Safety, tolerability and pharmacokinetics of single and multiple oral doses of IMU-935 in healthy volunteers: First clinical experience with an orally available small molecule inhibitor of IL-17

Thomas M Polasek, Frank Fliegert, Irina Betscheider, Manfred Groeppel, Daniel Vitt, Hella Kohlhof and Andreas Muehler

Introduction

IMU-935 is an inverse agonist of the RAR-related orphan receptor RORγt, with additional but less potent inhibition of dihydroorotate dehydrogenase (DHODH). IMU-935 inhibits the secretion of several pro-inflammatory cytokines, including interleukin (IL)-17A, IL-17F and IFN-γ, differentiation of T helper 17 (Th17) cells, proliferation of activated T cells, and allows normal thymocyte maturation. With the availability and success of IL-17 targeting antibodies, IMU-935 is designed to provide an oral medication option targeting IL-17 for plaque psoriasis patients.

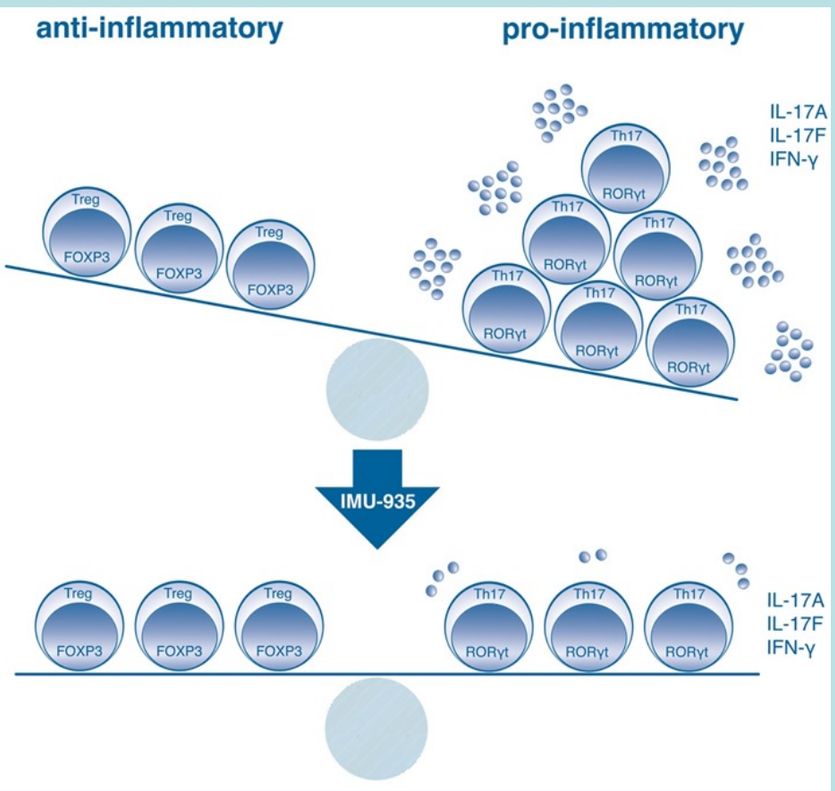

Figure 1 IMU-935 leads to a restoration of the balance between regulatory T cells and Th17 cells in an autoimmune setting

Methods

This is a first-in-human, double-blind, randomized, placebo-controlled clinical trial comprising three parts. In part A, healthy volunteers in cohorts of 8 subjects each were enrolled and received single ascending doses of IMU-935 or placebo (ratio 3:1). In Part B, multiple doses are currently being evaluated. In part C, patients with moderate to severe plaque-type psoriasis will take either two different dose levels of IMU-935 or placebo.

Results

Single dose pharmacokinetic (PK) evaluation of IMU-935 showed plasma concentrations in most subjects at 1 hour post-dose, T_{max} between 2 to 6 hours post-dose, half-life ranging from 16.5 to 31.0 hours and dose proportional increases of C_{max} and AUC across the investigated doses.

