A Randomized, Multiple-Dose Study of Subcutaneous UTTR1147A (IL-22Fc) in Patients with Neuropathic, Non-Healing Diabetic Foot Ulcers (DFUs)

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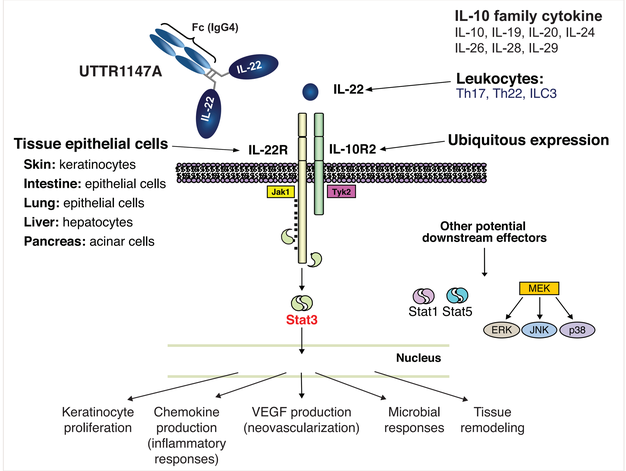
INTRODUCTION

Diabetic Foot Ulcers (DFUs)

- Complex, chronic wounds that have major, long-term impacts on patient morbidity, mortality, and quality of life
- Global DFU prevalence is 6.3%, but varies greatly by region (3% in Oceania to 13% in North America)
- Up to 80% of non-healing wounds are infected
- Primary unmet need is complete wound closure (CWC) to prevent secondary infection and loss of limb

UTTR1147A

Figure 1. UTTR1147A and the IL-22 receptor pathway.



ERK, extracellular signal-regulated kinse; Fc, crystallizable fragment; Ig, immunoglobulin; IL, interleukin; IL-10R2, IL-10 receptor 2; IL-22R, IL-22 receptor; ILC, innate lymphoid cell; Jak1, Janus kinase 1; JNK, c-Jun N-terminal kinase; MEK, MAPK/ERK kinase; STAT, signal transducer and activator of transcription; Th, T helper; Tyk2, tyrosine kinase 2; VEGF, vascular endothelial growth factor.

- Novel human interleukin (IL)-22-IgG4 Fc fusion protein
- Binds the IL-22 receptor heterodimer expressed on various epithelial tissues
- Mimics IL-22 effector function to promote epithelial proliferation and wound healing (**Figure 1**)
- Phase 1a trial
  - Safe and well tolerated at single intravenous (IV) doses up to 90 µg/kg and single subcutaneous (SC) doses up to 60 µg/kg in ongoing Phase 1 studies in inflammatory bowel disease (IBD)
  - Induced on-target skin effects, including dry lips and dry, erythematous skin

OBJECTIVE

- Evaluate safety, tolerability, pharmacokinetics, and preliminary healing activity of local SC injection of UTTR1147A in patients with neuropathic, non-healing, uninfected DFUs

METHODS

Study Population

- Adult patients (≥18 years) with an index neuropathic DFU considered non-healing, based on a 2-week run-in period
- Ulcer area, 0.8–6 cm^2; excluded patients with >50% increase or >25% decrease in ulcer surface area **(Table 1)**

Study Design

- Randomized, phase 1b, blinded, multiple ascending-dose trial
- Patients received standard-of-care (SOC; IWGDF 2015) DFU treatment during 2-week run-in period:
  - Below-knee, off-loading device, rendered unremovable
  - Weekly debridement and irrigation
- Patients received SC injections of placebo or 1000-µg, 2500-µg, or 5000-µg UTTR1147A around the ulcer circumference every 3 weeks (Q3W; 4 doses total) plus continuing SOC treatment for 12 weeks
- Planned treatment allocation: 12:6 (1000 µg); 12:6 (2500 µg); 10:5 (5000 µg)

