

IMP761, a novel immunosuppressive LAG-3 agonist antibody in the clinic

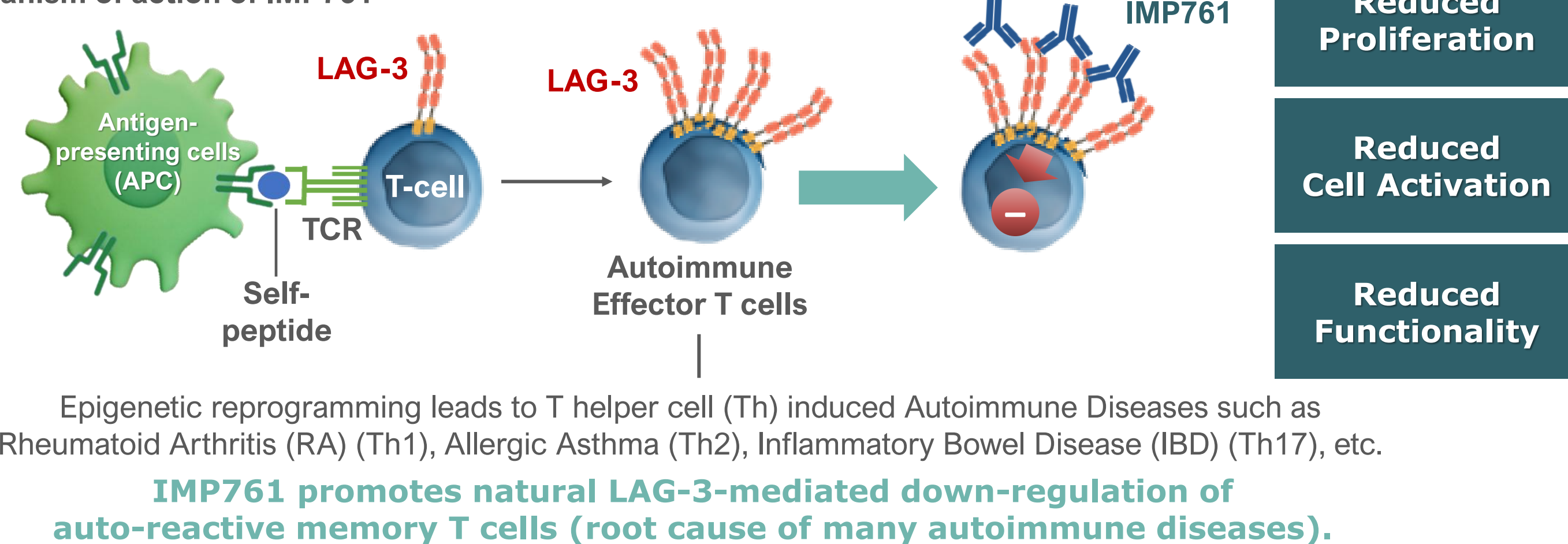
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BACKGROUND

- IMP761 is a novel, first-in-class, Lymphocyte Activation Gene-3 (LAG-3) agonist antibody targeting the root cause of many autoimmune diseases (1).
- Physiologically, LAG-3 interferes with T-cell stimulation by downmodulating T-cell receptor (TCR) signaling. IMP761, by forming LAG-3 "dimers of dimers", increases this physiological downmodulation of T-cell activity.
- In autoimmune diseases, memory T cells are chronically stimulated by the same self-peptide which leads to LAG-3 expression, a hallmark of auto-reactive memory T cells in inflamed tissues.
- Hence, binding of IMP761 to LAG-3 represents a targeted approach to key mediators of autoimmune diseases, upstream of current therapeutic interventions (Figure 1).
- Here, we report interim preliminary data from the single-ascending dose (SAD) part of our Phase 1 trial with IMP761 in healthy volunteers (HV).