Table 1 IMU-935 single dose pharmacokinetic parameters (Part A)

IMU-935 dose (number of subjects)	Median (range)	Mean (%CV)		
	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	$T_{1/2}$ (hr)
100 mg (N=5)	2.00 (2.00-3.00)	119 (38)	687 (25)	26.05 (27)
200 mg (N=6)	3.00 (2.00-4.00)	195 (95)	1290 (67)	24.38 (31)
300 mg (N=6)	3.50 (2.00-6.00)	182 (33)	1620 (42)	16.49 (27)
400 mg (N=6)	2.00 (2.00-6.00)	479 (27)	2530 (15)	31.00 (38)

Abbreviations: T_{max} = Time to maximum plasma concentration; C_{max} = Maximum plasma concentration; AUC_{last} = Area under the concentration time curve from 0 to the last time point; $T_{1/2}$ = Half-life

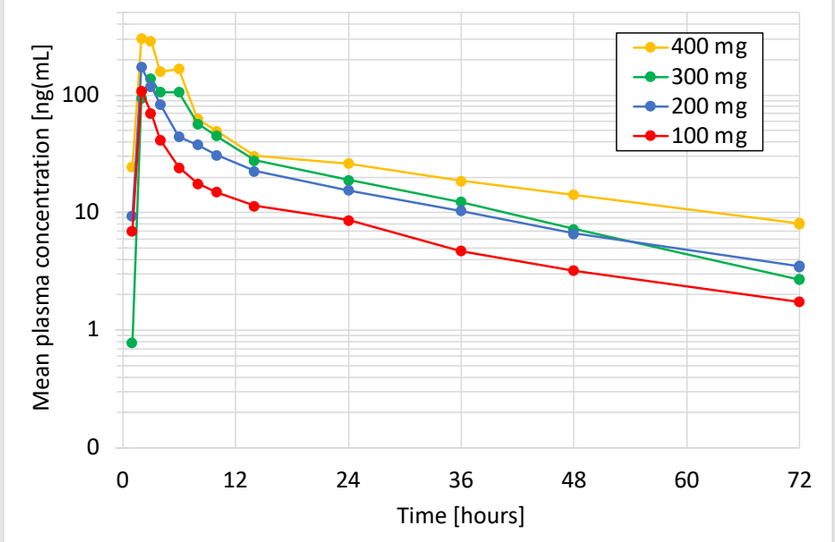

Figure 2 IMU-935 single dose plasma concentration over time (Part A)

Multiple dose PK evaluation showed slightly lower mean C_{max} on Day 14 (124 ng/mL) compared to Day 1 (177 ng/mL), with no change in median T_{max}. There was an increase in mean AUC_{tau} on Day 14 (803 hr*ng/mL) compared to Day 1 (757 hr*ng/mL). Mean half-life was 17.58 hr on Day 1 and 28.96 hr on Day 14. The geometric mean ratios (Day 14 vs. Day 1) for C_{max} and AUC_{tau} were 0.67 and 1.15, respectively, demonstrating slight accumulation.

Table 2 IMU-935 multiple dose pharmacokinetic parameters (Part B)

IMU-935 dose (number of subjects)	Median (range)	Mean (%CV)		
	T_{max} (hr)	C_{max} (ng/mL)	AUC_{tau} (hr*ng/mL)	$T_{1/2}$ (hr)
Low dose QD Day 1 (N=8)	3.00 (1.50-3.00)	177 (64)	757 (49)	17.58 (45)
Low dose QD Day 14 (N=7)	3.00 (2.00-3.00)	124 (45)	803 (21)	28.96 (29)

Abbreviations: T_{max} = Time to maximum plasma concentration; C_{max} = Maximum plasma concentration; AUC_{tau} = Area under the concentration time curve within the dosing interval (i.e., 24 hr); $T_{1/2}$ = Half-life

