IMP761, a Novel Immunosuppressive Lymphocyte Activation Gene-3 (LAG-3) Agonist Antibody in the Clinic

LB09

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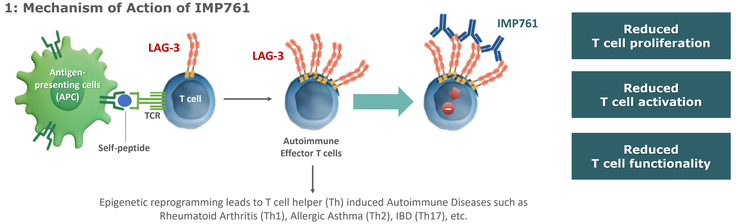
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BACKGROUND

- IMP761 is a novel, first-in-class agonistic IgG4 antibody targeting Lymphocyte Activation Gene 3 (LAG-3), an inhibitory immune checkpoint receptor expressed predominantly on chronically activated T cells at sites of inflammation (1).
- Under physiological conditions, LAG-3 functions as a natural brake on T cell activation by directly inhibiting T cell receptor (TCR) signaling.
- IMP761 amplifies this direct inhibition of TCR signaling, resulting in reduced T cell proliferation, activation and functionality.
- In autoimmune diseases, chronic stimulation by self-antigens drives persistent LAG-3 expression, a characteristic feature of autoreactive memory T cells in inflamed tissues (1, 2).
- By selectively engaging LAG-3-expressing pathogenic T cells, IMP761 represents a targeted therapeutic approach that acts upstream of currently available treatments (**Figure 1**).
- Here, we report preclinical findings and interim data from a randomized, double-blinded, placebo-controlled Phase I study (NCT06637865) alongside complementary pre-clinical findings.

Figure 1: Mechanism of Action of IMP761



Reduced T cell proliferation

Reduced T cell activation

Reduced T cell functionality

METHODS

PRE-CLINICAL DEVELOPMENT

- PBMCs from rheumatoid arthritis (RA) patients were stimulated with an RA-relevant joint-derived peptide pool (≥11-mer self-peptides derived from cartilage-associated self-antigens: citrullinated vimentin, -enolase, -fibrinogen β, collagen II, PAD4, and cartilage GP39) in the presence of IMP761 or isotype control (IgG4) at 300 ng/ml.
- The effect of IMP761 on activation and proliferation of CD4⁺ T cells was evaluated after 6 days. Expression of the activation marker CD25 was measured.

STUDY DESIGN

- The well-established keyhole limpet hemocyanin (KLH) challenge model was applied in a randomized, double-blinded, placebo-controlled Phase I study (3, 4).
- Sixty healthy volunteers (HV) were recruited and immunized with KLH through intramuscular injection on Day -47, -33 and -19 (**Figure 3**).
- HV were randomized to receive placebo or IMP761 (IV, single infusion), across 7 dose levels (0.03 - 14 mg/kg) on Day 0.
- A challenge with KLH by intradermal injection was performed on Day 1. For IMP761 dose levels ≥0.3 mg/kg and placebo, this was repeated on Day 8 and 22.

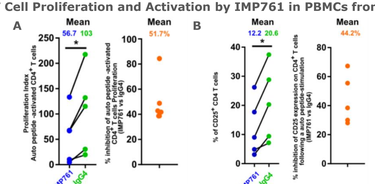
CLINICAL DEVELOPMENT – PHARMACODYNAMIC READOUTS AND EXPOSURE-RESPONSE ANALYSES

- Local vascular response, i.e., skin blood perfusion, and infiltration of CD3⁺ T cells in dermal interstitial fluids at the KLH injection site were analyzed on Day 2, 9 and 23 (24 hours after the KLH challenges) by Laser Speckle Contrast Imaging (LSCI) (**Figure 4A**) or by flow cytometry after harvesting (**Figure 4B**).
- IMP761 serum concentrations were quantified 1 and 6 hours and 1, 2, 4, 8, 15, 22, 29 and 44 days post infusion using a validated pharmacokinetic assay. HV were categorized into 4 exposure groups based on the quartile distribution of IMP761 circulating concentrations at the time of KLH challenges (low, low-to-intermediate, intermediate-to-high, high) (**Figure 5B**). Placebo was included into the low exposure group.
- Exposure-response analyses were used to evaluate the relationship between IMP761 concentrations at each KLH challenge and the pharmacodynamic assessments of skin blood perfusion (i.e., basal flow) and CD3⁺ T cell counts in dermal interstitial fluids. A Wilcoxon rank-sum test was used to compare the skin reactions across exposure groups.

PRE-CLINICAL DEVELOPMENT

- In PBMCs from RA patients, IMP761 significantly reduced both proliferation and activation of CD4⁺ T cells induced by an autoimmune peptide pool (p=0.043 and p=0.011) (**Figure 2**).

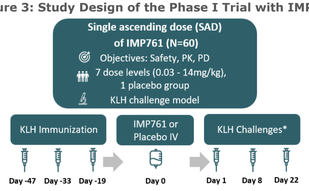
Figure 2: Inhibition of CD4⁺ T Cell Proliferation and Activation by IMP761 in PBMCs from Rheumatoid Arthritis (RA) Patients



PBMCs from RA patients were stimulated with an RA-relevant joint-derived peptide pool in the presence of IMP761 or isotype control (IgG4). CD4⁺ T cell proliferation index (A) and expression of the T cell activation marker CD25 (B) are shown together with the corresponding percentage of inhibition.