Figure 1. Mechanism of action of IMP761



PRE-CLINICAL DEVELOPMENT

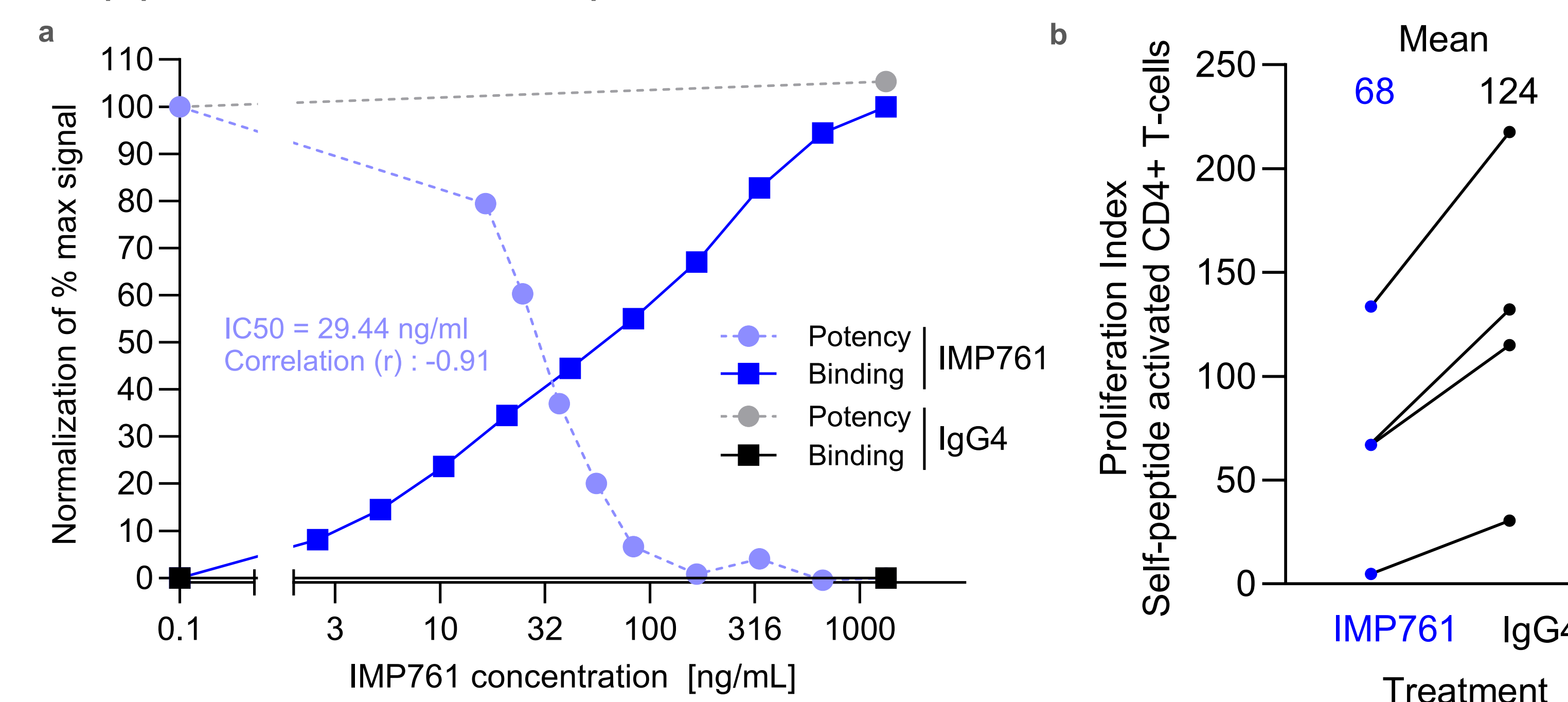
IMP761 SHOWS DIRECT INHIBITORY EFFECTS ON TCR SIGNALING

- IMP761 showed a direct inhibitory effect on TCR signaling in vitro on LAG-3⁺ engineered Jurkat T-cells with luciferase expression controlled by Nuclear Factor of Activated T-cells (NFAT) and stimulated with low concentrations of an anti-CD3 antibody (Figure 2a).
- Dose-dependent inhibition of TCR signaling by IMP761 was observed and correlated with its binding to LAG-3. The potency of IMP761 was measured by a reduction in luciferase signal caused by reduced NFAT activation downstream of TCR signaling.
- IMP761 reduced proliferation of self-peptide-activated CD4⁺ T-cells from rheumatoid arthritis (RA) patients (Figure 2b).