Outcomes and Assessments

- Safety
  - Nature, frequency, severity, and timing of adverse events (AEs)
  - Changes in vital signs, physical findings, and clinical laboratory results
- Pharmacokinetics
  - Serum UTTR1147A concentration at specified timepoints, analyzed by affinity capture followed by validated liquid chromatography with tandem mass spectrometery (LC-MS/MS) detection
  - Exploratory wound fluid (WF) UTTR1147A concentration collected at baseline, Day 4, and Day 22 on filter discs, and analyzed by LC-MS/MS
- Healing activity
  - Proportion of patients with CWC (complete epithelialization that persisted for at least 2 weeks after the initial determination by the assessing physician)
  - Percent change from baseline in index ulcer surface area (measured using a standardized digital image, digital tracing, and software-determined ulcer area), after 6 and 12 weeks of multiple dosing

RESULTS

Patient Demographics

Table 1. Patient Demographics and Baseline Characteristics.

		UTTR1147A		
	Placebo (n=20)	**1000 µg (n=7)**	**2500 µg (n=14)**	**5000 µg (n=20)**
Age (yrs)	56.1 (6.8)	62.6 (14.0)	62.3 (8.9)	58.8 (11.3)
Baseline weight (kg)	111.8 (30.3)	98.3 (22.8)	98.8 (23.7)	123.5 (31.5)
Gender				
Male	16 (80%)	4 (57%)	11 (79%)	18 (90%)
Female	4 (20%)	3 (43%)	3 (21%)	2 (10%)
Baseline ulcer area (cm^2)	2.04 (1.3)	2.85 (1.9)	3.1 (2.1)	2.17 (1.5)
Baseline ulcer area				
≤ 2 cm^2	12 (60%)	3 (43%)	6 (43%)	12 (60%)
> 2 cm^2	8 (40%)	4 (57%)	8 (57%)	8 (40%)

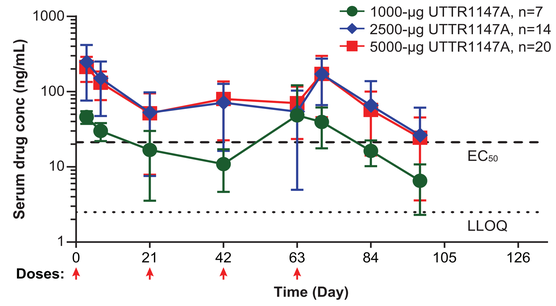
Data are mean (SD) or n (%).

Safety

- No deaths, dose-limiting AEs, or serious adverse events (SAEs) related to study treatment
- Most AEs were mild or moderate
- Proportion of patients experiencing AEs (>10%) was similar between placebo and UTTR1147A arms:
  - Placebo
    - Skin ulcer: 7/20 (35%)
    - Blister, stool occult blood positive, skin abrasion: 4/20 (20%)
    - Osteomyelitis, wound infection, contusion: 2/20 (10%)
  - 1000-µg UTTR1147A
    - Skin ulcer: 2/7 (29%)
  - 2500-µg UTTR1147A
    - Skin ulcer, erythema, infected skin ulcer, osteomyelitis, localized infection, limb injury, dry mouth: 2/14 (14%)
  - 5000-µg UTTR1147A
    - Skin ulcer: 5/20 (25%)
    - Rash: 2/20 (10%)
    - Infected skin ulcer, cellulitis: 3/20 (15%)
    - Stool occult blood positive: 5/20 (25%)
- No clinically significant abnormalities or treatment-related trends in vital signs, or laboratory or clinical chemistry parameters
- UTTR1147A, at SC doses up to 5000 µg, demonstrated an acceptable safety and tolerability profile

Pharmacokinetics

Figure 2. UTTR1147A Serum Concentration-Time Profile.



Data are mean (SD). EC_{50} (21.3 ng/mL) was based on IL-22Fc *in vitro* reporter assay in 293T cells. Red arrows indicate dosing Q3W (every 3 weeks). EC_{50}, half-maximal effective concentration; LLOQ, lower limit of quantification.

