

Dose Selection of BI 765423 for Phase II Study in Idiopathic Pulmonary Fibrosis (IPF) Using PK–Target Engagement Modeling

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Objective

To identify the dose/s which result in a pre-defined target engagement (TE) in at least 80% of patients at steady-state.

M-073

Introduction

- Interleukin-11 (IL-11) is recognized as a key profibrotic cytokine and an emerging therapeutic target in fibrotic diseases, including pulmonary fibrosis¹
- BI 765423 is a humanized monoclonal antibody targeted to block soluble IL-11 and is currently in development for the treatment of idiopathic pulmonary fibrosis (IPF)²
- Model-informed drug development approaches integrating pharmacokinetic (PK) and pharmacodynamic (PD) data support rational dose selection^{3,4}
- Target engagement (TE) modeling predicts the proportion of patients achieving pre-defined pharmacologic targets, supporting selection of dosing regimens for subsequent clinical development³

Methods

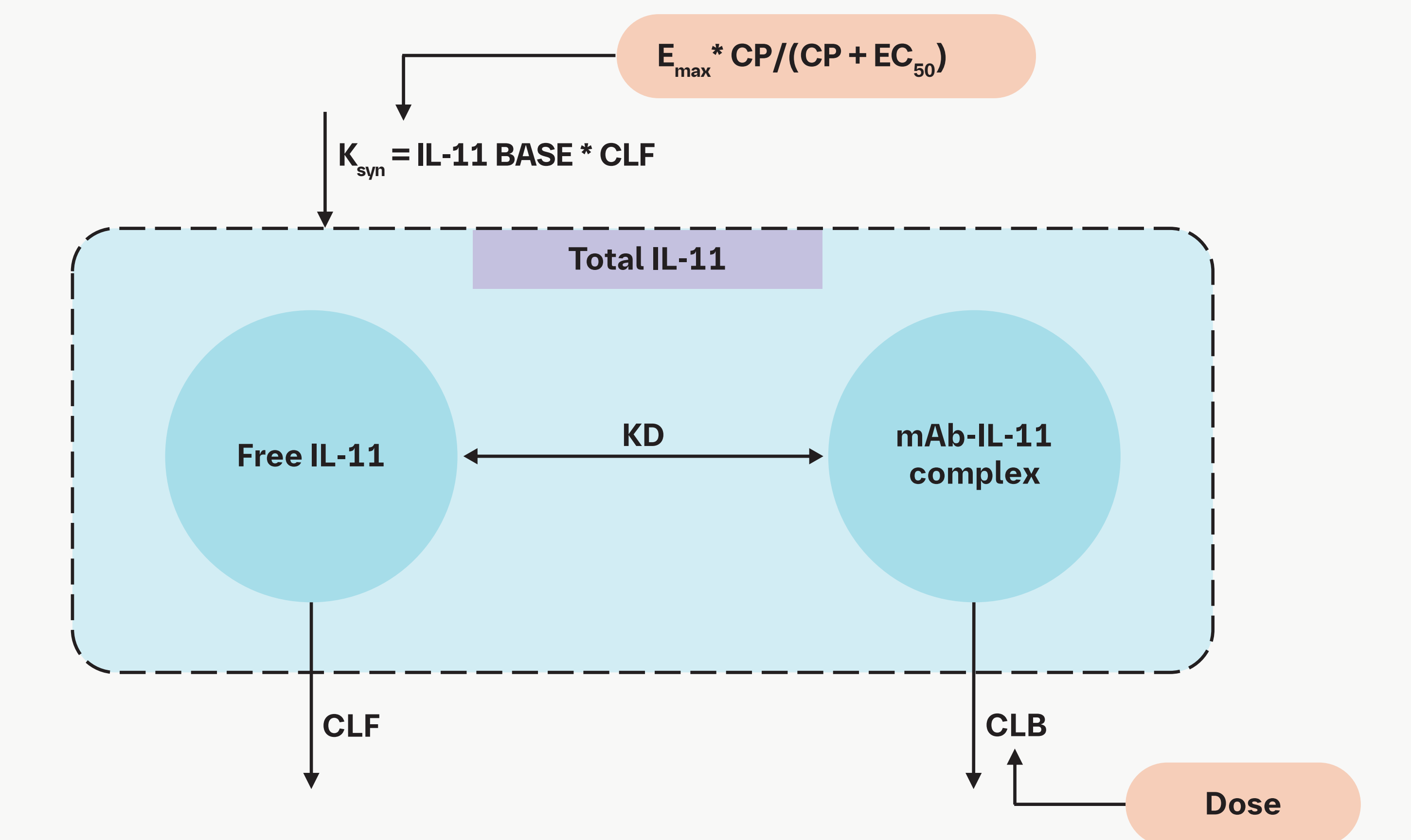
Study Data and Model Development

- PK and PD data were pooled from single and multiple rising dose studies (SRD, MRD) in healthy volunteers
- A population PK model was developed to describe BI 765423 exposure
- Estimated individual PK parameters were then fixed in a PK/PD model of TE, describing total IL-11 (**Figure 1**)
- Free IL-11 data were quantifiable, but nearly half of the observations were below the limit of quantification (BLQ). Thus, the observable free IL-11 data were only used to qualitatively inform binding affinity (KD) in the TE model
- Population PK and PK/PD model development was guided by precision of parameter estimates, goodness of fit criteria, and visual predictive checks (VPCs)

Simulations

- Population PK/PD simulations were performed for three intravenous (IV) dose levels using the final joint PK/PD model, including interindividual variability in PK and PD but no residual unexplained variability or uncertainty in model parameters
- TE was calculated as model-derived free IL-11 change from baseline (%)