Methods

- Binding of IMP761 or isotype control (IgG4) to LAG-3⁺ Jurkat T-cells was measured by flow cytometry.
- A luciferase reporter gene assay was used to measure T-cell activation triggered by TCR signaling.
- Peripheral blood mononuclear cells (PBMCs) from RA patients were stimulated for 6 days with a pool of ≥11-mer self-peptides derived from cartilage-associated self-antigens: citrullinated vimentin, -enolase, -fibrinogen β, collagen II, PAD4, and cartilage GP39.

Figure 2. Direct inhibitory effect on TCR signaling (NFAT activation) and inhibition of proliferation of self-peptide-activated T-cells from RA patients



a: Binding of IMP761 or isotype control (IgG4) to LAG-3 on Jurkat T-cells and the normalized signal intensity emitted by the luciferase reporter gene (potency). b: Proliferation index of CD4⁺ T-cells from RA patients, activated with self-peptides (cartilage-derived autoantigen peptide pool), in the presence of IMP761 or isotype control (IgG4).

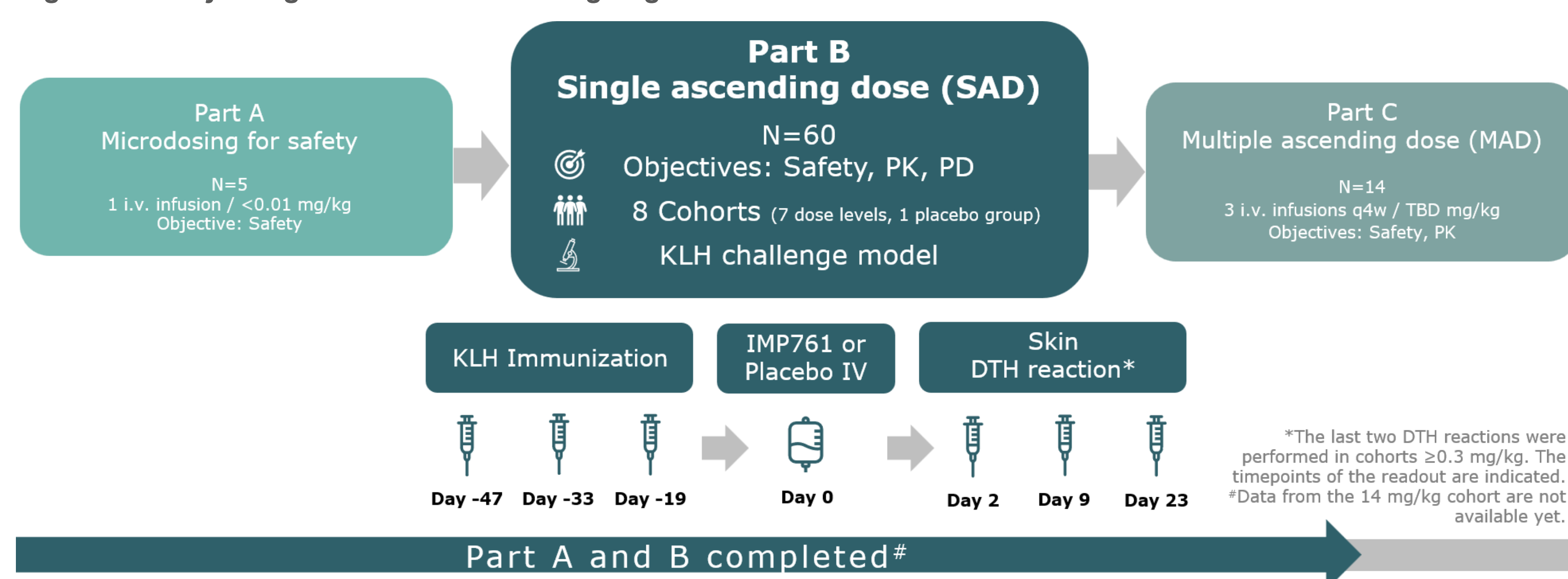
CLINICAL DEVELOPMENT

STUDY DESIGN AND METHODS

Study Design

- A randomized, placebo-controlled Phase 1 trial composed of three parts is being conducted (Figure 3) (NCT06637865).
- For Part B, 60 HV were recruited. The Keyhole Limpet Hemocyanin (KLH) neoantigen challenge model (2) was applied. Following immunization with KLH, HV were assigned to 8 different cohorts to receive single ascending doses (SAD) of IMP761 at 0.03 mg/kg – 14.0 mg/kg or placebo on Day 0 (Figure 3). A delayed-type hypersensitivity (DTH) reaction was elicited by intradermal injection of KLH on Day 1, Day 8, and Day 22.
- Skin blood perfusion and cell counts in skin blister fluids were measured 24 hours post KLH challenges (on Day 2, Day 9 and Day 23).
- Concentration of IMP761 in serum was measured 1 and 6 hours and 1, 2, 4, 8, 15, 22, 29 and 44 days post infusion.
- Part C of the study is planned to assess multiple ascending doses (MAD) of IMP761.

