Poster 1805

Results from a randomized, double-blind, placebo-controlled, monotherapy trial of IMO-8400 demonstrate clinical proof-of-concept for Toll-like receptor 7, 8 and 9 antagonism in psoriasis

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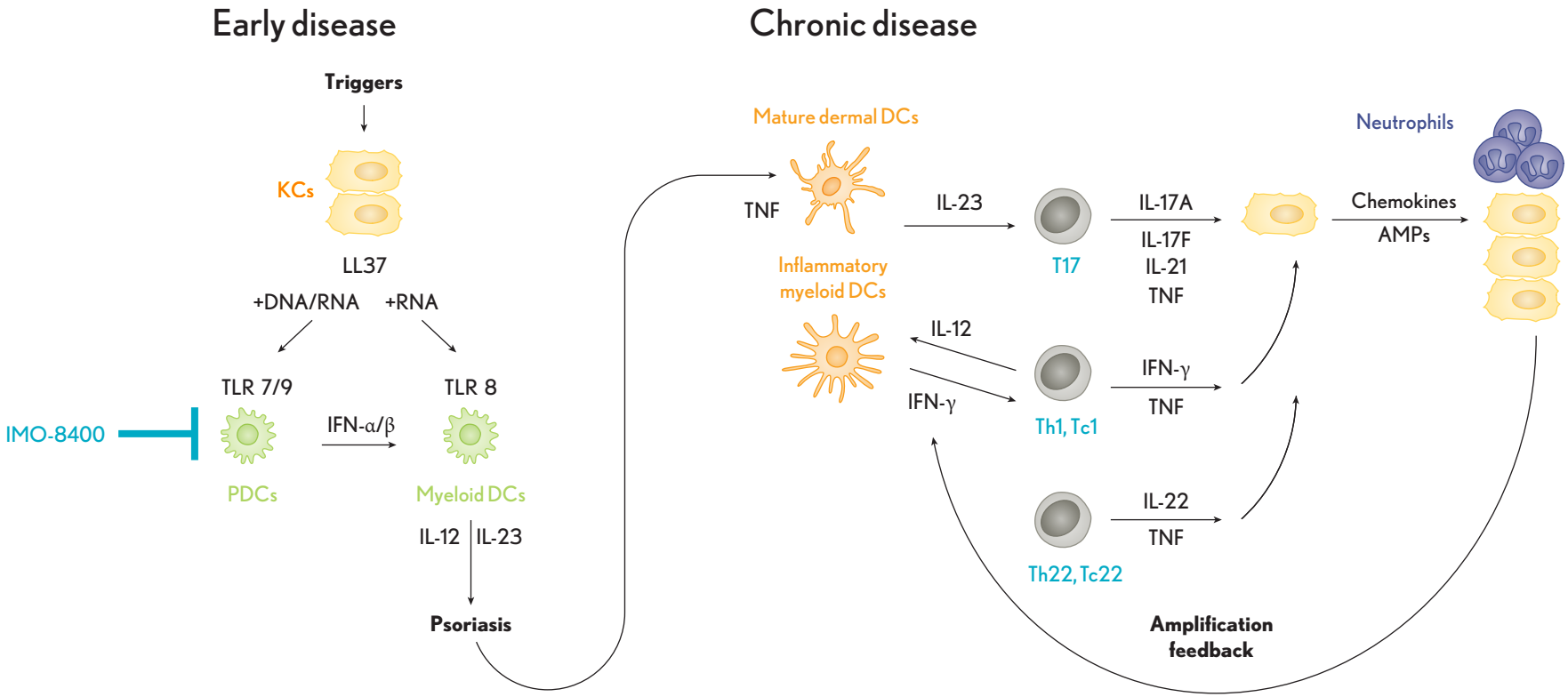
Study background