- Body weights were randomly sampled from adult men and women in the NHANES database to generate the simulated population
- A total of 1,000 subjects were simulated for each dose and for the duration of treatment
- The time course of percent TE was plotted by dose and the percentage of simulated subjects achieving a pre-defined TE at steady state was summarized

Figure 1. TE model schematic: BI 765423 and total IL-11 data were modeled to predict free IL-11



BASE, baseline free IL-11 concentration; CLB, clearance of bound IL-11; CLF, clearance of free IL-11; Dose, covariate effect of dose level on CLB; EC_{50} , drug concentration that elicits half of the maximal effect; E_{max} , maximum drug effect; IL-11, interleukin-11; IPF, idiopathic pulmonary fibrosis; IV, intravenous; KD, binding affinity; K_{syn} , synthesis rate; mAb, monoclonal antibody; MRD, multiple rising dose; PD, pharmacodynamic; PK, pharmacokinetic; SRD, single rising dose; TE, target engagement; VPC, visual predictive check.

Results

PK/PD Model

- 72 subjects (48 in SRD, 24 in MRD) contributed to the analysis
- The dataset included 2,091 PK concentration measurements and 2,447 total IL-11 observations
- BI 765423 PK was described by a two-compartment model with fixed allometric scaling on clearance and volume parameters and linear elimination
- A general equilibrium PK/PD model for soluble targets was used to describe total IL-11 kinetics, but with some modifications:
 - A saturable effect of BI 765423 concentration was applied to IL-11 synthesis, along with an effect of dose on elimination rate of total IL-11. These effects were required to describe the dose-dependent but saturable increase in observed total IL-11 dynamics
 - Separate elimination rates were estimated for monoclonal antibody (mAb) and total IL-11
- Additionally, the KD that was fixed after sensitivity analysis demonstrated that the level of percent TE from free IL-11 data was best described with the higher (than estimated) value of KD
- Parameters were estimated with good precision and model diagnostics showed that the model adequately described the observed total IL-11 data

