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Pharmacokinetic (PK) and pharmacodynamic (PD) results from a randomized, double-blind, placebo-controlled Cohort 2 of a Phase 1b study of an investigational, oral, live biotherapeutic, SER-155, in adults undergoing allo-HCT

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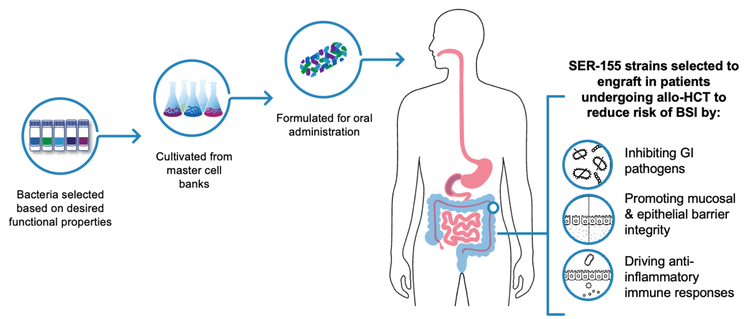
Introduction

In recipients of allo-HCT, microbiome disruption, characterized by low diversity and/or taxa domination, is associated with increased risk of bloodstream infections (BSIs) and acute graft-vs-host disease (aGvHD), contributing to significant morbidity and mortality[1, 2, 3].

SER-155 is an oral, live biotherapeutic with a novel therapeutic modality (see SER-155 drug design, below).

Here we summarize key safety and efficacy data and present SER-155 pharmacology data from a Phase 1b study (NCT04995653) in adults undergoing allo-HCT conducted in 2 phases, an open-label Cohort 1 and a placebo-controlled Cohort 2.

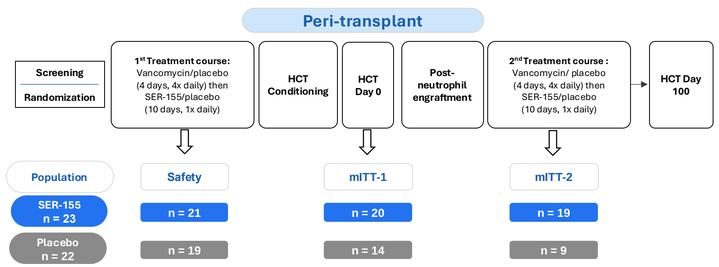
SER-155 Design Concepts



Methods

Cohort 2 participants (randomized 1:1) received vancomycin/SER-155 or placebo/placebo administered pre-HCT and post-neutrophil engraftment. Primary endpoints were safety and SER-155 drug strain engraftment (pharmacokinetics, PK, measured with specific molecular probes). Secondary efficacy endpoints included BSI incidence. Pharmacodynamic (PD) endpoints included GI domination by pathogenic bacteria (whole metagenome sequencing, WMS) and plasma biomarker concentrations (ELISA). PK and PD endpoint analyses presented here were performed with placebo-controlled Cohort 2 data; exploratory assessments of plasma biomarkers were performed with a combined analysis of Cohort 1 and Cohort 2 data. P-values provided are for exploratory purposes only and are not FDR or MHC corrected.

SER-155-001 study design & patient disposition



Demographics were mostly balanced between treatment arms (data not shown). Safety: received any amount of study drug, modified intent to treat-1 (mITT-1): proceeded to transplant, mITT-2: achieved neutrophil engraftment and received course 2. More placebo participants discontinued, impacting both stool and plasma sample numbers; however, there was a greater degree of stool sample loss for placebo participants compared with SER-155 participants.

Acknowledgments: The authors are indebted to study patients, collaborators, and site investigators and staff. Study sponsored by Seres Therapeutics.

References: 1. Taur Y, Xavier JB, Lipuma L et al. Clin Infect Dis 2012; 2. Peled JU, Gomes ALC, Devlin ALC, et al. NEJM 2020; 3. Taur Y, Jenq RR, Perales MA, et al. Blood 2014

Results: SER-155 Safety & Efficacy Summary

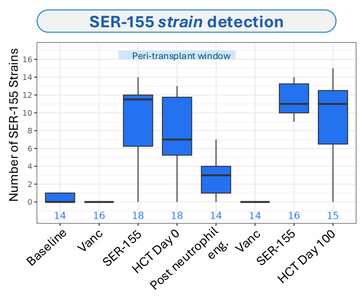
SER-155 was generally well tolerated. The safety profile was comparable between arms, and no treatment-related serious adverse events were observed. No SER-155 species were identified in any clinical culture specimens. Infection-related deaths were only observed in the placebo arm.

