EGL-003 First in human study: An IL-2 Mutein inducing potent and selective amplification of Treg with preferential activation of effector/memory skin homing Tregs

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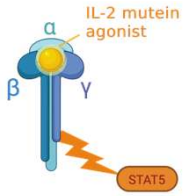
BACKGROUND

IL-2m Agonist Turns Tregs ON

- Expands Tregs
- STAT5 active
- IL-2Rα bias
- No effect on conv T cells



- **Regulatory T cells (Tregs)** are key to maintaining **immune homeostasis**, and impaired Treg function is associated with inflammatory diseases such as **atopic dermatitis (AD)**.
- **EGL-003** is a novel **IL-2 mutein Fc-fusion protein** designed to **potently and selectively expand Tregs**, with the potential to restore immune homeostasis.
- This **first-in-human study** evaluates the **safety, tolerability, PK and PD** of EGL-003 in a **SAD phase in healthy volunteers**, followed by a **MAD phase in patients with AD.**

HV (n=6) 0.5 µg/kg
HV (n=6) 1.5 µg/kg
HV (n=6) 5 µg/kg
HV (n=6) 2.5 µg/kg

IL-2 mutein-Fc. Phase I/ First-in-human Single Ascending Dose in Healthy Volunteers:

- 24 subjects, 4 dose levels
- 1 unique sc. administration

MATERIAL & METHODS

- **24 healthy volunteers**, aged 18–55 years, were enrolled in the SAD phase and received a **single subcutaneous dose** of EGL-003 across four ascending dose levels (N=6 volunteers per cohort).
- **Safety and tolerability** were assessed through TRAEs, vital signs, laboratory tests, ECGs, and injection-site reactions (ISRs).
- **PK and PD** were evaluated through **Day 56**.
- PD assessments included **deep peripheral blood immunophenotyping** to characterize Treg IL-2 signaling, activation, expansion, and tissue-homing markers, together with cytokine profiling.

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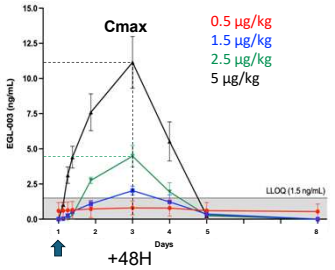
RESULTS

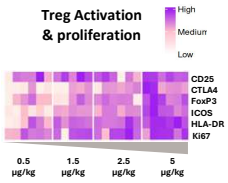
EGL-003, Dose dependent pharmacokinetics & no ADA

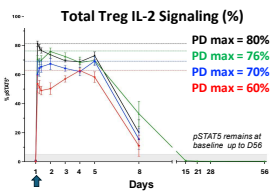
Cmax (+48H) was dose proportional and no anti-drug antibodies were detected up to Day 56 after a single injection.

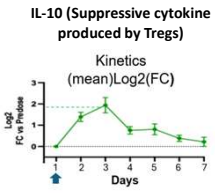


EGL-003 Leads to Potent IL-2R Signaling & Activation of Tregs

Treatment resulted in strong IL-2 signaling in Tregs, along with consistent dose-dependent upregulation of activation and suppressive function markers on Tregs (FACS on PBMC) including FOXP3, CD25, CTLA-4, ICOS, as well as enhanced proliferation (Ki67) and rise in serum IL-10 levels.

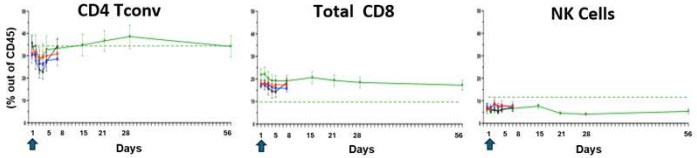






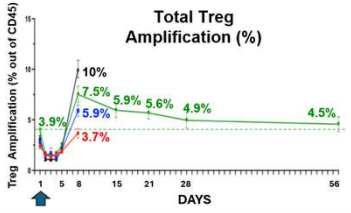
EGL-003 is Highly Selective to Treg

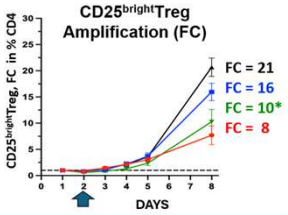
No impact on CD4 Tconvs, CD8 T cells and NK cells was observed.



EGL-003 Leads to Sustained Tregs Amplification

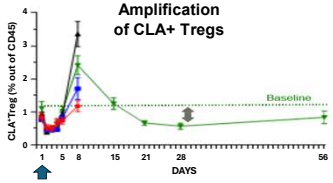
This heightened activation translated into a substantial expansion of the Treg population over time and total Treg elevation was sustained through Day 28. Focusing on CD25BRIGHT Tregs amplification, a dose dependent 7-21 Fold increase at Day 8.

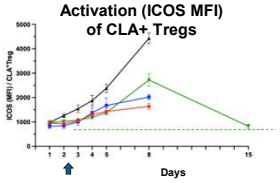




EGL-003 Induces Activation, Amplification & Transmigration of CLA+ "skin homing" Tregs

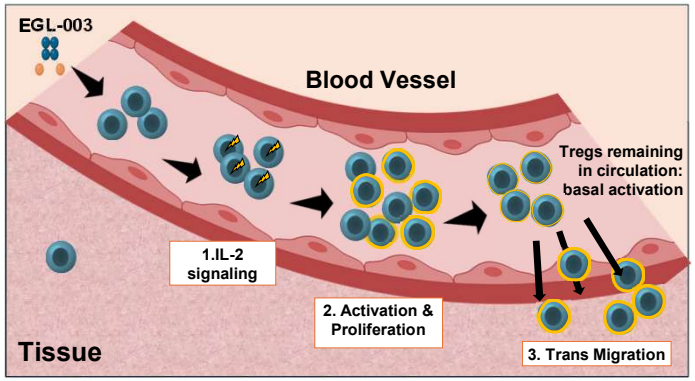
CLA+ Tregs are effector-memory cells with skin-homing capacity. EGL-003 induced their activation and expansion, followed by a decline below baseline consistent with migration out from the blood (likely into skin)





Cohort#1 (0.5 µg/kg) Cohort#2 (1.5 µg/kg), Cohort#4 (2.5 µg/kg), Cohort#3 (5 µg/kg)

SAD Data Highlight Potent Treg Activation, Amplification and Acquisition of Tissue Effector Functions



SAFETY & TOLERABILITY

EGL-003 Demonstrated a Favorable Tolerability Profile

- EGL-003 was **well tolerated** across the tested dose range (0.5 to 5 µg/kg)
- At doses of 0.5 and 1.5 µg/kg, TRAEs were limited to mild ISRs that consisted mainly of erythema, possibly associated with itching, swelling, pain and tenderness with a trend in dose-dependency.
- Doses of 2.5 and 5 µg/kg presented other AEs (FLU-like symptoms).
- **No severe or serious adverse events were reported.**
- No cohort / study stopping rules were met.

CONCLUSIONS

- EGL-003 demonstrates a **favorable safety profile and induces potent, selective Treg activation with sustained expansion**.
- E003 leads to **activation of effector memory Tregs with a skin homing profile.**
- These findings **support the continued clinical development of EGL-003** across autoimmune and inflammatory diseases. EGL-003 is currently being evaluated in a **multiple-ascending-dose study in patients with moderate-to-severe atopic dermatitis**.

ACKNOWLEDGEMENTS & CONFLICT OF INTEREST :
All authors are employees of Egle Therapeutics

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