PHARMACODYNAMIC EFFECTS OF NIROGACESTAT, A GAMMA SECRETASE INHIBITOR, ON B-CELL MATURATION ANTIGEN IN HEALTHY PARTICIPANTS

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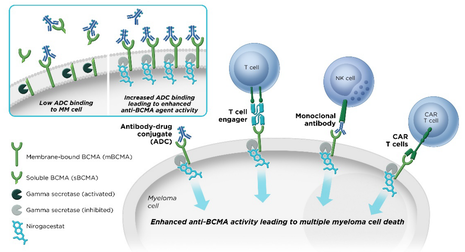
INTRODUCTION

- B-cell maturation antigen (BCMA) is expressed on the cell membrane of normal plasma cells and multiple myeloma (MM) cells
  - BCMA is the target of several approved products and investigational agents for the treatment of MM
  - Low BCMA receptor density may be associated with lower response rates, less durable responses, or resistance to BCMA-targeted therapies
- The enzyme gamma secretase (GS) cleaves BCMA from the cell surface, which results in reduced levels of membrane-bound BCMA (mbBCMA) and generation of soluble BCMA (sBCMA)
  - GS inhibitors (GSIs) have been shown to increase levels of mbBCMA, and in both preclinical and clinical studies, they have potentiated the therapeutic activity of several BCMA-targeted therapies when used in combination
  - Although the effect of GS inhibition on mbBCMA has been reproducibly characterized *preclinically*, additional studies are necessary to adequately characterize the effect on BCMA dynamics in humans
- Nirogacestat is an investigational, small-molecule GSI in clinical development as a monotherapy for desmoid tumors and ovarian granulosa cell tumors and is being evaluated in combination with several BCMA-directed therapies in ongoing or planned clinical trials[a] (**Figure 1**)

Figure 1. Nirogacestat Mechanism of Action in Combination With BCMA-Directed Therapeutics.



ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MM, multiple myeloma; NK, natural killer.

- The purpose of this study was to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of nirogacestat on mbBCMA cell-surface density on plasma cells isolated from whole blood (WB) and bone marrow (BM) in healthy participants
  - Though typically collected from BM aspirates (BMA), plasma cells can also be isolated from WB. The ability to evaluate mbBCMA on plasma cells in circulation has not been demonstrated previously but could provide significant advantages for patients over BMA

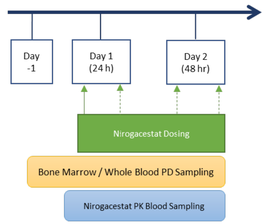
[a]NCT04126200, NCT05556798, NCT05573802, NCT05090566, NCT04722146, NCT04171843, NCT05259839, NCT04093596

STUDY DESIGN/METHODS

Overall Design

- This is a 3-part, open-label, randomized, parallel design, Phase 1 study to evaluate the PD, PK, safety, and tolerability of nirogacestat on BCMA in healthy adult men (**Figure 2**)

Figure 2. Study Design.



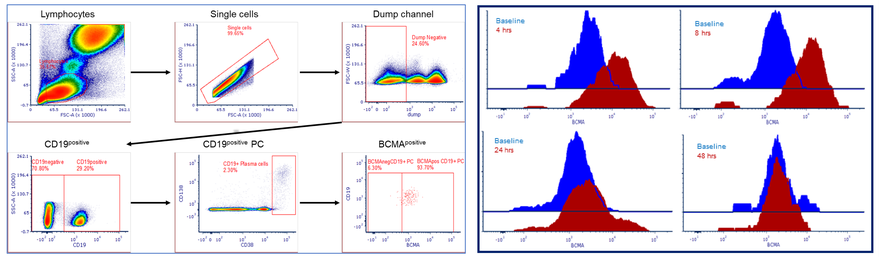
Dose (mg)	Dosing Schedule	n	mbBCMA: Whole Blood Timepoints (hours)	mbBCMA: Bone Marrow Timepoints (hours)*
0**	N/A	2	NA	NA
150	Single Dose	8	D-1, 4, 8, 24, 48	D-1, 4, 8, 24, 48
50	Single Dose	2	D-1, 2, 4, 8	D-1, 2, 4
300	Single dose	8	D-1, 1, 2, 4, 8, 24	D-1, 1, 2, 4, 8, 24
100	Twice daily (0, 12, 24, 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 subject 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 subject through the assigned post-dose timepoint.
**Two subjects were enrolled for whole blood and bone marrow collection to support assay qualification.

Methods

- WB and BMA were acquired from healthy donors at specified time points
  - BMA were filtered through a 70-µm filter, and total white blood cell counts in matched WB and BMA samples were enumerated in a Sysmex analyzer
  - Samples were subsequently stained with an antibody cocktail designed for enrichment of plasma cells and analysis of mbBCMA
  - Samples were run and data were acquired on a BD LSR Fortessa X-20 cytometer
- To analyze the PD effects of nirogacestat on mbBCMA, the following gating scheme was used (**Figure 3**)
  - Briefly, samples were first gated on live single-cell lymphocytes followed by exclusion of non–B-cell populations using a dump channel, composed of CD3, CD56, and CD14, where the negative population included our plasma cells of interest
  - Samples were then gated on $CD19^{+/-}$ expression, after which $CD38^{+}CD138^{+}$ cells were used to gate on plasma cells for final analysis of mbBCMA

Figure 3. Isolation of BCMA-Expressing Plasma Cells in WB and BMA.