Significantly lower incidence of BSI. SER-155 treated participants had a significantly lower incidence of BSI compared to placebo through HCT Day 100: **10% in SER-155 vs. 43% in placebo** (odds ratio 0.15 (95% CI, 0.01-1.13) *p*=0.0423; absolute risk reduction=33%, relative risk reduction=77%).

Results: Robust SER-155 drug engraftment

Robust SER-155 engraftment following both treatment courses (Fig. 1). After the 1st treatment course, the majority of SER-155 strains engrafted and engraftment did not significantly decrease at HCT Day 0. The 2nd course restored engraftment durably through HCT Day 100. Consistent with strain-specific detection, a post-hoc analysis showed the aggregated relative abundance of SER-155 species was high relative to placebo following both courses and reduced over time.

SER-155 *strain* detection



SER-155 *species* abundance (WMS)

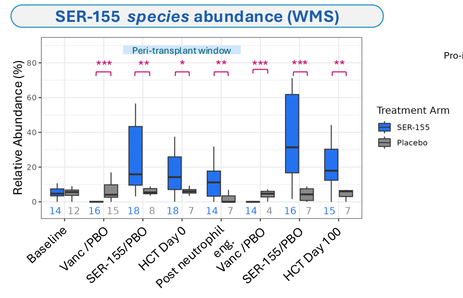


Figure 1. Detection of SER-155 strains with molecular probes (left) and SER-155 species relative abundance (via WMS, right). SER-155 species relative abundance is significantly higher than placebo (PBO) in SER-155 participants at all post-treatment visits; Mann-Whitney p-values (* = p <0.05, ** = p<0.01, *** = p<0.001). Numbers along x-axis represent sample count per group.

Results: Low prevalence of GI pathogen domination in study

Low prevalence of GI pathogen domination in study (Fig. 2). The prevalence of pathogen domination (relative abundance >30%) was low in both arms. Comparison to placebo was constrained by greater participant discontinuation in placebo, and greater stool sample loss in the placebo arm. In a historical comparator cohort from Memorial Sloan Kettering Cancer Center (MSKCC), domination events by *Enterobacteriaceae*, *Enterococcaceae, Staphylococcaceae* and *Streptococcaceae* increased across the peri-transplant window, while in the SER-155-001 study only events of *Enterobacteriaceae* and *Staphylococcaceae* domination were observed. In a post hoc analysis, domination in the SER-155 arm was numerically lower compared to the historical cohort.

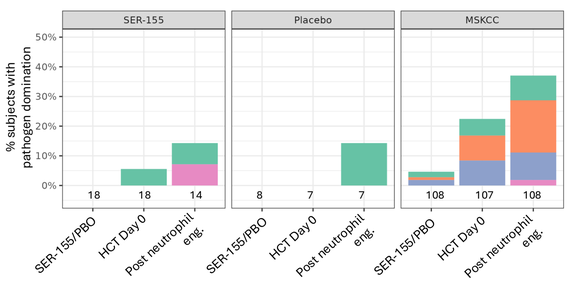


Figure 2. Percent of subjects per time point with indicated bacterial pathogen family >30% relative abundance of the GI microbiome via WMS (most abundant family used as representative in bar plot if > 1 family was dominating). No significant difference between SER-155 or placebo (PBO) with MSKCC for individual families or domination by any family (Fisher's exact test).

Results: Changes in cytokines with SER-155

Differences in plasma biomarkers of inflammation and immune homeostasis (Fig. 3, Fig.4). In a combined analysis of Cohort 1 and Cohort 2 to support signal seeking, pro-inflammatory cytokine concentrations were lower in the peri-transplant period in the SER-155 arm relative to placebo:

- IL-17 - significantly lower following the 1st treatment course and at HCT Day 0 (p<0.05)
- IFNγ - numerically lower at HCT Day 0 (p<0.1), significantly lower after neutrophil engraftment (p<0.05)
  - IFNγ differs significantly by arm at baseline; the post neutrophil engraftment visit remains p<0.05 when baseline is accounted for in the statistical model, glm(log10(biomarkers)~arm+baseline)
- TNFα - numerically lower after neutrophil engraftment (p < 0.1)
- Other inflammatory cytokines were lower reduced relative to placebo but not significantly (**Fig. 3**).

