A Phase 1 Safety and Tolerability of Single Ascending Doses of a Novel Engineered Cationic Peptide, PLG0206, in Healthy Subjects

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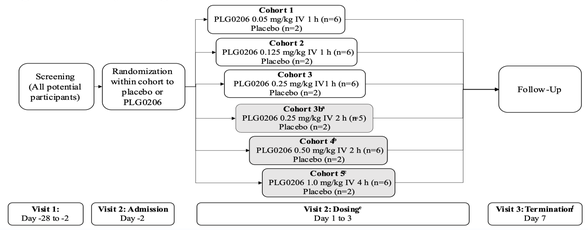
Introduction

- PLG0206 is a novel engineered cationic antimicrobial peptide for treatment of antimicrobial resistant pathogens (1)
- •PLG0206 is a broad-spectrum antimicrobial agent against multidrug resistant organisms, has rapid activity against biofilms, does not have significant local or systemic toxicity in animal models (2)
- This Phase 1, randomized, double-blind, placebo-controlled, single ascending dose (SAD) first in human study assessed the safety, tolerability, and PK of PLG0206 in healthy subjects

Methods

- Six (6) cohorts of 8 subjects received escalating single IV infusions of PLG0206 from 0.05 up to 1 mg/kg dose or placebo
- Participants were randomized to receive either PLG0206 (6 per cohort) or placebo (2 per cohort)
- At each dose level, there were 2 sentinel subjects (1 active, 1 placebo) who were dosed at least 48 hours in advance of the other subjects in their group
- Serial pharmacokinetic samples were taken at pre-dose, at the midpoint of infusion, within 1 minute of the end-of-infusion, and at 0.5, 1, 2, 4, 6, 8, 12, 20, 24, 36, and 48 hours after the end-of-infusion
- Safety and tolerability was assessed throughout the study.
- Subjects were followed for 7 days after dosing (Figure 1)
- There was at least a 7-day period after dosing at each of the dose levels before dose escalation

Figure 1. Study Design for the PGL0206 SAD IV Study



Objectives

- Primary: To evaluate the safety and tolerability of ascending, single doses of PLG0206 administered intravenously in normal healthy subjects
- Secondary: To characterize the PK profile of single doses of PLG0206 administered intravenously in normal healthy subjects

Results

- A total of 47 subjects were enrolled in the study: 35 received treatment with PLG0206 and 12 received placebo
- Two (2) subjects in Cohort 3 prematurely discontinued study drug administration (both received PLG0206) due to AEs; these 2 subjects did not receive the complete dosing of PLG0206 and were excluded from the PK population
- Overall, all 47 (100%) randomized subjects were included in the Safety population and 33 (94.3%) of 35 subjects dosed with PLG0206 were included in the PK population
- Therapeutic exposures were achieved at 1 mg/kg
- The incidence of treatment emergent adverse events related to study drug administration was low and most events mild (Grade 1) in severity and was similar between the PLG0206 treatment and placebo groups (Table 1)
- There were no SAEs, life-threatening events or deaths throughout the study
- IV PLG0206 exhibited linear PK over the dose range of 0.05 to 1.0 mg/kg. (Figures 2 and 3)
- Median terminal half-life ($t_{½}$) ranged from 7.37 to 19.97 hours
- $AUC_{0-\infty}$ increased with increasing PLG0206 dose ranging between 1581.41 and 21141.52 ng.hr/mL (Figures 2 and 3)
- C_{max} ranged between 256 and 2653 ng/mL (Figures 2 and 3)
- The mean apparent volume of distribution (V_z) increased and was between 25.49 and 94.2 L, and mean clearance (C_L) wassimilar across all and ranged from 2.42 to 4.18 L/hour

Results

Table 1. Safety Summary by Cohort and Overall

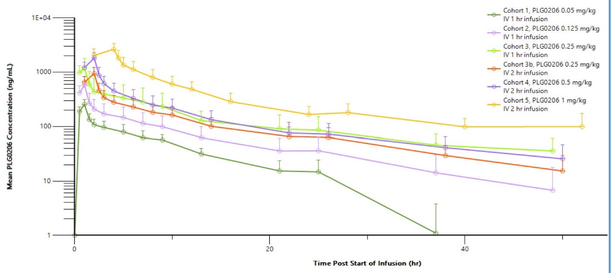
	0.05 mg/kg IV 1 hr (N=6) n (%)	0.125 mg/kg IV 1 hr (N=6) n (%)	0.25 mg/kg IV 1 hr (N=5) n (%)	0.25 mg/kg IV 2 hr (N=6) n (%)	0.5 mg/kg IV 2 hr (N=6) n (%)	1 mg/kg IV 4 hr (N=6) n (%)	Pooled PLG0206 (N=35) n (%)	Pooled Placebo (N=12) n (%)
Serious adverse events (SAEs)	0	0	0	0	0	0	0	0
TEAE*	1 (16.7%)	0	3 (60.0%)	0	3 (50.0%)	6 (100%)	13 (37.1%)	17 (36.2%)
TEAE Leading to Study Withdrawal	0	0	0	0	0	0	0	0
TEAE Leading to Study Drug Discontinuation	0	0	2 (40.0%)	0	0	0	2 (5.7%)	2 (4.3%)

*Treatment emergent adverse events: Mild infusion related reactions (IRRs). Increasing the volume and slowing rate of infusion mitigated frequency and severity of IRRs observed

Figure 2. PK Dose Response

Results

Figure 3. PLG0206 Plasma Concentration over time grouped by study cohort in semi-log scale



Conclusions

- Following single IV infusion to healthy subjects, PLG0206 was safe and well-tolerated at doses ranging from 0.05 to 1 mg/kg
- IV PLG0206 exhibits linear PK over the dose range
- These findings support the ongoing development of IV PLG0206 and will inform dosing regimens in future studies to investigate its utility as an antimicrobial agent

References

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