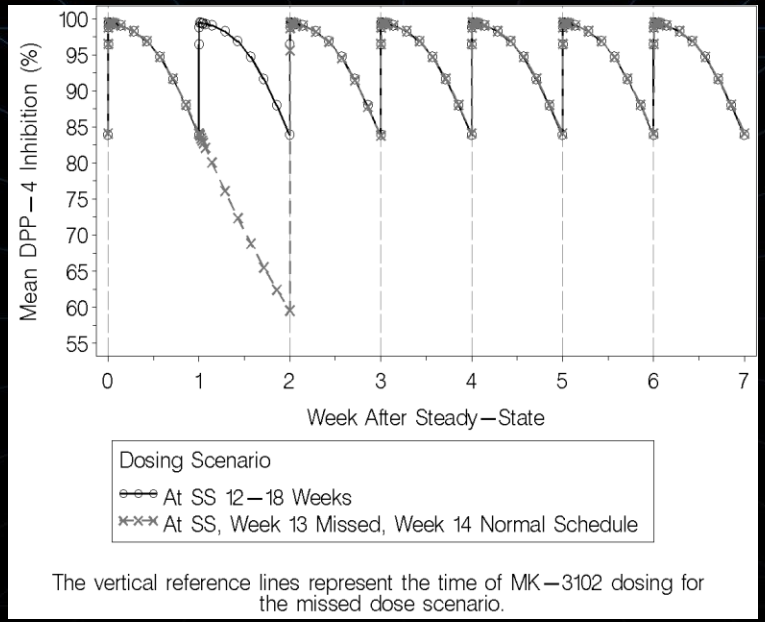
Case Study 1 – Omarigliptin Dose Rationale in Diabetes Patients Including Missed Dosing Instructions



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of simulated subjects is above each box. The median exposure is to the right of each box. The solid and dashed horizontal lines represent the median and bounds of 0.5 and 2 fold for subjects with normal renal function.

*The models adequately described PK and PD characteristics of omarigliptin and supported the dosing and administration section of the omarigliptin label.

Case Study 1 – Omarigliptin Dose Rationale in Diabetes Patients Including Missed Dosing Instructions



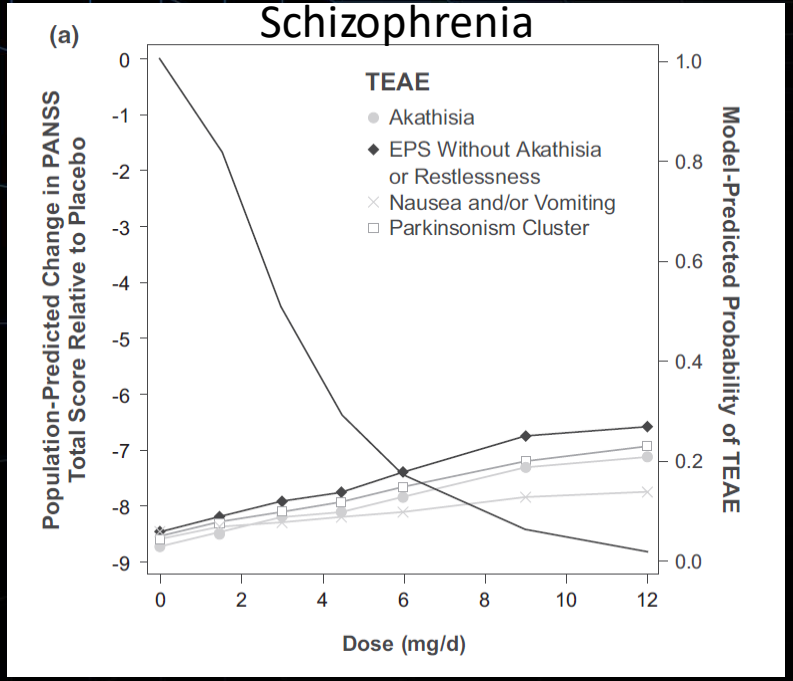
*The models adequately described PK and PD characteristics of omarigliptin and supported the dosing and administration section of the omarigliptin label.