- Serum PK reflected systemic drug exposure **(Figure 2)**:
  - C_{max} values for the 2500-µg and 5000-µg groups were at least 10X higher than the *in vitro* EC_{50} (~21.3 ng/mL)
  - C_{trough} values at Week 12 were at least 3X higher
- Exploratory wound fluid PK confirmed local drug exposure (data not shown)
  - Concentrations at Day 4 post dose were higher than the *in vitro* EC_{50}
- Both serum PK and wound fluid PK had large inter-subject variability and were not dose proportional

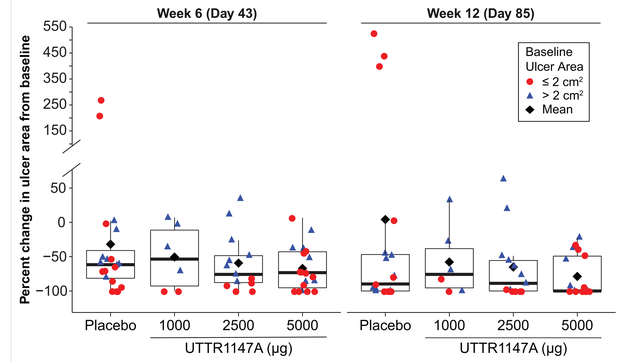
Preliminary Healing Activity

Table 2. Proportion of Patients with CWC at Week 6 and Week 12.

		UTTR1147A		
	Placebo (n=20)	**1000 µg (n=6)**	**2500 µg (n=13)**	**5000 µg (n=19)**
Week 6 (Day 43)				
Patients included in analysis	20	6	13	19
Patients with events	3 (15%)	2 (33%)	2 (15%)	5 (26%)
80% CI for event rates[a]	5.6, 30.4	9.3, 66.7	4.2, 36.0	13.4, 43.4
Difference in event rates		18.3	0.4	11.3
80% CI[b]		-4.2, 45.1	-15.2, 18.6	-5.4, 27.6
Week 12 (Day 85)				
Patients included in analysis	19	6	13	18
Patients with events	7 (37%)	2 (33%)	4 (31%)	10 (56%)
80% CI for event rates[a]	21.8, 54.1	9.3, 66.7	14.2, 52.3	38.0, 72.1
Difference in event rates		-3.5	-6.1	18.7
80% CI[b]		-27.2, 25.1	-26.0, 15.7	-2.2, 37.5

Last observed non-missing value was carried forward to fill in missing values at clinical evaluation. Confidence intervals (CIs) determined by [a]Pearson-Clopper or [b]Wilson methodologies.

Figure 3. Percent Change from Baseline in Ulcer Area at Week 6 and Week 12 (by Baseline Ulcer Area).



Last observed non−missing value was carried forward to fill in missing values at clinical evaluation.

- No clear treatment effect was observed in the percentage reduction in ulcer size and incidence of ulcer closure at Weeks 6 and 12 **(Table 2; Figure 3)**
- Patients with small baseline ulcers tend to have a higher percent decrease at Week 6
- No obvious difference among treatment groups by baseline ulcer area

Table 3. Mean and Median Percent Change from Baseline in Ulcer Area.

			UTTR1147A		
		Placebo (n=20)	**1000 µg (n=6)**	**2500 µg (n=13)**	**5000 µg (n=19)**
Week 6 (Day 43)	n	17	6	10	17
	Mean	-23.8	-50.5	-54.5	-63.4
	SD	104.0	47.1	43.6	31.7
	Median	-58.8	-53.5	-69.8	-71.8
	Range	-100.0 to 268.7	-100.0 to 6.9	-91.5 to 34.4	-100.0 to 6.7
Week 12 (Day 85)	n	18	6	11	17
	Mean	-27.4	-57.8	-74.3	-80.6
	SD	164.8	51.7	36.8	29.8
	Median	-96.7	-75.8	-94.7	-100.0
	Range	-100.0 to 438.6	-100.0 to 32.6	-100.0 to 19.8	-100.0 to -22.0

- No obvious differences between treatment groups **(Table 3)**

CONCLUSIONS

- UTTR1147A administered SC around non-healing DFU up to doses of 5000 µg has an acceptable safety and tolerability profile
- Serum PK confirmed systemic drug exposure; wound fluid PK confirmed local drug exposure
- No meaningful improvements in wound healing with UTTR1147A treatment in addition to SOC
- Neuropathic DFUs, including non-healing ulcers, had higher than expected healing rates when IWGDF-prescribed SOC was implemented

ACKNOWLEDGEMENTS

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