Figure 3. Study design and status of the ongoing Phase 1 trial with IMP761

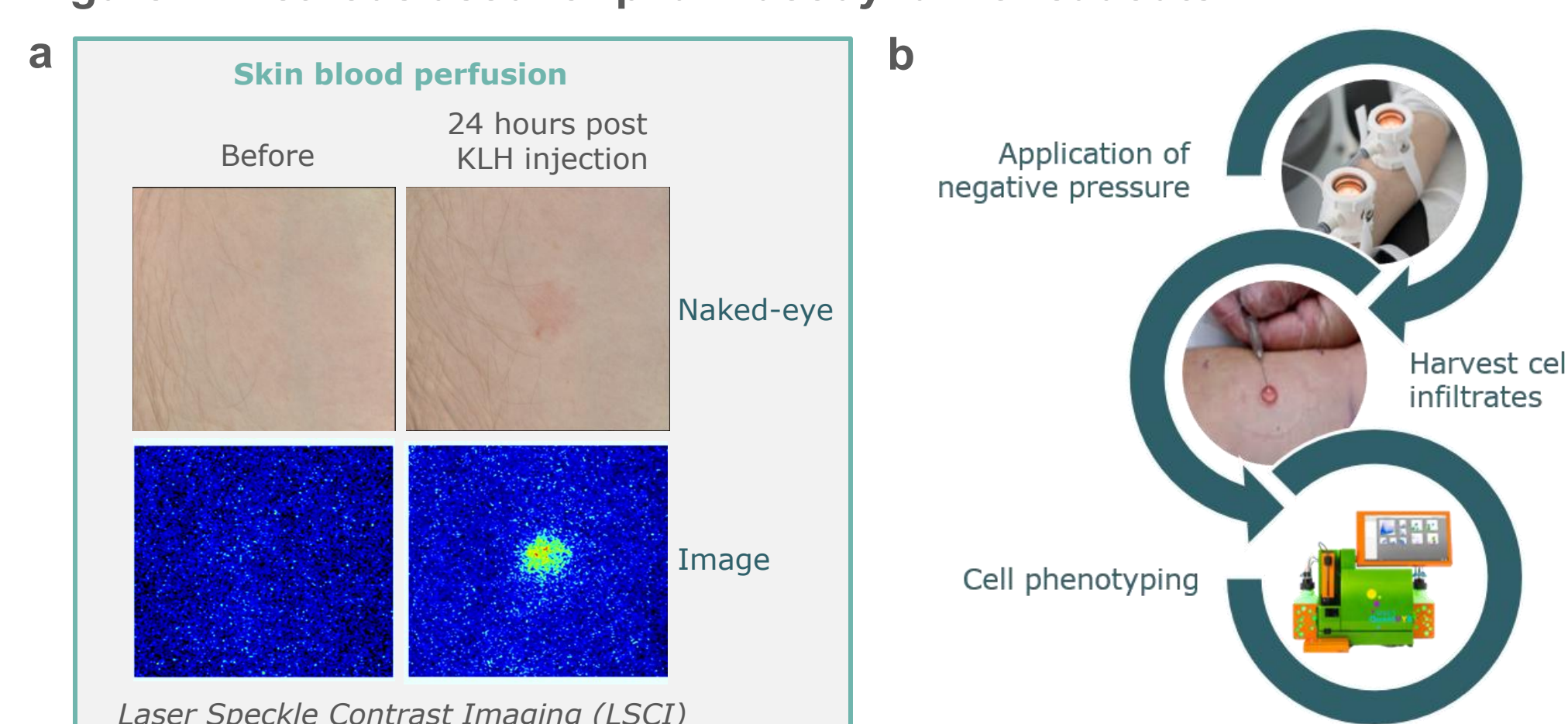


*The last two DTH reactions were performed in cohorts ≥0.3 mg/kg. The timepoints of the readout are indicated. *Data from the 14 mg/kg cohort are not available yet.

Methods

- Blood perfusion was analyzed on Day 9, 24 hours post KLH injection, by Laser Speckle Contrast Imaging (LSCI) (Figure 4a).
- Skin blister fluids were harvested on Day 9 and cell phenotyping was performed using flow cytometry to quantify local cell infiltration (Figure 4b).