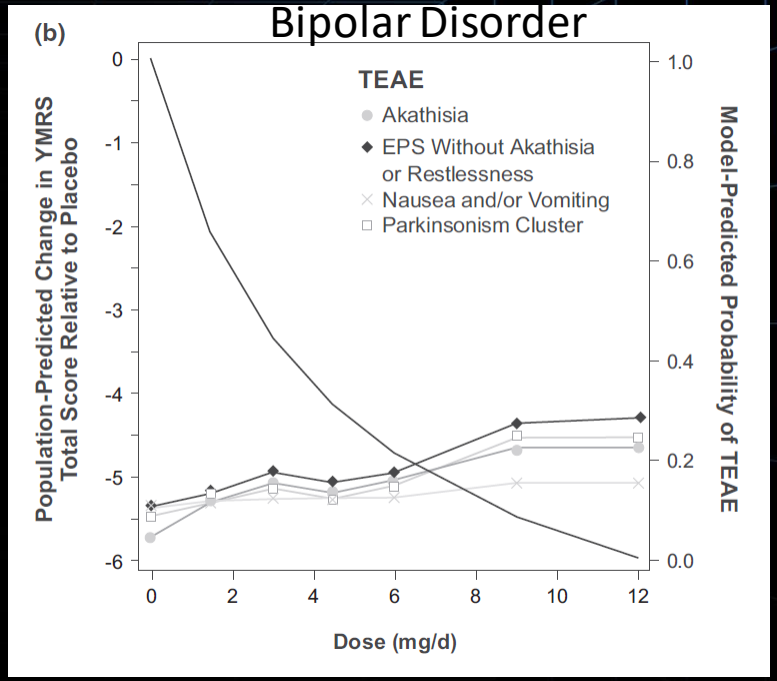
Case Study 2 – Benefit:Risk for Cariprazine in Schizophrenia and Bipolar Disorder

- Goal - investigated the relationship between drug exposures and efficacy/safety within patients enrolled in the cariprazine clinical development program for schizophrenia and bipolar mania.
- Exposure-efficacy and exposure-safety models were used to quantify the risk:benefit tradeoffs associated with increases in dose and exposure.

Periclou A, et al. Relationship between plasma concentrations and clinical effects of cariprazine in patients with schizophrenia or bipolar mania. Clin Transl Sci. 2019.

Case Study 2 – Benefit:Risk for Cariprazine in Schizophrenia and Bipolar Disorder





Case Study 2 – Benefit:Risk for Cariprazine in Schizophrenia and Bipolar Disorder

- The analyses revealed that doses ≤ 6 mg/d have a favorable benefit-risk balance, with increases in efficacy that are coupled with less pronounced increases in the probability of adverse events compared with doses > 6 mg/d.
- These results support the recommended clinical dose ranges of 1.5–6 mg/d for schizophrenia and 3–6 mg/d for bipolar mania, respectively.

Periclou A, et al. Relationship between plasma concentrations and clinical effects of cariprazine in patients with schizophrenia or bipolar mania. Clin Transl Sci. 2019.

Case Study 3 – Reslizumab Modeling & Simulations

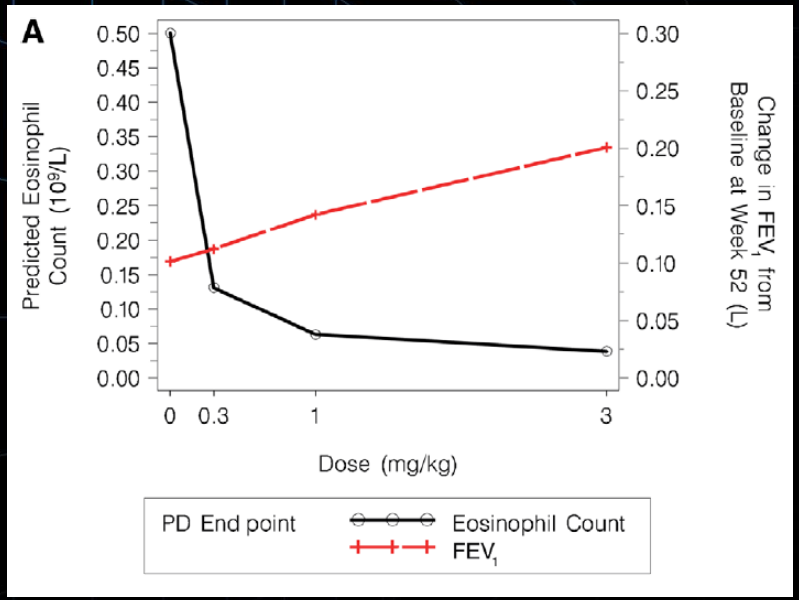
- Reslizumab 3.0 mg/kg has demonstrated efficacy in clinical studies of patients with eosinophilic asthma and a history of exacerbations.
- A pop PK model was developed to determine whether 3.0 mg/kg weight-based dosing is appropriate to obtain consistent reslizumab exposures in all patients.
  - PK data in healthy volunteers and patients 12 years with moderate to severe asthma, eosinophilic asthma, or nasal polyposis were analyzed from 4 phase 1, 2 phase 2, and 2 phase 3 studies of intravenous (IV) reslizumab (N = 804).
  - Covariates evaluated included age, race, sex, baseline weight, renal and liver function, concomitant medications, and antidrug antibody status.
- Exposure-response models were developed to characterize key efficacy (blood eosinophil levels, forced expiratory volume in 1 second [FEV1], Asthma Control Questionnaire [ACQ-7] scores), and safety endpoints (muscle disorder adverse events [AEs]).
- Vial-based dosing was evaluated as an alternative to weight-based dosing.