- Toll-like receptors (TLRs) are a key component of the innate immune system
  - In various immune-mediated inflammatory diseases (IMIDs), including psoriasis, TLRs are engaged by self nucleic acids, leading to induction of pro-inflammatory cytokines and disease propagation
  - TLRs represent potentially attractive targets for the treatment of IMIDs due to their role in regulating the inflammatory response upstream of immune cell activation and cytokine induction
- IMO-8400 is a novel, oligonucleotide antagonist of endosomal TLRs 7, 8 and 9
  - In an IL-23-induced skin inflammation mouse model, IMO-8400 treatment resulted in modulation of more than 2,300 disease-associated genes, strongly decreased IL-17A expression (>12-fold reduction), and normalized IL-17 induced genes such as beta-defensin and CXCL1[1]
  - In a Phase 1 healthy volunteer trial, IMO-8400 was generally well tolerated
  - In addition, a previously completed Phase 2a trial of a separate TLR 7 and 9 antagonist candidate showed improvements in PASI score in subjects with moderate to severe plaque psoriasis. In biopsies from a subset of subjects, there was a significant improvement in the expression profile of MAD-3 and IL-17 genes[2]
- A Phase 2 clinical trial of IMO-8400 was designed to evaluate the safety, tolerability, and clinical activity of IMO-8400 in patients with moderate to severe plaque psoriasis
  - This randomized, single-center, double-blind, placebo-controlled, monotherapy, dose-ranging trial evaluated four IMO-8400 doses of 0.075, 0.15, 0.30 and 0.60 mg/kg/week

1. Suárez-Fariñas, et al. Suppression of Molecular Inflammatory Pathways by Toll-Like Receptor 7, 8, and 9 Antagonists in a Model of IL-23-Induced Skin Inflammation. PLOS One. 2013 Dec 27;8(12):e84634. **2.** Data presented at International Investigative Dermatology 2013.

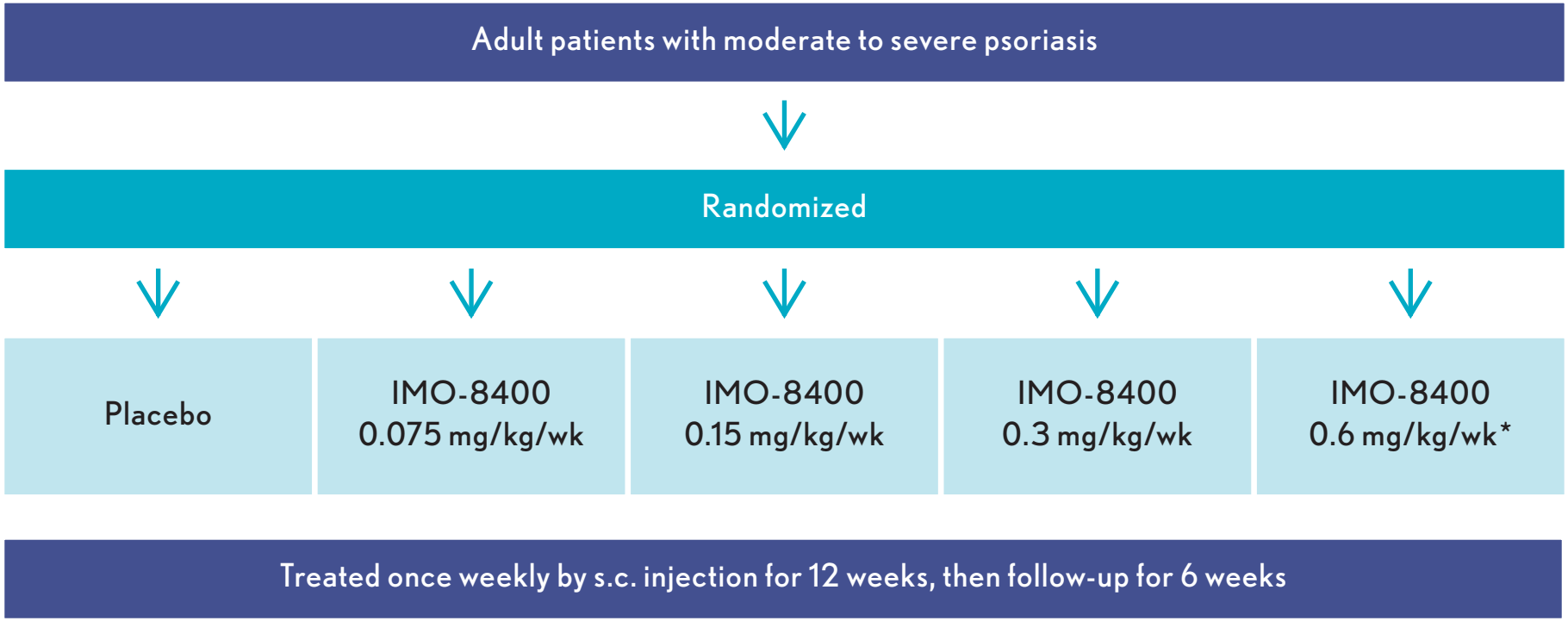
Endosomal TLRs play a critical role in the pathogenesis of psoriasis



Graphic adapted from: Lowes, et al. Immunology of Psoriasis. *Annu Rev Immunol*. 2014. 32:227-55.

