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

Abstract 8027
Poster Board 19

Todd Shearer, PhD,[1] Rex L. Williams Jr, PhD,[1] Mark Johnson, PhD,[1] Ewa Cendrowicz, PhD,[2] Cathrine Leonowens, PharmD, FCCP,[3] Margaret Smith, BA,[1] Todd Baughman, MSC,[1] Caroline J. Breitbach, PhD,[1] Shinta Cheng, MD, PhD[1]

[1]SpringWorks Therapeutics, Stamford, CT, USA; [2]ICON BioAnalytical Laboratories, Assen, The Netherlands; [3]Nuventra Pharma Sciences, Durham, NC, USA

INTRODUCTION

- B-cell maturation antigen (BCMA) is expressed on the cell membrane of normal plasma cells (PCs) and multiple myeloma (MM) cells
  - BCMA is the target of several investigational agents and approved products for the treatment of MM
  - Low BCMA receptor density may be associated with lower response rates, less durable responses, or resistance to BCMA therapies
- BCMA is cleaved from the cell surface by the enzyme γ secretase (GS), which results in reduced levels of membrane-bound BCMA (mbBCMA) and generation of soluble BCMA (sBCMA)
  - GS inhibitors (GSIs) have been shown to increase mbBCMA, and potentiation of the activity of several BCMA-targeted therapies has been demonstrated *in vitro* and in clinical studies in combination with GSIs
  - While the effect of GS inhibition on mbBCMA has been reproducibly characterized *in vitro*, the effect on BCMA dynamics has yet to be adequately characterized in humans
- Nirogacestat is a selective small molecule GSI in clinical development as a monotherapy (desmoid tumors, ovarian granulosa cell tumors) and as combination therapy with 8 BCMA-directed therapies in ongoing or planned clinical trials

OBJECTIVE

- Evaluate the pharmacodynamics (PD) of the GSI nirogacestat on BCMA cell surface density on PCs in healthy participants

DISCLOSURES: *Todd Shearer, Rex L. Williams Jr., Mark Johnson, Margaret Smith, Todd Baughman, Caroline J. Breitbach, and Shinta Cheng are employees of SpringWorks Therapeutics and may have an equity or other financial interest. Ewa Cendrowicz is an employee of ICON BioAnalytical Laboratories and may have an equity or other financial interest. Cathrine Leonowens is an employee of Nuventra Pharma Sciences and may have an equity or other financial interest.*

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METHODS

STUDY DESIGN

- An adaptive design clinical study in healthy participants used quantitative flow cytometry to evaluate BCMA receptor density on PCs collected from bone marrow and whole blood following administration of nirogacestat (**Figure 1**)
- Part 1: Fresh whole blood and bone marrow samples were collected in untreated healthy participants for assay development
- Part 2: Participants received a single, 150 mg dose of nirogacestat
  - Matched whole blood and bone marrow samples were collected at pre-dose, 4, 8, 24 and 48-hours post-dose
  - Each participant provided one pre-dose whole blood and bone marrow sample along with one post-dose sample, with at least 2 participants at each timepoint
  - Fold-change in post-dose BCMA density was evaluated by comparing the results to the participant-matched pre-dose samples
- Part 3: Dose and sampling times selected for Part 3 were based on preliminary pharmacokinetic (PK)-PD analysis of the Part 2 results
  - Part 3 included low (50 mg) and high (300 mg) single doses of nirogacestat and multiple dosing at 100 mg *BID*

ANALYTICAL TESTING

- PCs from whole blood and bone marrow aspirates were analyzed by flow cytometry (scan QR code for **Supplemental Figure 1**)
- Serum concentrations of nirogacestat were determined using a validated liquid chromatography with tandem mass spectrometry assay
- A PK model was initially developed to describe the PK of nirogacestat in the healthy participants enrolled in this study
- An exposure-response (ER) model was then developed describing the relationship between the PK of nirogacestat and the PD response (BCMA receptor density) following administration of nirogacestat
- The BCMA ER model was then utilized to simulate dose and schedules to optimize the maintenance of a minimum increase in BCMA receptor density

MODEL SELECTION CRITERIA

- A "fit-for-purpose" model was developed to describe the ER relationship between nirogacestat and changes to the receptor density of BCMA on PCs isolated from whole blood
  - Due to the limited dataset available for bone marrow, the ER modeling was restricted to whole blood **only**
  - However, correlation analysis suggests that measurement of BCMA levels on PCs in whole blood may be a good surrogate for bone marrow
- The following criteria were utilized during model selection: objective function value (OFV), condition number, precision (% relative standard error [%RSE]) and plausibility of parameter estimates, values of inter-individual variability (IIV) and residual error, standard goodness-of-fit plots (GOF), visual predictive checks (VPC), and prediction-corrected VPC (pcVPC)