Figure 4. Methods used for pharmacodynamic readouts

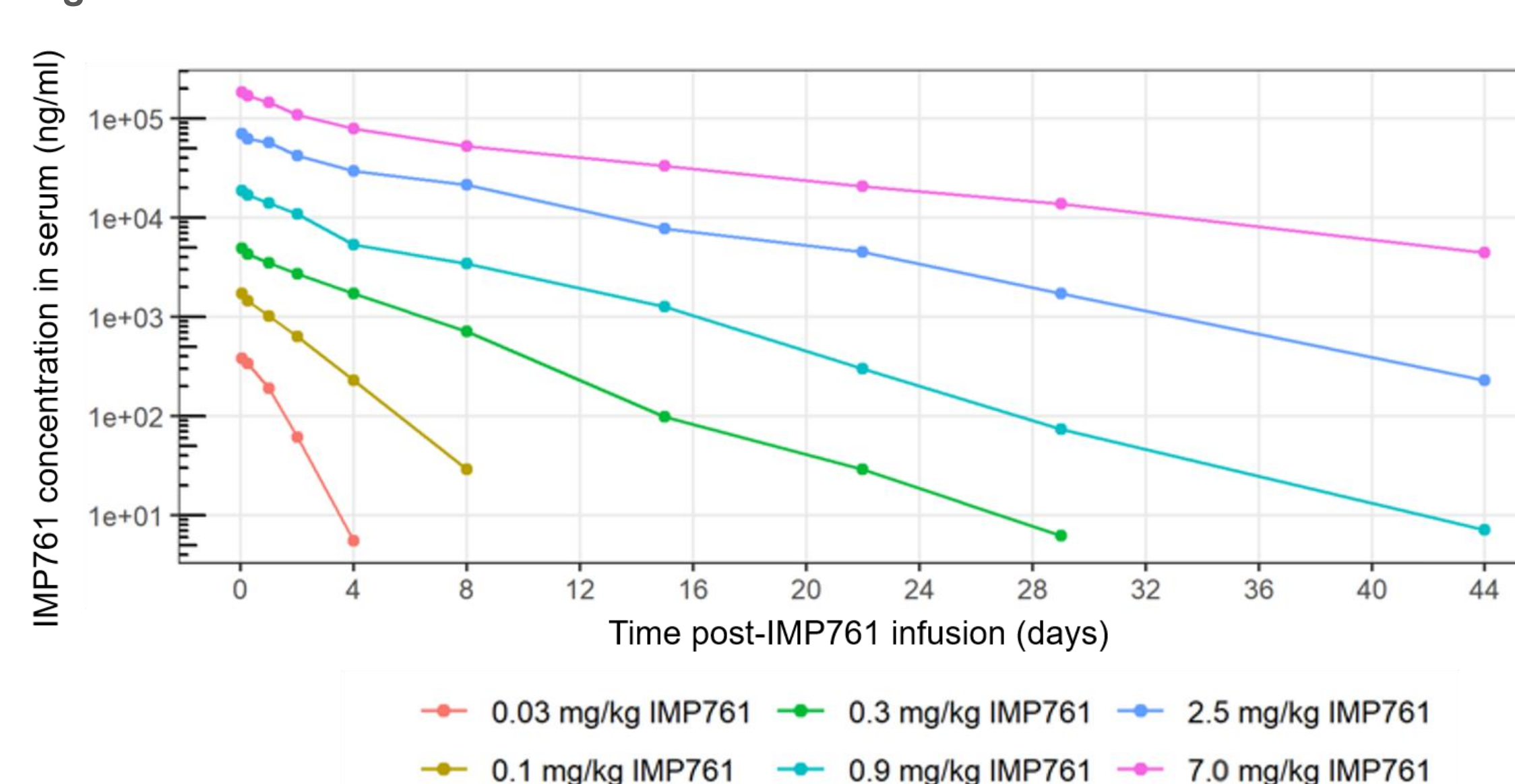


INTERIM RESULTS

IMP761 SHOWS PHARMACOKINETICS SUITABLE FOR 4-WEEKLY DOSING

- Over the 0.03–7 mg/kg dose range, exposure increased in a more-than-dose-proportional manner (Figure 5).[#]
- Clearance decreased with increasing dose, while half-life increased, indicating a dose-dependent reduction in elimination.
- These findings indicate nonlinear pharmacokinetics consistent with saturation of a target-mediated mechanism.
- The serum half-life supports a MAD regimen of repeat dosing every 4 wk.

Figure 5. Pharmacokinetics of IMP761



Concentration of IMP761 in serum of HV at indicated timepoints. IMP761 was administered i.v. on Day 0 only.