- Cells damaged by injury or infection release self DNA, self RNA and other molecules to form Damage Associated Molecular Patterns (DAMPs)
- DAMPs stimulate TLR signaling in dendritic cells and keratinocytes leading to induction of pro-inflammatory cytokines and T-cell activation
- Inflammation causes activation and proliferation of keratinocytes, leading to formation of psoriasis plaques

Design of a Phase 2 randomized, double-blind, placebo-controlled, proof-of-concept trial of IMO-8400 in moderate to severe plaque psoriasis



Major entry criteria:

- Aged ≥18 years
- Psoriasis area and severity index (PASI) score ≥12
- Body surface area ≥10%

*Part B expansion to 0.6 mg/kg/wk.

Primary outcome measure:

- Safety and tolerability of four IMO-8400 doses

Secondary outcome measures included:

- PASI score
- Individual characteristics of psoriasis severity

Minimum discontinuation intervals required for prior treatments for psoriasis

Treatment class	Specific examples	Discontinuation interval*
Topical	retinoids, corticosteroids, vitamin D analogs	2 weeks
Phototherapy	any	4 weeks
Systemic retinoids	acitretin	4 weeks
Systemic non-biologic immune modulators	methotrexate, cyclosporine, oral corticosteroids, fumaric acid esters	4 weeks
	antimalarials, (e.g., hydroxychloroquine)	8 weeks
Biologic immune modulators	etanercept	4 weeks
	ustekinumab	26 weeks
	other monoclonals (including adalimumab, infliximab)	8 weeks

*Minimum interval from the last dose of treatment to the first dose of study treatment (i.e., Day 1).

Subjects enrolled and disposition

	IMO-8400 (mg/kg)				Placebo	Overall
	0.075	0.15	0.30	0.60		
Subjects treated	9	9	8	9	11	46
Prematurely discontinued treatment	2 (22.2%)	2 (22.2%)	2 (25.0%)	0	2 (18.2%)	8 (17.4%)
AE not related to treatment	1 (11.1%)	0	0	0	1 (9.1%)	2 (4.3%)
Withdrawal of consent	1 (11.1%)	2 (22.2%)	0	0	0	3 (6.5%)
Lack of efficacy	0	0	2 (25.0%)*	0	1 (9.1%)	3 (6.5%)

*One patient discontinued treatment after experiencing a severe treatment-emergent adverse event that was unlikely related to study treatment; however, termination was listed as due to lack of efficacy.

- 46 subjects enrolled and treated
- 8 (17%) discontinued early

Baseline characteristics were generally balanced across treatment groups

PARAMETER	IMO-8400 dose				Placebo (n=11)
	0.075 mg/kg (n=9)	0.15 mg/kg (n=9)	0.30 mg/kg (n=8)	0.60 mg/kg (n=9)	
Age, years					
Mean (SD)	48.8 (15.1)	35.0 (16.0)	42.3 (17.2)	47.9 (13.3)	47.2 (13.4)
Gender, n (%)					
Male	5 (55.6%)	6 (66.7%)	6 (75.0%)	8 (88.9%)	9 (82.8%)
Female	4 (44.4%)	3 (33.3%)	2 (25.0%)	1 (11.1%)	2 (18.2%)
BMI, kg/m^2					
Mean (SD)	25.8 (4.5)	24.1 (4.9)	27.1 (1.3)	28.1 (5.8)	29.8 (3.9)
Race, n (%)					
White	5 (56%)	8 (89%)	6 (75%)	9 (100%)	8 (73%)
Asian	0	0	2 (25%)	0	2 (18%)
Mixed	2 (22%)	0	0	0	1 (9%)
Other	2 (22%)	1 (11%)	0	0	0
Disease characteristics, mean (SD)					
PASI	14.1 (2.6)	14.1 (2.0)	14.8 (2.7)	14.2 (2.0)	14.1 (2.5)

BMI = body mass index; PASI = psoriasis area and severity index.