Figure 1. Study Design, Dosing, and Sampling Schedule

Dose (mg)	Dosing Schedule	n	mbBCMA: Whole Blood Timepoints (hours)	mbBCMA: Bone Marrow Timepoints (hours)*
0**	NA	2	NA	NA
150	Single dose	8	D-1, 4, 8, 24, 48	D-1, 4, 8, 24, 48
50	Single dose	2	D-1, 2, 4, 8	D-1, 2, 4
300	Single dose	8	D-1, 1, 2, 4, 8, 24	D-1, 1, 2, 4, 8, 24
100	Twice daily (0, 12, 24, 36 h)	4	D-1, 2, 4, 8, 24, 48	D-1, 24, 48

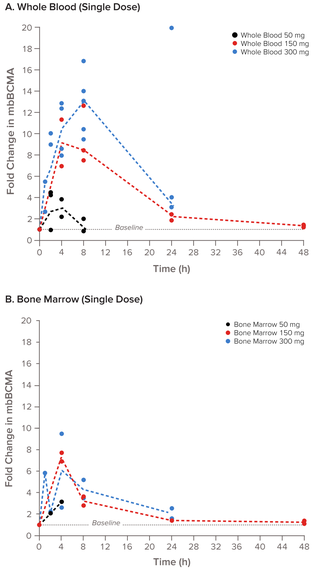
D-1 = Day -1, baseline whole blood and bone marrow samples were collected 1 day prior to dosing.
*Each dosed participant contributed one pre-dose and one post-dose bone marrow sample. (n=2 per post treatment timepoint). Sampling timepoints based on randomization/enrollment scheme. Rich PK sampling and all indicated whole blood mbBCMA samples were collected from each participant through the assigned post-dose timepoint.
**Two participants were enrolled for whole blood and bone marrow collection to support assay qualification.

RESULTS

FOLD CHANGE IN mbBCMA IN WHOLE BLOOD AND BONE MARROW

- Rapid and robust dose-related increases in BCMA receptor density were observed on PCs isolated from both whole blood and bone marrow (**Figure 2A and 2B**)
- Increases in mbBCMA levels generally returned to near baseline levels by 24 to 48 hours post-dose (**Figure 2C**)
- Following repeat doses of nirogacestat at 100 mg *BID*, BCMA receptor density generally remained at least ≥2-fold higher than baseline throughout the dosing interval in both whole blood and bone marrow (**Figure 2C**)

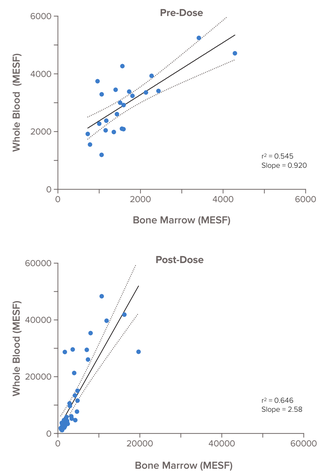
Figure 2. Nirogacestat Treatment Produces a Dose-Dependent Increase in mbBCMA on PCs After a Single Administration (A and B) and Repeated Administration (C)



Fold increase in mbBCMA on PCs isolated from whole blood or bone marrow after single doses (panels A and B) or multiple 100 mg *BID* doses (panel C; 2 to 4 doses) of nirogacestat. Data points represent individual sample results; dashed lines indicate median for each sample time point. mbBCMA = membrane-bound B-cell maturation antigen.

- Following treatment with nirogacestat, the increase in BCMA receptor density was correlated between whole blood and bone marrow; however, the BCMA response was approximately 2.5-fold higher in whole blood compared with bone marrow (**Figure 3**)
- Although there was a difference in the magnitude of the response in the respective matrices, the close relationship allows the use of whole blood as a surrogate for bone marrow when evaluating BCMA receptor density on PCs

Figure 3. Correlation Between BCMA Receptor Density on PCs Isolated from Whole Blood and Bone Marrow Samples



MESF = molecules of equivalent soluble fluorophores.

