Population Pharmacokinetic-Pharmacodynamic Model of Nirogacestat Effects on B-Cell Maturation Antigen in Healthy Subjects

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INTRODUCTION

■ B-cell maturation antigen (BCMA) is overexpressed on the cell surface of activated B-cells (PB cells), plasma cells (PCs), and multiple myeloma (MM) cells.

■ BCMA is the target of several investigational agents and the target for the treatment of MM.

■ Low BCMA receptor density may be associated with lesions in myeloma patients, or minimization to BCMA down-regulation.

■ BCMA is cleared from the cell surface by the proteolytic cleavage and an ectosome (EV), which results in limited levels of membrane bound BCMA (mbBCMA) and generation of BCMA (bcMA) (EV).

■ GBM & GBM-like GBG have been shown to increase expression, cleavage, and proteolysis by the activity of several BCMA-targeted therapies.

■ Pharmacokinetic-pharmacodynamic (PK-PD) studies in clinical studies are needed to evaluate BCMA in healthy volunteers.

■ When the effects of GBM inhibition in patients has not been reproduced in vitro. The effect on BCMA dynamics has yet to be adequately characterized in humans.

■ Nirogacestat is a selective small-molecule GBG in clinical development as a monoclonal (monodeuterium), second-generation targeting of MM and B-cell malignancies.

■ BCMA-directed therapies in MM have been shown to be well tolerated with limited toxicity profiles and encouraging clinical outcomes.

■ Nirogacestat is a selective GBG in clinical development as a monoclonal (monodeuterium), second-generation targeting of MM and B-cell malignancies.

OBJECTIVE

■ Evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profile of nirogacestat (Niro) in healthy participants.

■ Evaluate the BCMA response to Niro in healthy participants.

■ Evaluate the relationship between BCMA receptor density and BCMA pharmacodynamic response with Niro.

■ Evaluate the BCMA pharmacodynamic response to Niro in healthy participants.

METHODS

STUDY DESIGN

An adaptive design clinical study in healthy participants was conducted to evaluate BCMA receptor density on PBs collected from baseline and on day 5 of nirogacestat treatment in healthy participants.

■ Part 1: Measured BCMA receptor density was observed on PBs isolated from both baseline and at the end of treatment (Figure 2A).

■ Part 2: Assessed the effect of nirogacestat on BCMA receptor density in PBs isolated from one baseline and one treatment day.

■ Part 3: Dose and sampling times selected for Part 3 were based on the final PK-PD model.

■ The BCMA ER model was then utilized to simulate dose and sampling times selected for Part 3.

■ A PK model was initially developed to describe the PK of nirogacestat in the healthy participants enrolled in this study using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay.

■ The whole blood ER model was used to simulate dose and sampling times selected for Part 3.

■ The BCMA ER model was used to simulate dose and sampling times selected for Part 3.

■ The whole blood ER model was used to simulate dose and sampling times selected for Part 3.

RESULTS

FOLO CHANGE IN mbBCMA IN WHOLE BLOOD AND BONE MARROW

■ Rapid and robust dose-related increases in BCMA receptor density were observed on PBs isolated from both baseline and at the end of treatment (Figure 2A).

■ Increases in mbBCMA levels gradually returned to baseline levels by 24–48 hours post-treatment (Figure 2B).

■ Over the entire dose range, increases in BCMA receptor density were observed in both PBs and bone marrow samples (Figure 2C).

■ Correlation Between BCMA Receptor Density on PBs isolated from Whole Blood and Bone Marrow Samples

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■ The BCMA ER model was used to simulate dose and sampling times selected for Part 3.

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CONCLUSIONS

■ Nirogacestat treatment results in both robust and rapid changes in BCMA levels in both whole blood and bone marrow.

■ A dose-related increase in BCMA was observed in PBs isolated from whole blood (50–300 mg) in both whole blood and bone marrow.

■ Greater increases (5–6-fold) in mbBCMA were observed in PBs isolated from whole blood compared to PBs isolated from bone marrow.

■ Turnover rate of BCMA is rapid, levels return to baseline by 48–72 hours after nirogacestat dosing, corresponding to clinical effect.

■ An exploratory exposure-response model was developed to understand the relationship between BCMA PK and BCMA PD response observed in whole blood.

■ Linked bone-marrow increase and variability of the samples persisted the most in bone marrow compared with whole blood.

■ The whole blood ER model was used to predict BCMA response following future dosing and dosing schedules of nirogacestat.

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