Summary of adverse events assessed as related to study drug by preferred term (≥1 event)

Preferred Term (≥1 event)	All IMO-8400-related n=35	All placebo-related n=11
Any event	24 (69%)	6 (54%)
Diarrhea	6 (17%)	–
Fatigue	6 (17%)	–
Influenza-like illness	6 (17%)	1 (9%)
Nausea	3 (9%)	–
Abdominal discomfort	2 (6%)	–
Vomiting	2 (6%)	–
Somnolence	2 (6%)	–
Polyuria	2 (6%)	–
Muscle spasms	–	2 (18%)

Summary of injection site reactions (ISRs)

ISR type	IMO-8400 dose				Placebo (n=11)
	0.075 mg/kg (n=9)	0.15 mg/kg (n=9)	0.30 mg/kg (n=8)	0.60 mg/kg (n=9)	
Any ISR	4 (44%)	3 (33%)	7 (87%)	9 (100%)	1 (9%)
Erythema	4 (44%)	2 (22%)	6 (75%)	9 (100%)	1 (9%)
Induration	–	1 (11%)	4 (50%)	8 (89%)	1 (9%)
Pruritus	2 (22%)	–	5 (62%)	5 (56%)	–
Tenderness	–	1 (11%)	4 (50%)	4 (44%)	–
Pain	–	–	2 (25%)	1 (11%)	–

