Phase 1 clinical trial of IMO-8400, an antagonist of Toll-like receptors 7, 8 and 9

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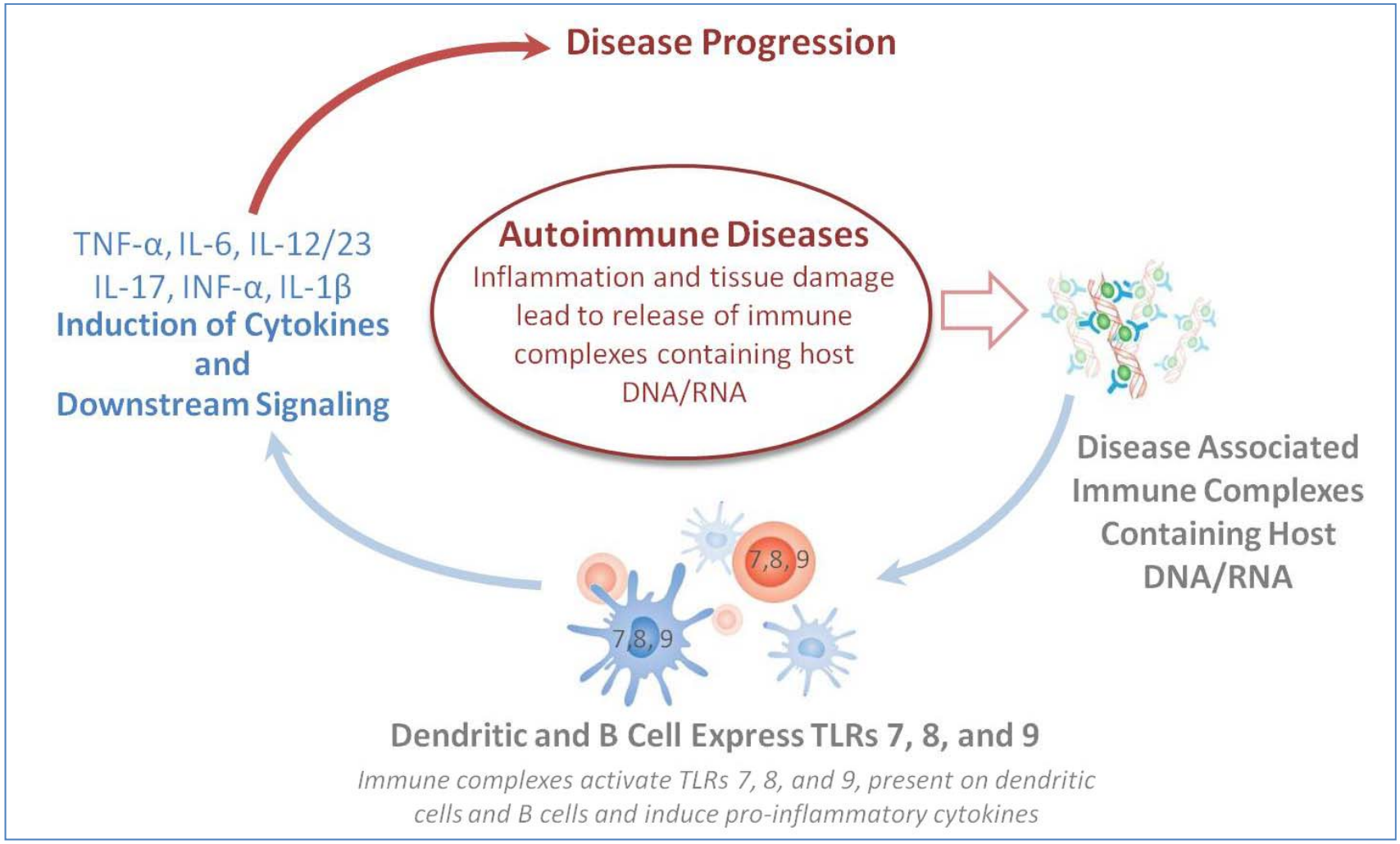
Introduction

- IMO-8400 is a first-in-class antagonist of Toll-like Receptors (TLRs) 7, 8, and 9 in clinical development for the treatment of autoimmune diseases. IMO-8400 was evaluated for safety, pharmacodynamics, and pharmaco-kinetics in a recent Phase 1 clinical trial in healthy subjects. A Phase 2 trial in patients with moderate to severe plaque psoriasis is on-going.