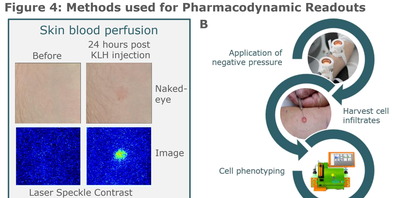
METHODS - continued

Figure 3: Study Design of the Phase I Trial with IMP761



*The last two KLH challenges were performed for dose levels ≥0.3 mg/kg and placebo only. KLH: keyhole limpet hemocyanin.

Figure 4: Methods used for Pharmacodynamic Readouts

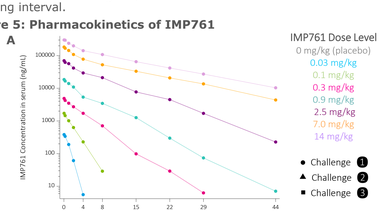


CLINICAL DEVELOPMENT

IMP761 SHOWS PHARMACOKINETICS SUITABLE FOR 4-WEEKLY DOSING

- Following single IV administration, IMP761 showed biphasic, non-linear pharmacokinetics consistent with target-mediated drug disposition, trending towards linearity at doses ≥2.5 mg/kg (**Figure 5A**).
- Sustained pharmacologically relevant concentrations through Day 29 with higher dose levels (2.5–14.0 mg/kg) support a 4-weekly dosing interval.

Figure 5: Pharmacokinetics of IMP761



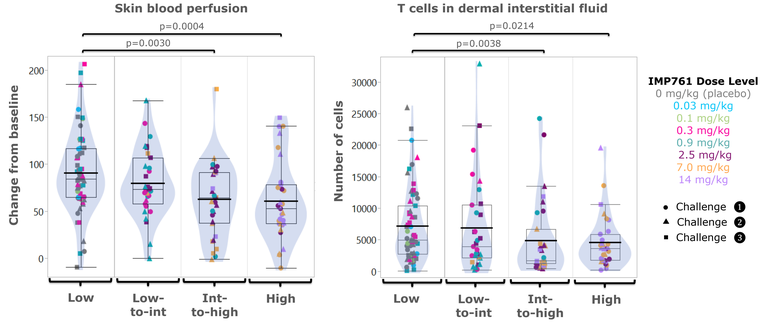
A: Concentration of IMP761 in serum of HV and the 3 challenges with KLH at indicated timepoints. IMP761 was administered IV on Day 0 only. B: Categorization of IMP761 serum concentration measurements at the three KLH challenges into exposure groups based on quartile distribution.

CLINICAL DEVELOPMENT - continued

IMP761 SHOWS SIGNIFICANT IMMUNOSUPPRESSIVE ACTIVITY IN RELATION TO EXPOSURE

- Skin blood perfusion and T cell counts in dermal interstitial fluids from blisters were measured 24 hours after the KLH challenges.
- Increasing IMP761 exposure at the time of KLH challenge was associated with increasing inhibition of both the vascular and cellular components of the KLH-induced response (**Figure 6**). These findings demonstrate a clear exposure-dependent pharmacodynamic effect of IMP761 in this model.

Figure 6: Inhibition of Keyhole Limpet Hemocyanin-induced Responses in Relation to IMP761 Exposure



Local reactions at all challenge occasions assessed by skin blood perfusion and CD3⁺ T cell counts in dermal interstitial fluids are shown by IMP761 exposure group. The participants were categorized in 4 groups based on the quartile distribution of IMP761 circulating concentrations at the time of intradermal KLH challenges to define low (up to the first quartile), low-to-intermediate (low-to-int; between the first quartile and the median), intermediate-to-high (int-to-high; between the median and the third quartile) and high (above the third quartile) exposure groups. Violin-box plots show individual values, means and medians. Symbols indicate KLH challenge occasions and colors indicate dose levels. P-values indicate comparisons with the low exposure group.

IMP761 SHOWS FAVORABLE SAFETY PROFILE

- IMP761 was well tolerated across all dose levels with comparable incidence of treatment-emergent adverse events (TEAE) between IMP761- and placebo-treated groups. In the IMP761 group, 95.8% of participants experienced a TEAE versus 91.7% in the placebo group.
- The number of TEAEs reported per participant was similar between the groups (3.1 for IMP761 vs 3.2 for placebo).
- The majority of reported events (97.8%) were mild in nature and no severe or serious adverse events were reported. Incidence and severity of TEAEs did not show any dose-dependency.

SUMMARY & CONCLUSIONS

- IMP761 significantly inhibits proliferation and activation of T cells from RA patients in vitro.
- PK profile supports a 4-weekly dosing regimen for multiple ascending dose testing.
- IMP761 significantly reduced immune responses induced by the potent antigen KLH in healthy volunteers and was well tolerated at all evaluated dose levels.
- These findings provide a strong rationale for LAG-3 agonism as a novel therapeutic approach for RA and other autoimmune diseases with a strong T cell component by direct inhibition of TCR signaling.

ABBREVIATIONS

CD…cluster of differentiation
Ev…events
HV…healthy volunteer
IBD…inflammatory bowel disease
IgG4…Immunoglobulin G4
IV…intravenous
KLH…Keyhole Limpet Hemocyanin
LAG-3…Lymphocyte Activation Gene-3
LCSI…Laser Speckle Contrast Imaging
PBMCs…peripheral blood mononuclear cells
P…participant
PD…pharmacodynamics
PK…pharmacokinetics
RA…rheumatoid arthritis
SAD…single ascending dose
TCR…T cell receptor
TEAE…treatment-emergent adverse event

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CONFLICT OF INTERESTS

- Mueller C, Leite Pereira A, Brignone C and Triebel F: Immutep (Employment (Employee/Salaried Positions))
- Moerland M, Niemeyer-van der Kolk T and Plasmeijer H: Nothing to disclose.

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