Safety results

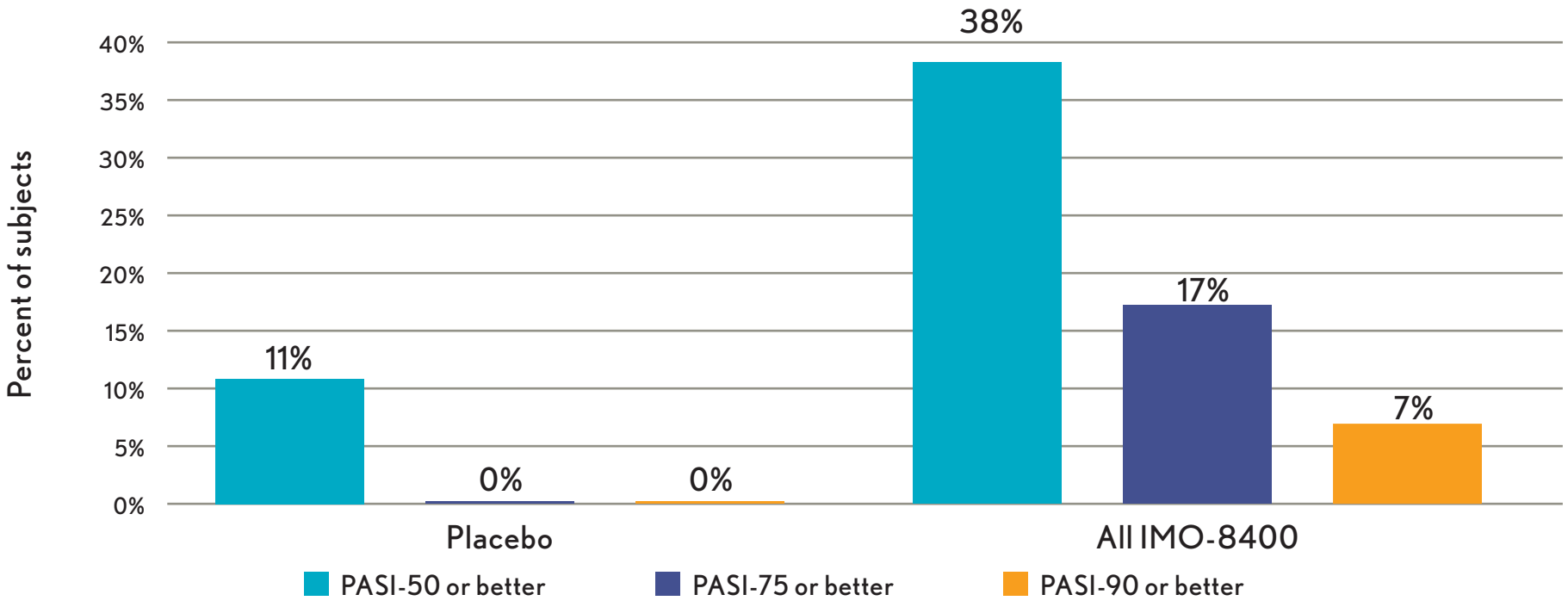
Summary

- There were no SAEs, no treatment-related severe AEs, and no discontinuations due to treatment-related AEs
- The frequency of diarrhea, fatigue and influenza-like illness was numerically higher among IMO-8400-treated subjects
- No abnormalities of laboratory results of hematology, chemistry, coagulation and urinalysis were attributed to study drug
  - Analysis of the primary data by numerical values and by Common Terminology Criteria grading showed no differences between the subjects treated with IMO-8400 or placebo

Injection-site reactions

- There was a dose-related increase in the frequency of ISRs in IMO-8400-treated subjects
- All ISRs were assessed as mild or moderate
- No blistering, ulceration, or necrosis was observed in any subject
- Mild Koebner reactions involving the development of small (2-4 cm) plaques of psoriasis at the site of injection were observed in 2 (25%) subjects in the 0.3 mg/kg group and 4 (44%) subjects in the 0.60 mg/kg group

Psoriasis Area and Severity Index (PASI) responder analysis



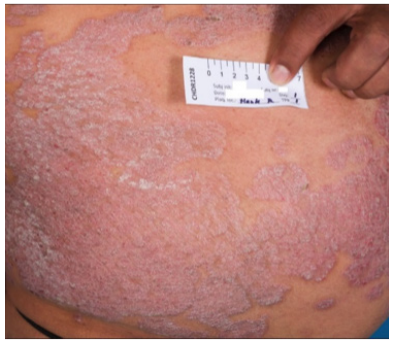
RESPONSE	Placebo (N=9)	IMO-8400 (mg/kg)				
		All IMO-8400 (N=29)	0.075 (N=7)	0.15 (N=7)	0.30 (N=6)	0.60 (N=9)
PASI-50 or better	1 (11%)	11 (38%)	3 (43%)	3 (43%)	3 (50%)	2 (22%)
PASI-75 or better	0	5 (17%)	2 (29%)	2 (29%)	0	1 (11%)
PASI-90 or better	0	2 (7%)	2 (29%)	0	0	0

There were no statistically significant differences in the percent change in PASI score between treatment groups.
PASI-50 = 50% reduction in PASI score; PASI-75 = 75% reduction in PASI score; PASI-90 = 90% reduction in PASI score.