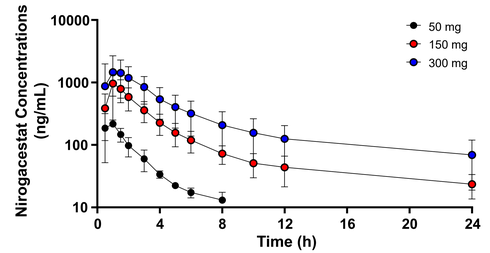


BCMA, B-cell maturation antigen; BMA, bone marrow aspirates; FSC-A, forward scatter area; FSC-H, forward scatter height; FSC-W, forward scatter width; SSC-A, side scatter area; PC, plasma cell; WB, whole blood.

RESULTS

- Serum concentrations of nirogacestat increased rapidly, with a T_{max} of approximately 1 hour, and declined quickly over the first 12 hours (**Figure 4**)

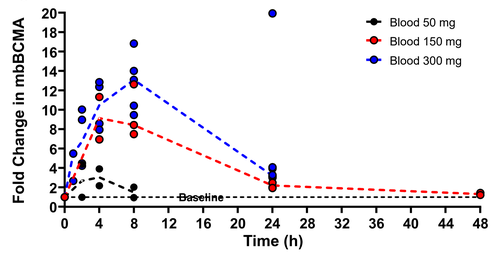
Figure 4. Single-Dose Nirogacestat Is Rapidly Cleared From Systemic Circulation.



Serum concentrations of nirogacestat following a single dose of 50, 150, or 300 mg.

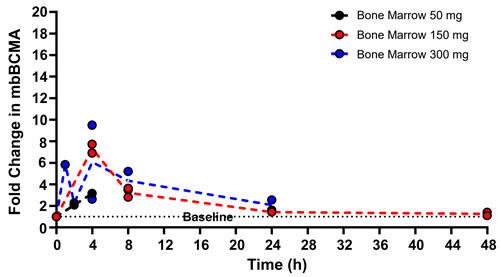
- Nirogacestat treatment resulted in both a rapid (within 2 hours) and robust (9- to 19-fold) increase in mbBCMA level on plasma cells in both WB and BMA after single-dose administration (**Figures 5** and **6**)
  - A dose-related increase in mbBCMA level was observed across the range of administered doses of nirogacestat (50 to 300 mg) in both WB and BMA
  - Increases in mbBCMA level were greater on plasma cells isolated from WB than on those isolated from BMA. BMA mbBCMA levels exhibited greater variability than did WB mbBCMA levels, most likely because of difficulties collecting and processing BMA samples versus WB

Figure 5. Nirogacestat Treatment Produces a Dose-Dependent Increase in mbBCMA on Plasma Cells Isolated From WB After a Single Administration.



Fold increase in mbBCMA on plasma cells isolated from WB after administration of a single 50-, 150-, or 300-mg dose of nirogacestat. Data points represent individual sample results; dashed line indicates the median for each sample time point. mbBCMA, membrane-bound B-cell maturation antigen; WB, whole blood.

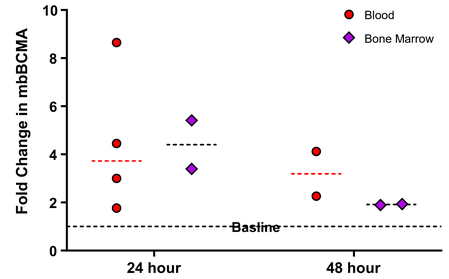
Figure 6. Nirogacestat Treatment Produces a Dose-Dependent Increase in mbBCMA on Plasma Cells Isolated From BM After a Single Administration.



Fold increase in mbBCMA on plasma cells isolated from BMA after administration of a single 50-, 150-, or 300-mg dose of nirogacestat. Data points represent individual sample results; dashed line indicates the median for each sample time point. BM, bone marrow; BMA, bone marrow aspirates; mbBCMA, membrane-bound B-cell maturation antigen.

- Turnover rate of mbBCMA was rapid, as levels returned to baseline by 24 to 48 hours after nirogacestat dosing, corresponding with a decline in nirogacestat PK concentrations
- mbBCMA levels remained elevated throughout the nirogacestat dosing interval when nirogacestat was administered at 100 mg twice daily (**Figure 7**)

Figure 7. Twice-Daily Nirogacestat Regimen Results in a Sustained Increase in mbBCMA on Plasma Cells Isolated from WB and BM.



Fold increase in mbBCMA on plasma cells isolated from WB and BM after administration of multiple 100-mg BID doses (2 to 4) of nirogacestat. BID, twice daily; BM, bone marrow; mbBCMA, membrane-bound B-cell maturation antigen; WB, whole blood.

- Dose-related reductions in sBCMA were observed following treatment with nirogacestat, although the baseline levels were low in this healthy population and the effect was modest (data not shown)

OBJECTIVES

Primary

- To evaluate the PD of nirogacestat on BCMA

Secondary

- To evaluate the PK of serum nirogacestat after single- and multiple-dose administration of nirogacestat
- To evaluate the safety and tolerability of single- and multiple-dose nirogacestat in healthy male participants

Exploratory

- To establish an assay to measure mbBCMA antibody binding density on plasma cells from WB in healthy participants
- To evaluate the gene expression in plasma cells that correlates with changes in mbBCMA levels

CONCLUSIONS

- Nirogacestat treatment resulted in rapid and robust increases in mbBCMA levels on plasma cells isolated from BM and WB
- Continuous inhibition of GS is necessary to sustain elevated levels of mbBCMA on plasma cells
  - BID dosing of nirogacestat is recommended to sustain inhibition of GS on plasma cells and increase mbBMCA receptor density
  - A 100-mg, twice-daily dose of nirogacestat is being tested in clinical trial subjects with MM who are receiving BCMA-directed therapy
- Evaluating mbBCMA dynamics in plasma cells isolated from either BM or WB is feasible
  - These analyses are planned in clinical trials evaluating nirogacestat in combination with BCMA-directed therapy in MM patients

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