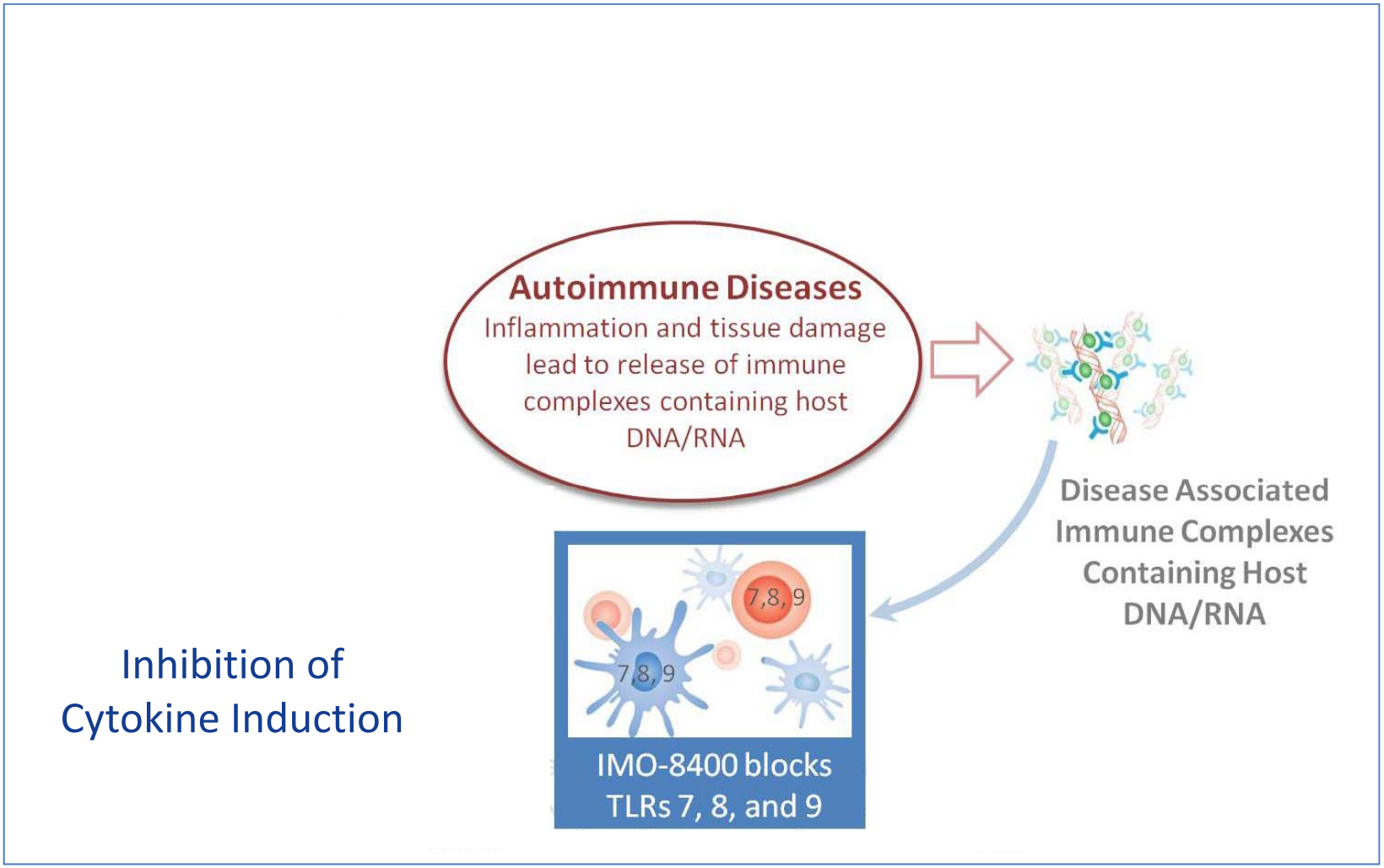
- In autoimmune diseases, damaged tissues release self nucleic acids that form complexes with antibodies, peptides, and lipids (panel to right). These complexes engage the endosomal TLRs 7, 8, and 9 in dendritic cells and B cells. Ligand binding activates downstream signaling cascades, resulting in the induction of pro-inflammatory cytokines, such as IL-12, IL-23, IL-17, IL-6, and IL-1, thereby exacerbating the disease.