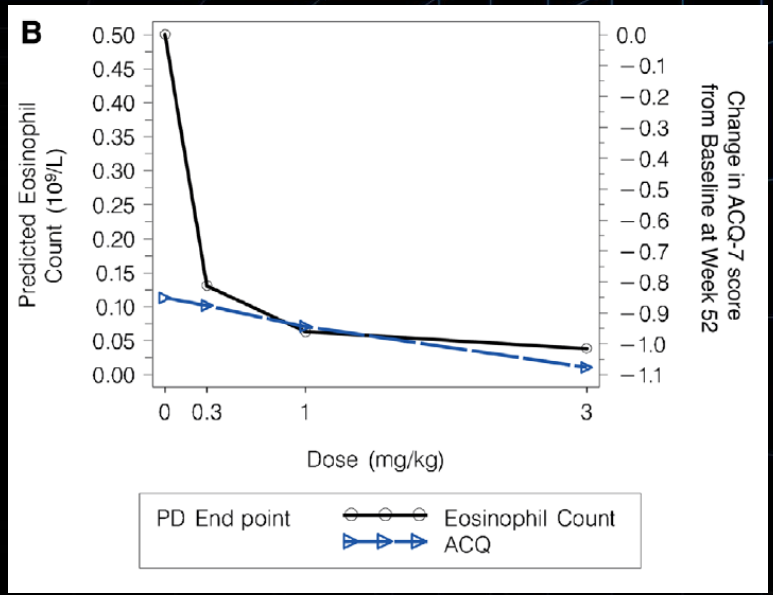
Passarell J, et al. Population pharmacokinetic and pharmacokinetic/pharmacodynamic modeling of weight-based intravenous reslizumab dosing. Journal of Clinical Pharmacology. 2020;60(8):1039-50.

Case Study 3 – Reslizumab Modeling & Simulations

- IV reslizumab PK was accurately described by a 2-compartment PK model with 0-order input and first-order elimination.
  - Body weight was the only covariate that significantly influenced PK parameters. However, with weight-based dosing, comparable steady-state exposures were observed across high and low body weights.
- Greater eosinophil lowering and longer response duration were observed with increasing dose
- Exposure-related effects on FEV1 and ACQ-7 were also seen, demonstrating the clinical importance of a dosing regimen to optimize reslizumab exposure.
- The probability of a muscle disorder AE appeared to increase with increasing exposure.

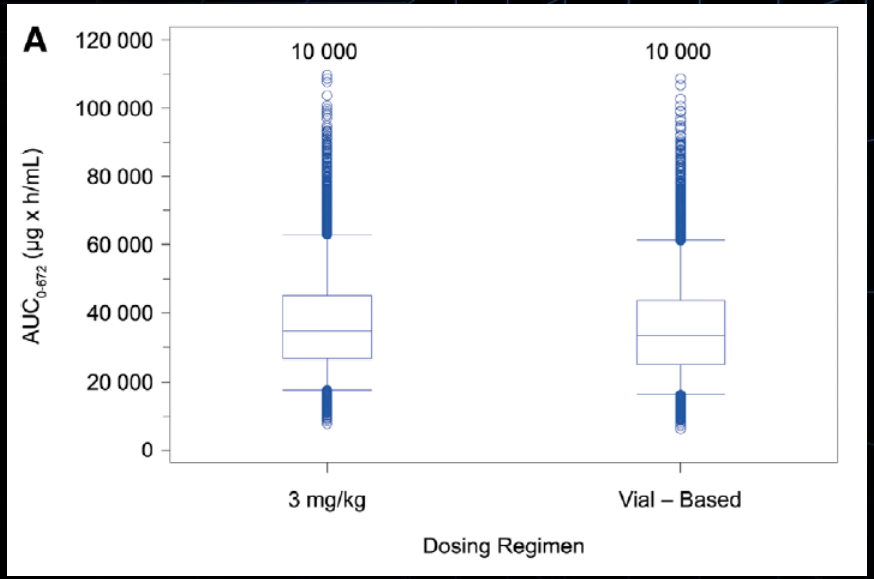
Case Study 3 – Reslizumab Modeling & Simulations





Case Study 3 – Reslizumab Modeling & Simulations

- Steady-state exposure measures were similar for both dosing regimens, showing vial-based dosing as an alternative method of achieving the benefits of weight-based dosing.



Case Study 3 – Reslizumab Modeling & Simulations

- “Innovative M&S based strategy in place of a clinical efficacy study showed that vial-based dosing, an alternative paradigm for weight-based dosing in Europe, can be used to achieve the benefits of weight-based dosing while minimizing drug wastage”

Conclusion

- Pharmacometrics plays a key role in regulatory assessment of treatment regimens leading to appropriate efficacy and safety outcomes

Q&A

Questions & Answers

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