DDW2025
Digestive Disease Week®

MAY 3–6, 2025 | SAN DIEGO, CA

Su2009: Pharmacokinetic and Pharmacodynamic (PK & PD) Results from a Randomized, Double, Placebo-Controlled Cohort of a Phase 1b study of Investigational, Oral, Live Biotherapeutic, SER-155, in Adults Undergoing Allo-HCT

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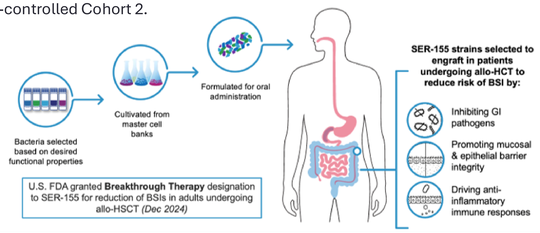
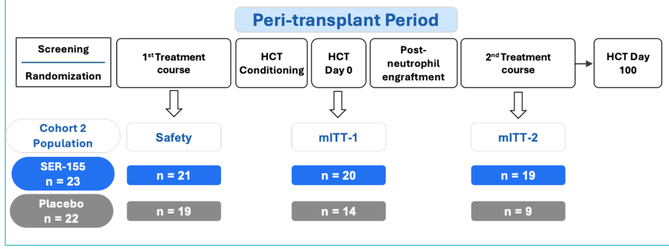
INTRODUCTION

- In recipients of allo-HCT, microbiome disruption is associated with increased risk of bloodstream infections (BSIs) and acute graft-vs-host disease (aGvHD), contributing to significant morbidity and mortality1, 2, 3.
- SER-155 is an oral, live biotherapeutic representing a novel therapeutic modality.
- 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 an open-label Cohort 1 and a placebo-controlled Cohort 2.



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 strain engraftment (pharmacokinetics, PK measured with molecular probes, whole metagenome sequencing, WMS). Secondary efficacy endpoints included BSI incidence. Pharmacodynamic (PD) endpoints included GI domination by pathogenic bacteria (WMS), and fecal albumin and plasma biomarker concentrations (ELISA). PK/PD endpoint analyses of stool were performed with Cohort 2 data; exploratory assessments of plasma biomarkers were performed with Cohort 1 (N=15 enrolled) and Cohort 2 (N=45 enrolled) data.



Cohort 2 demographics were mostly balanced between treatment arms (data not shown). Participant conditioning regimen: 79% reduced intensity, 18% myeloablative, 3% non-myeloablative. Post-transplant cyclophosphamide GvHD prophylaxis: 79%. Safety: received any study drug, modified intent-to-treat-1 (mITT-1): proceeded to transplant, mITT-2: achieved neutrophil engraftment and received course 2. The 1st and 2nd treatment course include vancomycin/placebo (4 days, 4x daily) then SER-155/placebo (10 days, 1x daily). More placebo participants discontinued, impacting stool and plasma sample numbers; stool sample loss was further reduced for placebo participants compared with SER-155.

RESULTS

SER-155 Clinical Safety & Efficacy Summary

SER-155 was generally well tolerated

- The safety profile was comparable between treatment arms.
- No treatment-related serious adverse events were observed.
- No SER-155 species were identified in any clinical specimen cultures.
- Infection-related deaths were observed only in the placebo arm.

SER-155 showed significantly lower incidence of BSI.

- SER-155 treated participants had a significantly lower incidence of BSI: **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% (HCT D0-100).
- All BSIs occurred between HCT days 4 and 15, before neutrophil engraftment.

SER-155 Pharmacokinetics

SER-155 engraftment was robust following both treatment courses

- A majority of SER-155 strains engrafted in a majority of participants after course 1, prior to HCT conditioning, and after course 2, following neutrophil engraftment (**Fig. 1A**).
- The aggregated relative abundance of SER-155 species was high relative to placebo following both courses and reduced over time (**Fig. 1B**).

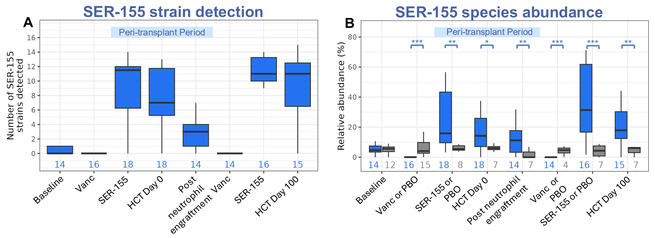


Figure 1. SER-155 drug engraftment. (A) Detection of SER-155 strains with molecular probes and (B) SER-155 species relative abundance (via WMS). SER-155 species relative abundance is significantly higher than placebo (PBO) at all post-treatment visits; Mann-Whitney p-values (* = p <0.05, ** = p<0.01,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

SER-155 Pharmacodynamics: Pathogen domination

Low prevalence of GI pathogen domination in study

- Prevalence of pathogen domination (relative abundance >30%) was low in both arms; placebo detection of domination was constrained by higher participant discontinuation and sample loss relative to SER-155.
- Compared to a historical allo-HCT cohort from Memorial Sloan Kettering Cancer Center (MSKCC), domination in SER-155-001 was numerically lower through the peri-transplant period.