- Current approaches to treatment of autoimmune diseases include monoclonal antibodies against individual cytokines, such as TNF-α, IL-12/23, IL-6, IL-1β, and IL-17, which inhibit elevated cytokines associated with disease, but also block constitutive cytokine activity.

Induction of Cytokines and Signaling Cascades Mediated through Toll-like Receptors is Central to the Autoimmune Disease Cycle



IMO-8400 Blocks Autoimmune Disease Cycle Upstream of Cytokine Induction



IMO-8400 blocks the induction of multiple cytokines induced by activation of TLRs 7, 8, and 9.

TLR Antagonism: Preclinical and Clinical Proof of Concept

Our approach to the treatment of autoimmune diseases involves specific inhibition of TLR responses to self nucleic acid complexes, thereby blocking the induction of multiple cytokines without affecting constitutive cytokine activity. As previously reported, our TLR antagonist compounds

- inhibit endosomal TLR-mediated immune activation in cell-based assays and in vivo in primates,[1]
- have potent activity in pre-clinical models of multiple autoimmune diseases including psoriasis and lupus.[2]

Further, IMO-8400, an antagonist of TLR8 as well as TLRs 7 and 9, was more potent than IMO-3100, an earlier TLR7 and 9 antagonist.[3]

TLR Antagonism: Preclinical and Clinical Proof of Concept

In our initial clinical proof-of-concept Phase 2 trial in patients with moderate to severe plaque psoriasis, treatment with IMO-3100 for only four weeks resulted in significant improvement in PASI scores. Further, those clinical responses were associated with improvement in psoriasis disease-associated gene profile, including the IL-17 pathway.[4]

Trial Overview

Design: Placebo-controlled, double-blind, randomized trial

Objectives:

- Evaluate the safety and tolerability of escalating single and multiple doses of IMO-8400 administered by subcutaneous injection
- Characterize the pharmacodynamic and pharmacokinetic profiles of IMO-8400

Three sequential single dose levels

- 0.1, 0.3 and 0.6 mg/kg
- N=6 per dose level and N=6 placebo

Two sequential multiple dose levels:

- 0.3 and 0.6 mg/kg once weekly for 4 weeks
- N=6 per dose level and N=6 placebo

Site: Single US center

Single Ascending Dose Trial Study Events

	Study Day					
Event	**1**	**2**	**3**	**5**	**8**	**30**
Dosing	✓					
Vital Signs	✓	✓	✓	✓	✓	✓
Physical Examination		✓			✓	✓
Safety Labs		✓		✓	✓	✓
Pharmacokinetics	✓	✓	✓		✓	
Pharmacodynamics	✓		✓		✓	
Safety Monitoring	|---- From Day 1 to Day 30 ----|					

Multiple Ascending Dose Trial Study Events

	Study Day									
Event	**1**	**2**	**5**	**8**	**15**	**22**	**23**	**24**	**29**	**57**
Dosing	✓			✓	✓	✓				
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical Examination		✓			✓	✓			✓	✓
Safety Labs		✓		✓	✓	✓	✓		✓	✓
Pharmacokinetics	✓	✓				✓	✓	✓		
Safety Monitoring	|---------- From Day 1 to Day 57 ----------|									

Subject Demographics

	Single-dose Cohorts (mg/kg)				Multiple-dose Cohorts (mg/kg/wk x 4 wk)		
	0.1	0.3	0.6	PLA	0.3	0.6	PLA
N	6	6	6	6	6	6	6
Age (yr, mean)	43.3	35.8	39.7	43.7	39.5	39.2	38.7
BMI (Mean)	27.9	28.5	28.5	28.6	30.2	25.9	26.1