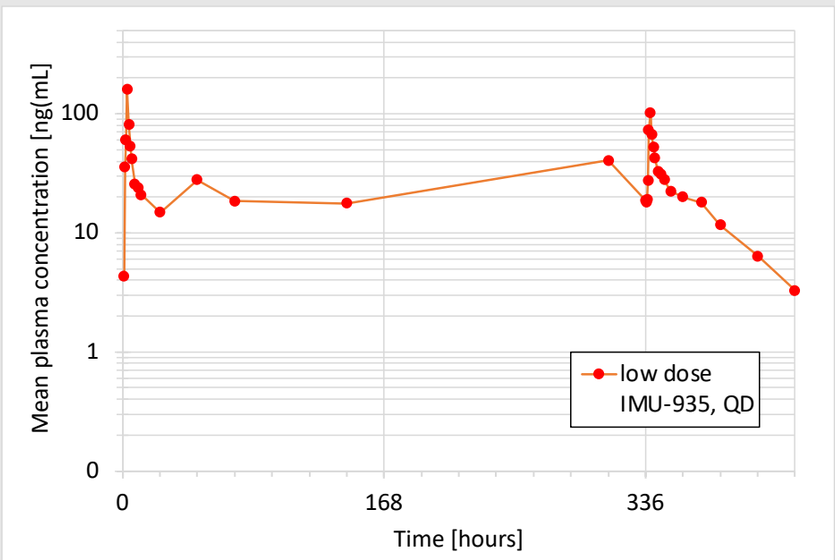

Figure 3 IMU-935 multiple dose plasma concentration over time (Part B)

Safety evaluation of single ascending doses of IMU-935 or placebo (blinded data) showed a very low incidence of related treatment-emergent adverse events (TEAEs). The most common events included constipation (3 subjects), headache and abdominal distension (2 subjects each). The incidence of TEAEs were comparable across the various dose groups. A maximum tolerated dose was not identified.

There were no other clinically meaningful findings relative to safety and tolerability, as assessed by clinical laboratory tests, vital signs, and 12-lead ECGs following study treatment.

Table 3 Related treatment-emergent adverse events after single dosing (Part A)

MedDRA Preferred Term	Number (%) of subjects with related TEAEs [Number of TEAEs reported]				
	100 mg IMU-935 or placebo (N=7)	200 mg IMU-935 or placebo (N=8)	300 mg IMU-935 or placebo (N=8)	400 mg IMU-935 or placebo (N=8)	Total Subjects (N=31)
Constipation		1 (13%) [1]		2 (25%) [2]	3 (10%) [3]
Headache		1 (13%) [1]	1 (13%) [1]		2 (6%) [2]
Abdominal distension		2 (25%) [2]			2 (6%) [2]
Diarrhea		1 (13%) [1]			1 (3%) [1]
Nausea		1 (13%) [1]			1 (4%) [1]
Abdominal pain upper				1 (13%) [1]	1 (3%) [1]
Dizziness				1 (13%) [1]	1 (1%) [1]
Limb injury		1 (13%) [1]			1 (1%) [1]
Lipase increased				1 (13%) [1]	1 (1%) [1]
Neutropenia	1 (14%) [1]				1 (1%) [1]
Somnolence	1 (14%) [1]				1 (1%) [1]

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAEs = treatment-emergent adverse events.
Results are presented in a blinded manner, where each treatment group includes subjects allocated to IMU-935 or placebo at a 3:1 ratio.

Safety evaluation of multiple doses of IMU-935 or placebo (blinded data) showed a very low incidence of related TEAEs. The most common event was headache (2 subjects).

There were no other clinically meaningful findings relative to safety and tolerability, as assessed by clinical laboratory tests, vital signs, and 12-lead ECGs following study treatment.

Table 4 Related treatment-emergent adverse events after multiple dosing (Part B)

MedDRA Preferred Term	Number (%) of subjects with related TEAEs [Number of TEAEs reported]
	Low dose IMU-935 or placebo QD (N=8)
Headache	2 (25%) [2]
Epistaxis	1 (13%) [2]
Diarrhea	1 (13%) [1]
PR interval prolongation	1 (13%) [1]
Somnolence	1 (13%) [1]

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily dosing; TEAEs = treatment-emergent adverse events.
Results are presented in a blinded manner, where each treatment group includes subjects allocated to IMU-935 or placebo at a 3:1 ratio.

A headache reported after single dose treatment with 200 mg IMU-935 or placebo was moderate in intensity. All other treatment related TEAEs were assessed as mild in severity. There were no TEAEs that led to study withdrawal or interruption of dosing.

Conclusion

- IMU-935 has dose-linear pharmacokinetics and a plasma half-life that allows for once daily dosing.
- IMU-935 is safe and well tolerated with a very benign adverse event profile.
- Ongoing recruitment into this study will provide data on the safety and activity of IMU-935 in psoriasis patients.

Thomas M Polasek

Clinical Pharmacology Registrar
Royal Adelaide Hospital, SA Health
Adelaide, Australia

Government of South Australia
SA Health

Irina Betscheider

Clinical Operations Program Lead
Immunic AG
Gräfelfing, Germany

Immunic THERAPEUTICS