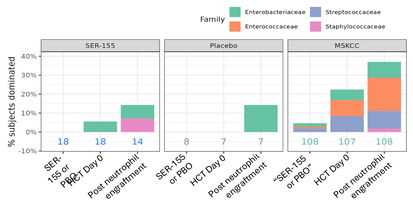


Figure 2. Domination prevalence (%) across peri-transplant. MSKCC samples were matched to SER-155-001 study timepoints.

SER-155 Pharmacodynamics: Epi Barrier Integrity

Fecal albumin, a biomarker of GI barrier integrity, is lower following SER-155

- SER-155 participants had significantly lower fecal albumin following the 1st treatment course (SER-155 or PBO) compared to placebo (**Fig 3A, 3B**: mean 77% lower in SER-155 arm compared to placebo, GLM p=0.0006); SER-155 was significantly lower than a self-reported healthy cohort following treatment (GLM p=0.03) and statistically similar to healthy through the remainder of the peri-transplant period (GLM: HCT Day 0, p=0.44; Post-neutrophil engraftment, p=0.96).
- Samples collected *after* the start of HCT conditioning regimen (Post-SER-155 or PBO planned visit) show that PBO recipients had elevated fecal albumin while SER-155 recipients remained low (**Fig 3C**: interaction between arm and 'timing relative to HCT conditioning', GLM p=0.0007).
- Participants with a post-HCT BSI had elevated fecal albumin levels prior to transplant, after completion of course 1 (SER-155 or PBO) (**Fig 3D**: Post-SER-155 or PBO, GLM p=0.04).

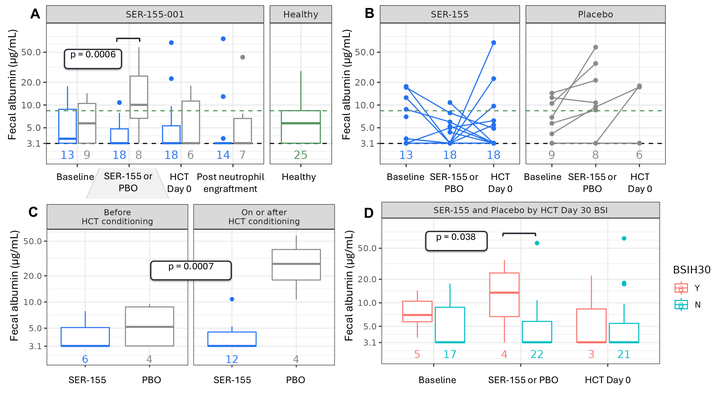


Figure 3. Fecal albumin concentrations (ng/mL). SER-155 = blue, Placebo = grey, Healthy = green. Numbers along x-axis represent sample count per group. (A) SER-155 and placebo arms compared to a healthy cohort; p-value reported from a Wald test of the generalized linear model (GLM), $\log_{10}$(biomarker) ~ arm. (B) Participant-level concentrations through HCT Day 0 when placebo sample loss limits arm comparisons. (C) Concentrations from samples collected before HCT conditioning start and those collected on or after; p-value reported from a Wald test of the GLM interaction term, $\log_{10}$(biomarker) ~ arm * 'timing relative to HCT conditioning'. (D) Concentrations colored by whether participant experienced a BSI within HCT Day 0-30 (BSIH30).

SER-155 Pharmacodynamics: Systemic Immunity

Low levels of systemic inflammation and immune homeostasis

- Pro-inflammatory and immune homeostasis cytokine concentrations were lower in the peri-transplant period in the SER-155 arm relative to placebo.

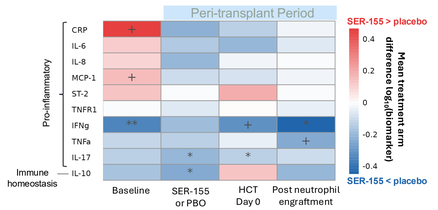


Figure 4. Plasma biomarker concentrations. Heatmap shows the mean difference of $\log_{10}$ transformed concentrations between arms for plasma biomarkers. Red = SER-155 > placebo, blue = SER-155 < placebo. P-values reported from a Wald test of the generalized linear model $\log_{10}$(biomarker) ~ arm

(+ = p < 0.1, * = p <0.05, ** = p<0.01).

CONCLUSIONS & SUMMARY

- SER-155 is an oral, live biotherapeutic product (LBP) comprised of 16 strains of human-commensal bacteria, selected for their functional properties.
- SER-155 was investigated in allo-HSCT participants in a Phase 1b study
- SER-155 engrafted in the GI tract prior to HCT conditioning.
- Participants receiving SER-155 had significantly fewer BSI than participants receiving placebo.
- In the peri-transplant period, pathogen domination was numerically lower in the SER-155 arm compared with a historical allo-HCT MSKCC cohort.
- Lower fecal albumin levels in SER-155 arm vs. placebo suggest that SER-155 protects the GI barrier at onset of HCT conditioning, at the same point in time when lower levels of pro-inflammatory cytokines are observed in SER-155 participants.
- These pharmacology results are consistent with the intended SER-155 mechanisms of action as well as the observation of lower BSI incidence in SER-155 participants.
- Collectively, these data suggest microbiome therapeutics may also have potential benefits in inflammatory diseases like IBD.

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

ACKNOWLEDGEMENTS

The authors are indebted to study participants, collaborators, and site investigators and staff. Study sponsored by Seres Therapeutics. SER-155 preclinical development funded by CARB-X.