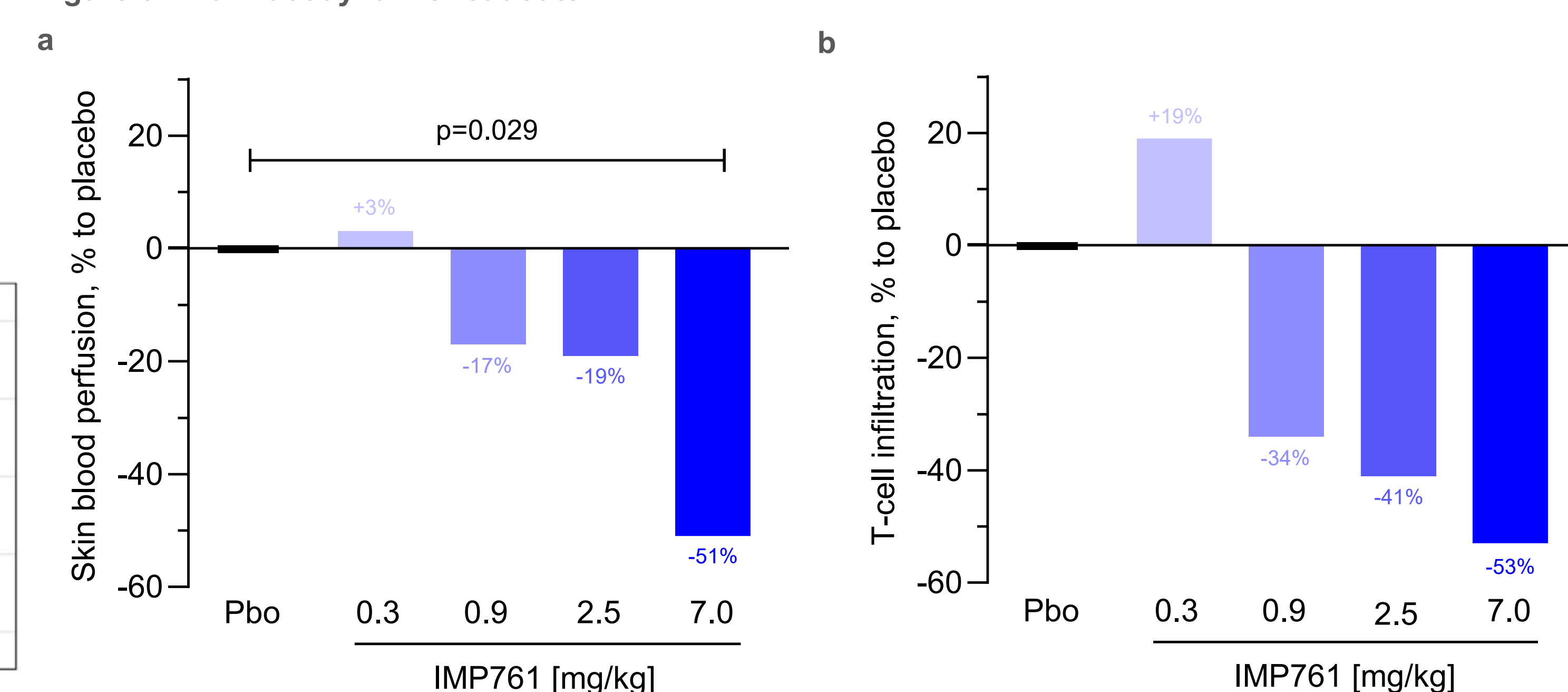
IMP761 SHOWS FAVORABLE SAFETY PROFILE

- A single injection of IMP761 at doses of 0.3–7.0 mg/kg was very well tolerated with possibly related AEs reported as only mild or moderate in severity.[#]
- Out of the AEs that were reported as at least possibly related to IMP761, only three were moderate in severity (n=2 gastroenteritis, n=1 rhinitis). The remainder were reported to be mild.
- No severe or serious adverse events were reported.

IMP761 SIGNIFICANTLY INHIBITS A DAY 9 DTH REACTION TO KLH AT DOSES ≥0.9 mg/kg

- On Day 9, skin blood perfusion was reduced compared to placebo with doses of IMP761 ≥0.9 mg/kg. Reduction was statistically significant at 7 mg/kg (Wilcoxon rank-sum test, p = 0.029) (Figure 6a).[#]
- T-cell counts in skin blister fluid were substantially reduced as well (Figure 6b).[#]

Figure 6. Pharmacodynamic readouts



Pharmacodynamic readouts of the DTH reaction, measured on Day 9, 24 hours after intradermal injection with KLH. Performed in cohorts from the 0.3 mg/kg dose level and above. Pbo: Placebo. a: Cutaneous blood perfusion in challenged area expressed as basal flow change from baseline, in relation to placebo. b: T-cell counts in skin blister fluid, in relation to placebo.

SUMMARY & CONCLUSION