Simulation Results

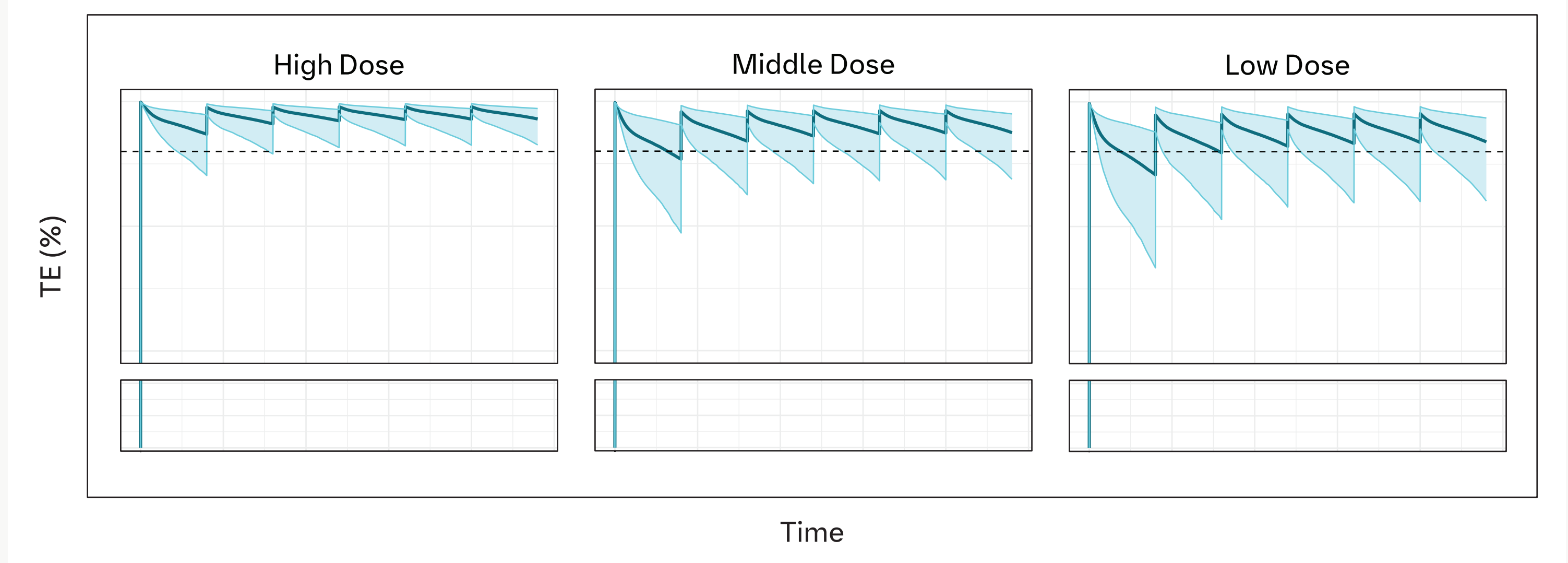
- At the end of treatment 97.5%, 79.8%, and 66.0% of simulated subjects receiving high, middle, and low IV dose regimens, respectively, achieved $\geq$ the pre-defined TE (**Table 1**)
- The middle and high dose regimen met the pre-defined target (**Figure 2**)

Table 1. Percentage (%) of simulated subjects who achieved the pre-defined TE at midpoint and end of treatment

IV Dose	Percentage of subjects above pre-defined TE (%)	
	Midpoint	End of Treatment
High Dose	96.2	97.5
Middle Dose	74.7	79.8
Low Dose	59.6	66.0

TE, target engagement.

Figure 2. TE (%) versus time for simulated subjects, by dosing regimen



Simulations were performed by randomly sampling 1000 subjects from NHANES. The thick blue lines represent the medians. The shaded areas represent pre-defined prediction intervals. The dashed black line represents the pre-defined TE. TE, target engagement.

Conclusions

- PK/PD modeling successfully characterized BI 765423 exposure and TE. TE was modelled using total IL-11 to predict binding of free IL-11 to circulating BI 765423
- Simulations demonstrated dose-dependent achievement of TE
- At the middle and high dose, $\geq 80\%$ of patients achieved the pre-defined TE criterion in the simulated population

Abbreviations

BASE, baseline free IL-11 concentration; BLQ, below the limit of quantification; CLB, clearance of bound IL-11; CLF, clearance of free IL-11; EC_{50} , drug concentration that elicits half of the maximal effect; E_{max} , maximum drug effect; IL-11, interleukin-11; IPF, idiopathic pulmonary fibrosis; IV, intravenous; KD, binding affinity; K_{syn} , synthesis rate; mAb, monoclonal antibody; MRD, multiple rising dose; PD, pharmacodynamic; PK, pharmacokinetic; SRD, single rising dose; TE, target engagement; VPC, visual predictive check.

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Poster developed for
ACoP 2026,
October 11–14, 2026,
Maryland, USA.

Acknowledgement

Boehringer Ingelheim was given the opportunity to review the publication for medical and scientific accuracy, as well as intellectual property considerations. Pranav Nayak (PhD), an employee of Indegene Limited, Bangalore, India, provided writing, editorial, and formatting support, which was contracted and funded by Boehringer Ingelheim.

Disclosures

*JK was an employee of Metrum Research Group and previously Boehringer Ingelheim during the time of the study and analysis conduct, and is now an employee of GlaxoSmithKline.