Additionally, immune homeostasis cytokine IL-10 was significantly lower after the 1st treatment course in the SER-155 arm compared to placebo.

Lower levels of pro-inflammatory cytokines during peri-transplant period

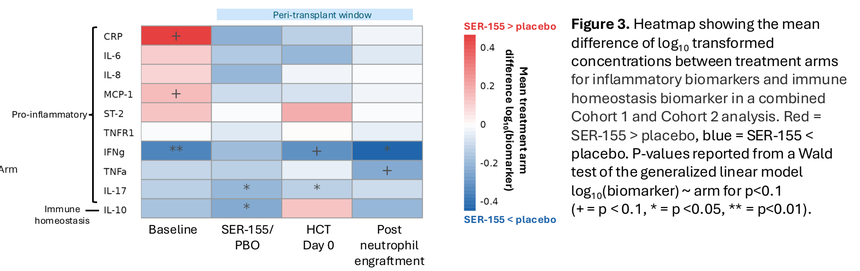
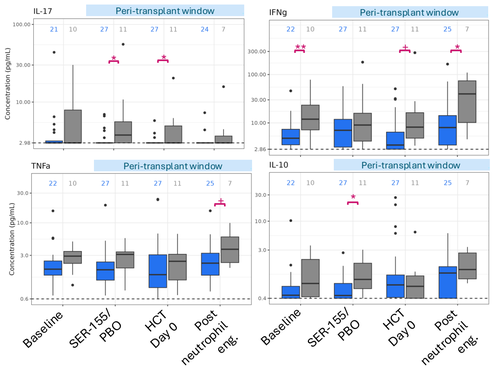


Figure 3. Heatmap showing the mean difference of $\log_{10}$ transformed concentrations between treatment arms for inflammatory biomarkers and immune homeostasis biomarker in a combined Cohort 1 and Cohort 2 analysis. Red = SER-155 > placebo, blue = SER-155 < placebo. P-values reported from a Wald test of the generalized linear model $\log_{10}$(biomarker) ~ arm for p<0.1 (+ = p < 0.1, * = p <0.05, ** = p<0.01).



Mean concentrations (pg/mL)

Visit	SER-155	Placebo	% Difference
IL-17			
SER-155/PBO	3.39	9.18	-63.1
HCT Day 0	3.14	5.21	-39.7
Post-neutrophil eng.	3.22	5.02	-35.9
TNFα			
SER-155/PBO	2.57	2.84	-9.5
HCT Day 0	3.60	2.60	38.5
Post-neutrophil eng.	2.93	4.73	-38.1
IFNγ			
SER-155/PBO	10.96	28.79	-61.9
HCT Day 0	8.87	35.04	-74.7
Post-neutrophil eng.	20.93	47.95	-56.4
IL-10			
SER-155/PBO	0.71	1.32	-46.2
HCT Day 0	2.92	1.21	141.3
Post-neutrophil eng.	1.26	1.81	-30.4

Figure 4. Plasma biomarker concentrations by treatment arm (left; SER-155, blue, placebo, gray). p-values from a Wald test reported for coefficients in a combined Cohort 1 + Cohort 2 analysis, glm(log10(biomarker)~arm); (+ = p < 0.1, * = p <0.05, ** = p<0.01). Mean concentrations (pg/mL) and % difference between arms shown in the table (right).

Conclusions

SER-155 engraftment is robust at the onset of HCT conditioning and at HCT Day 0

- SER-155 was delivered to the GI tract ahead of the peri-transplant period of acute barrier damage and microbiome disruption, during which subjects are immunosuppressed and can experience local and systemic inflammation and vulnerability to infection.

Pharmacodynamic results are consistent with design goals for SER-155: inhibit pathogens & reduce inflammation

- Comparison to a historical comparator cohort suggests SER-155 reduced pathogen domination
- Lower levels of several inflammatory cytokines in SER-155 vs. placebo during the peri-transplant period

These pharmacological results support the observation of significantly lower incidence of BSI in participants who received SER-155.