PK MODEL FOR NIROGACESTAT IN HEALTHY PARTICIPANTS

- Nirogacestat PK was described by a 2-compartment model with linear absorption and linear clearance
- A dose effect on bioavailability was noted upon inspection of VPC plots and simulations, thus a fit-for-purpose dose effect on bioavailability, as an F_{max} model, was added to the base model (**Figure 4**)
- Residual error was low, and IIV was moderate for all three PK parameters (scan QR code for **Supplemental Figure 2**)
- Parameter precision was low, except for absorption rate (KA), which could be improved with more data during the absorption phase (**Table 1**)

Figure 4. VPCs for the Nirogacestat Dose Effect PK Model by Dose

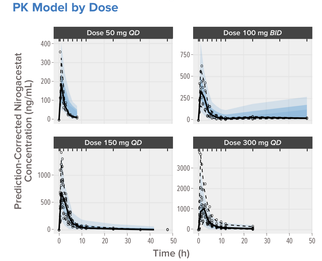


Table 1. PK Parameter Estimates for the Nirogacestat Dose Effect Model

Parameter	Estimate (95%CI)	%RSE	IIV
CL (L/h)	44.2 (36.1, 54.1)	0.962	56.5
V (L)	44 (36, 54)	0.946	49
KA (1/h)	1.49 (1.09, 2.02)	40	44.8
Q (L/h)	28.2 (22.8, 34.9)	1.06	NA
V2 (L)	352 (291, 426)	0.762	NA
F1 (fraction)	0.171 fixed	NA	NA
F_{max}	2 fixed	NA	NA
D_{50} (mg)	150 fixed	NA	NA
Proportional Error (%)	24.7	NA	NA

CL = clearance; D_{50} = dose that exhibits 50% of maximum effect on bioavailability; F1 = bioavailability; F_{max} = maximum effect on bioavailability; IIV = inter-individual variability; KA = absorption rate; Q = intercompartmental distribution rate; RSE = relative standard error; V = volume.

ER MODEL

- A fit-for-purpose sequential PD model of nirogacestat effect on whole blood mbBCMA included an indirect response model described by appearance (k_{in}) and depletion (k_{out}) of mbBCMA and drug effect as an E_{max} model with Hill coefficient (gamma) (**Table 2**)
- Observed data were adequately described by the model (pcVPCs), and the model had good parameter precision (**Figure 5**)
- Residual error was high, likely due to low amount of data and high variability in response (**Table 2** and scan QR code for **Supplemental Figure 3**)

Figure 5. VPCs of the Nirogacestat-BCMA ER Model by Dose

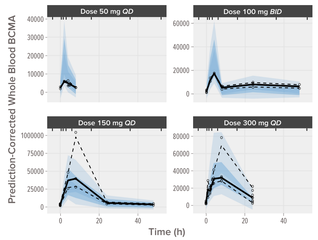


Table 2. Parameter Estimates for the BCMA ER Model

Parameter	Estimate (95%CI)	%RSE	IIV
EC_{50} (nM)	37.2 nM (26, 53.3)	5.06	NA
E_0 (MESF)	2170 (1630, 2890)	1.9	58.9
E_{max}	0.92 fixed	NA	1
k_{out} (h^{-1})	4.16 fixed	NA	NA
Gamma	2 fixed	NA	NA
Residual Additive Error (MESF)	2940	NA	NA

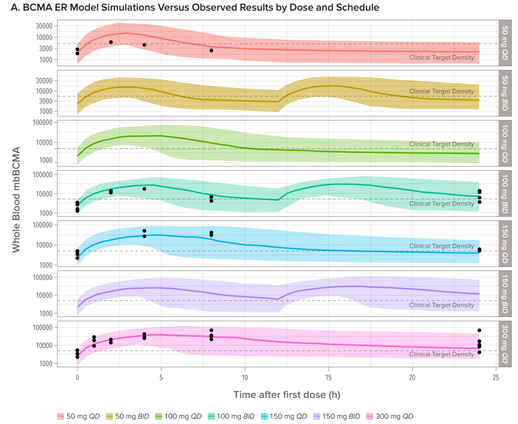
EC_{50} = serum concentration of nirogacestat which generates a 50% response in MESF; E_{max} = maximum MESF; E_0 = baseline MESF; Gamma = Hill slope; IIV = inter-individual variability; k_{out} = receptor turnover rate; MESF = molecules of equivalent soluble fluorophores; RSE = relative standard error.