- IMP761, a novel LAG-3 agonist antibody, directly inhibits T-cell receptor signaling into self-antigen-specific T-cells and thereby could address the root cause of many auto-immune diseases upstream of current therapeutic interventions.
- Single dose PK of IMP761 support a 4-weekly dosing for repeated administrations.
- IMP761 was very well tolerated.
- A single i.v. infusion of IMP761 significantly inhibits delayed type hypersensitivity reactions to KLH, a strong foreign antigen. Effects were observed at doses ≥0.9 mg/kg.
- Conclusion: Based on interim data, this novel therapeutic approach has the potential to become a transformative therapy across multiple autoimmune indications driven by T-cell mediated inflammation. Further investigation in a Phase 2 trial is warranted.

[#]Interim preliminary data are shown. Data from the 14 mg/kg cohort are not available yet.

REFERENCES

- Angin M et al., J Immunol. 2020;204(4):810-818
- Ronier MN et al., Front Pharmacol. 2026;16:1717333

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ABBREVIATIONS

- CD... cluster of differentiation
- DTH... delayed type hypersensitivity
- HV... healthy volunteer
- i.v... intravenously
- KLH... Keyhole Limpet Hemocyanin
- LAG-3... Lymphocyte Activation Gene-3
- MAD... multiple ascending dose
- mo... months
- NFAT... nuclear factor of activated T-cells
- Pbo... placebo
- RA... rheumatoid arthritis
- SAD... single ascending dose
- TCR... T-cell receptor
- Th... T helper cell
- wk... week



ABBREVIATIONS