Abstract N°: ID-1261

Topic: Atopic dermatitis/ Eczema

ENS-002 in atopic dermatitis, a microbiome-safe live biotherapeutic product that suppresses S. aureus growth and virulence

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Introduction

Virulence factors regulated by the agr quorum sensing system in *Staphylococcus aureus*, especially the PSMα toxin and V8 protease, exacerbate atopic dermatitis (AD). PSMα can cause inflammation while V8 protease can induce pruritus. Though *S. aureus* appears in 60–93% of AD patients, the *S. aureus* component of AD's etiology has proven difficult to address. Notably, broad-spectrum antibiotics leave the ecological niche open, enabling rapid recolonization of *S. aureus*. Moreover, antibiotics diminish natural *S. aureus*-subduing mechanisms in other skin commensals. Here we introduce ENS-002, an investigational new product to inhibit *S. aureus* proliferation, quorum sensing by agr, and downstream effectors of agr (e.g. PSMα)—without disrupting the native microbiome. A live biotherapeutic product (LBP), ENS-002 comprises three skin-derived bacterial strains that act in tandem to robustly achieve these therapeutic effects. We hypothesized that topical *in vivo* application of ENS-002 would inhibit *S. aureus* growth and virulence without affecting microbial diversity, thereby facilitating skin recovery.

Materials and Methods

kChip, a powerful coculture screening platform, generated over 5 million microbial combinations each consisting of a *S. aureus* gene expression reporter and either two, three, or seven additional skin bacterial strains. From these cocultures, we identified a three-strain combination optimally suited to specifically inhibit *S. aureus* virulence (*agr*, *psmα*, *saeR*, *ccpA*), stress (*sigB*), and proliferation (*gmk*) in a manner that was robust to any additional strain or nutrient present. Designating this combination ENS-002 ("Ensemble No.2"), we validated the inhibition of *S. aureus* on an *in vitro* epidermis model. ENS-002 subsequently underwent a first-in-human dose escalation study. Eight participants (pts) with mild to moderate AD (EASI 5–21) enrolled into two cohorts. Dosing escalated from QD for seven days at 1x10^7 CFUs applied to a single lesion in Cohort 1, to QD for 14 days at 1x10^8 CFUs applied to all lesions in Cohort 2. Microbiome, eczema severity, and QOL were tracked during the application period and for 28 days after the last dose.

Results

ENS-002 potently suppressed *S. aureus* on the kChip coculture screening system: Virulence genes *agr*, *psmα*, and *saeR* were inhibited by 99.3%, 99.5%, and 91.5%, respectively and growth, as measured by *gmk,* by 97.0%. ENS-002 effects on *S. aureus* were robust to the presence of additional microbial communities (suppressive effects in 95% of additional communities tested were as strong as ENS-002 alone). ENS-002 activity was validated on an *in vitro* human epidermis model where *S. aureus* growth (*gmk*) was suppressed by 96% and virulence (*agr*) by 91%.

In pts with AD, ENS-002 proved safe with no drug related AEs of any grade reported. On 4/4 pts with *S. aureus*-positive lesional skin at baseline, *S. aureus* abundance dropped—and to nearly 0% in 3 of these (See figure 1)—without

compromising microbiome diversity. Encouraging trends were observed in clinical measurements despite the short treatment window, especially in Cohort 2: EASI score improved in 4/4 pts (by 41% on average); peak pruritus (PPNRS) in 4/4 pts (by 1.5 points on average); and IGA in 2/4 pts. In addition, pts consistently reported improvements in daily diary metrics (general eczema feeling, dryness, itchiness, rash, and scaliness).

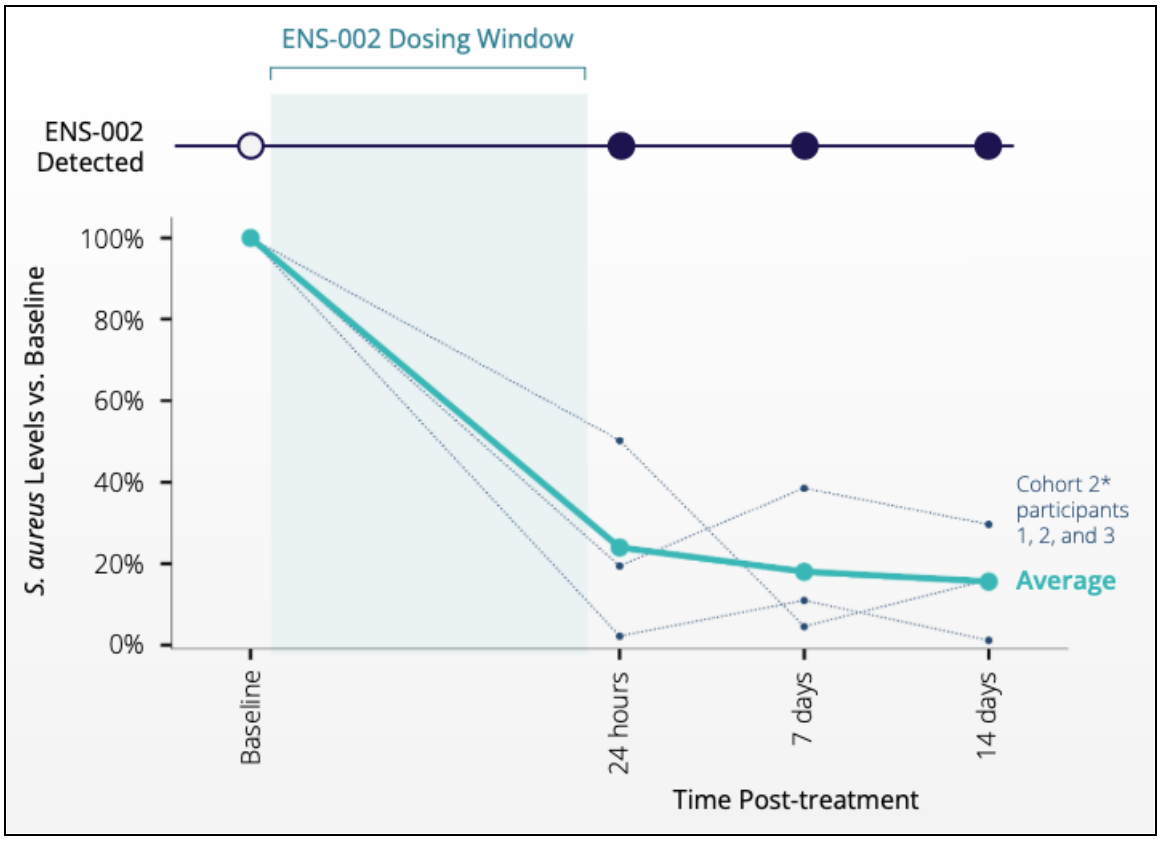

Figure 1: S. aureus levels dropped in cohort 2 participants and remained low for two weeks after dosing of ENS-002 stopped. ENS-002 was detectable for at least 14 days after the last dose.

Conclusions

Our data demonstrate the potential of ENS-002 to counteract *S. aureus* virulence without collateral damage to the skin microbiome. A modality missing from our therapeutic armamentarium, ENS-002 would complement existing approaches to address the complex etiology of AD. The safety profile and clinical improvements observed in the ENS-002 first-in-human study support initiation of a Phase 2a study.