Example of psoriasis plaque improvement in an IMO-8400-treated subject

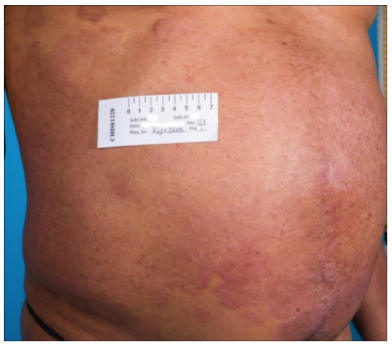
Pre-Treatment

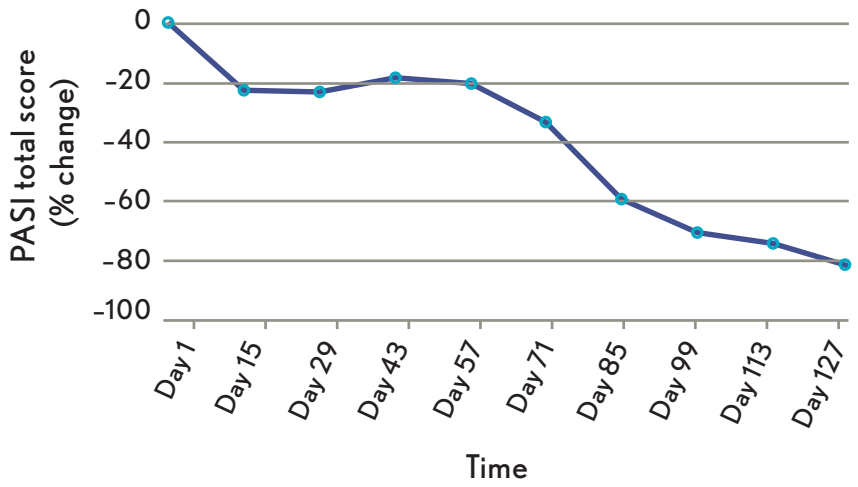
Baseline PASI: 16.6



4 weeks after 12 weeks Tx

End-of-study response: -82.5%

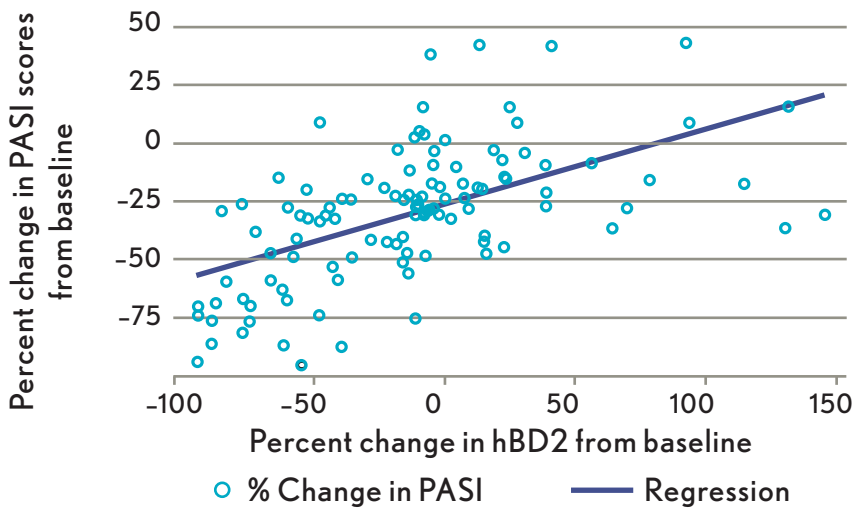




Note: Subject was in 0.075 mg/kg treatment group.

Correlation of percent change in PASI and human beta-defensin 2, a marker of epithelial cell activation

- Plasma samples were collected at multiple time points during the study including during pre-treatment, treatment and follow-up periods to assess cytokine levels
- Human beta-defensin 2 (hBD2) is an antimicrobial peptide produced by keratinocytes following stimulation due to contact with microorganisms or pro-inflammatory cytokines
- There was a significant correlation between percent change in PASI score and hBD2 ($r = 0.57$, $p < 0.0001$)



Clinical activity results

Summary

- Improvements in PASI scores of 50% to 92% were observed in 11 (38%) of IMO-8400-treated patients; only 1 (11%) placebo-treated patient had an improvement in this range
- Evidence of a persistent treatment effect was observed in 8 (28%) IMO-8400-treated patients, who had PASI-50 or better at the follow-up visit 6 weeks after the last dose of study drug. A similar effect was not observed in the placebo group
- All doses showed evidence of clinical activity and a clear dose-response relationship was not observed

Conclusions

- The trial met its primary objective of demonstrating the safety and tolerability of IMO-8400 treatment for up to 12 weeks in patients with moderate to severe plaque psoriasis
- IMO-8400-treated patients were more likely to demonstrate an improvement in PASI score compared to placebo-treated patients
  - 11 (38%) IMO-8400-treated subjects achieved PASI-50 or better versus 1 (11%) placebo-treated subject
- These findings demonstrate clinical proof of concept for TLR 7, 8 and 9 antagonism with IMO-8400 and support its continued development as a potential treatment for IMIDs in which TLRs are implicated
- Planning is now underway to initiate clinical development of IMO-8400 in patients with dermatomyositis, a rare and severe IMID with skin and muscle manifestations

Acknowledgements and disclosures

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- R. Rissman and J. Burggraaf are employed by the Centre for Human Drug Research, which received payment from Idera Pharmaceuticals to assist with the conduct of this study
- T. Sullivan is an employee of Idera Pharmaceuticals and may own Idera Pharmaceuticals stock or stock options
- R.D. Arbeit is a consultant to and former employee of Idera Pharmaceuticals and may own Idera Pharmaceuticals stock or stock options