BCMA ER MODEL SIMULATIONS

- The BCMA ER model was used to simulate 100 participants per dose/regimen
- Simulations adequately captured the observed data (with slight overprediction at 50 mg) (**Figure 6A**)
- Simulated data at steady state was contextualized with clinical benchmarks: maintaining a clinical target BCMA receptor density of 5000 MESF or an approximately 2-fold increase from baseline BCMA (**Figure 6B**)

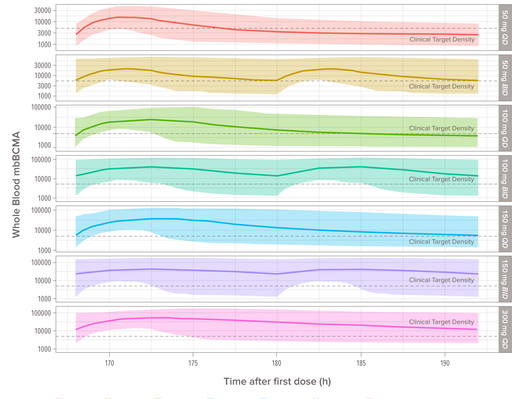
Figure 6. BCMA ER Model Simulations

A. BCMA ER Model Simulations Versus Observed Results by Dose and Schedule



Black dots = observed data; solid lines = median mbBCMA.
Ribbon = 90% prediction interval (i.e., 5th and 95th percentiles).

B. BCMA ER Model Simulations to Steady-State by Dose and Schedule



Solid lines = median mbBCMA.
Ribbon = 90% prediction interval (i.e., 5th and 95th percentiles).

BCMA ER MODEL

- At steady state, at least 50% of simulated participants maintained ≥ 2-fold change from baseline in BCMA during the dosing interval for the following dosages: 100 mg *BID*, 150 mg *BID*, and 300 mg *QD* (**Table 3**)
- 50 mg *BID* maintained ≥ 2-fold change from baseline in BCMA for approximately 43% of participants while the 100 mg *QD* dose only met the target for 20% of the participants (**Table 3**)

Table 3. Percent (%) Simulated Participants Who Sustained ≥ 2-fold increase in BCMA over the Dosing Interval at Steady State (Day 7)

Dose (mg)	Dosing Interval (h)	Simulated Participants Who Sustained ≥ 2-fold increase in BCMA (%)
50	12	43
50	24	6.0
100	**12**	**70**
100	24	20
150	12	75
150	24	43
300	24	62

CONCLUSIONS

- Nirogacestat treatment results in both a rapid (within 1 hour) and robust (9–19-fold) increase in mbBCMA on PCs in both whole blood and bone marrow
  - A dose-related increase in BCMA was observed across the range of administered doses of nirogacestat (50–300 mg) in both whole blood and bone marrow
  - Greater increases (~2-fold) in mbBCMA were observed on PCs isolated from whole blood as compared with bone marrow following treatment with nirogacestat
  - Treatment-related effects of nirogacestat on BCMA in bone marrow were correlated with the effects observed in whole blood samples
  - Turnover rate of BCMA is rapid as levels return to baseline by 24 to 48 hours after nirogacestat dosing, corresponding with a decline in nirogacestat PK concentrations
- An exploratory exposure-response model was developed to define the relationship between nirogacestat PK and the BCMA response observed in whole blood
  - Limited bone marrow data and high variability of the samples precluded the development of an ER model in bone marrow
- The whole blood ER model was used to predict BCMA response following various doses and dosing schedules of nirogacestat
  - Given the 2-fold lower response of BCMA in bone marrow compared with whole blood, a 2-fold increase in BCMA density (approximately equivalent to a receptor density of 5000 MESF) in whole blood was utilized as a minimum clinical target effect
- Steady-state simulations suggest that the 100 mg *BID* dose of nirogacestat is an optimal dosing regimen to sustainably increase BCMA receptor density on PCs
  - While steady-state simulations indicate that 150 mg *BID* resulted in a slight increase in the percentage of participants achieving the clinical target receptor density over the dosing interval, the difference between 100 mg and 150 mg *BID* was minimal
  - For patients with MM, nirogacestat will be administered only in combination with BCMA-directed therapies and the 100 mg *BID* dose is likely to offer an improved benefit-risk profile for this combination
- While an ER model for bone marrow could not be developed due to the limited dataset, a relationship between whole blood and bone marrow BCMA response to treatment was observed
  - These results suggest that BCMA dynamics in whole blood may be utilized as a surrogate for bone marrow, precluding the need to collect bone marrow samples to monitor the treatment effect of nirogacestat in clinical trials of patients with MM