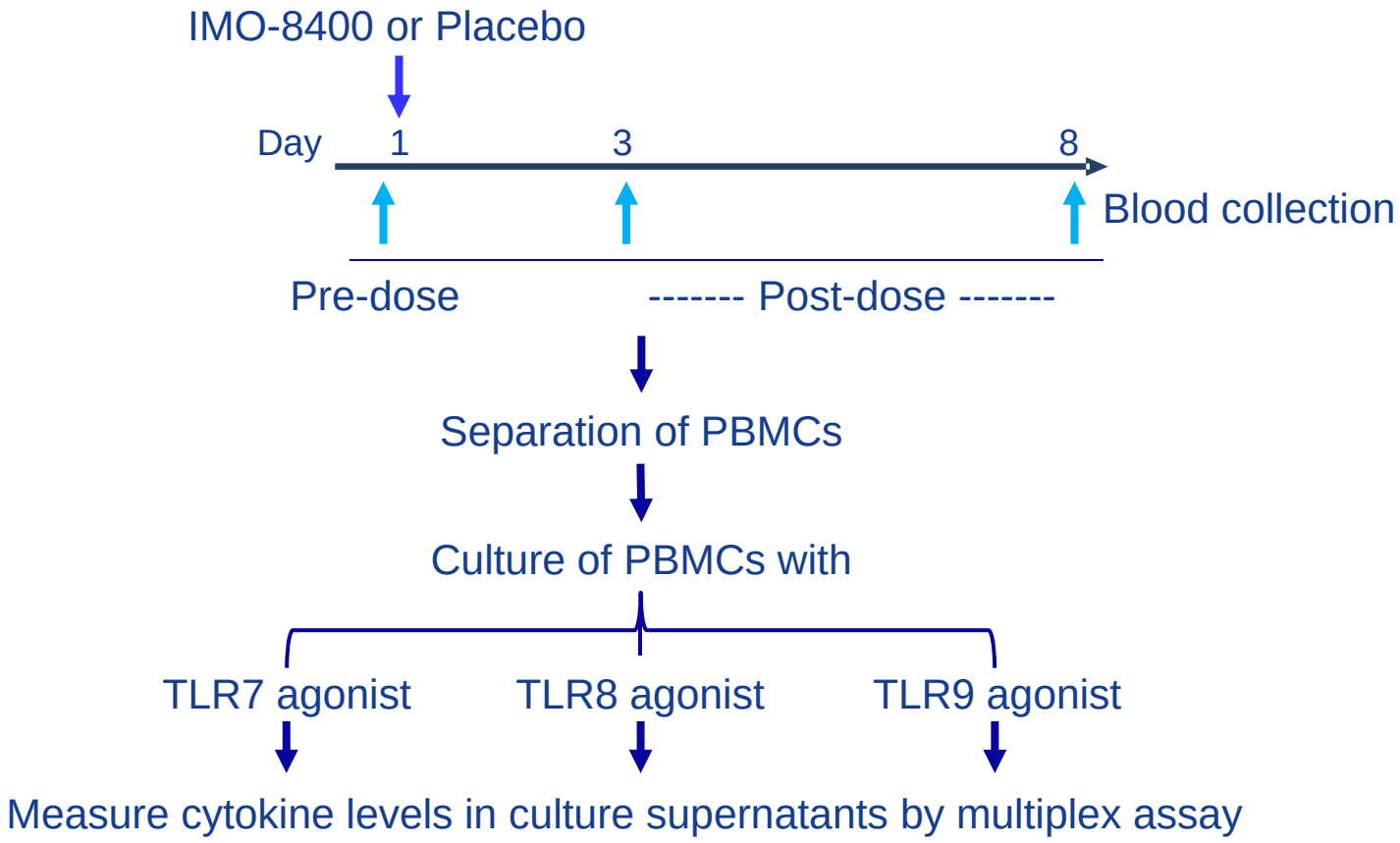
Safety

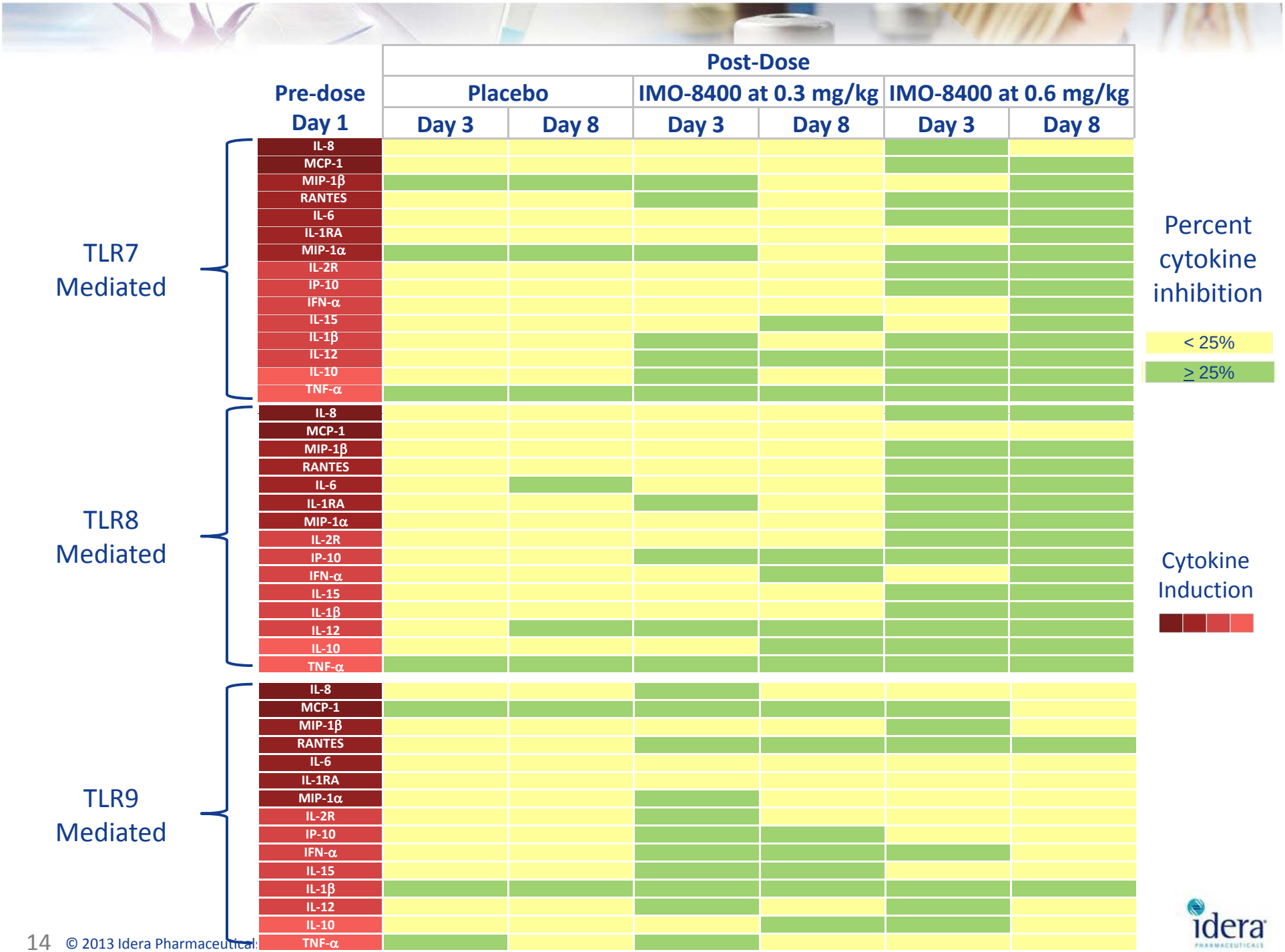
- Well tolerated in all treatment groups, single- and multiple-dose
  - No severe adverse events (AEs), no serious AEs
  - No treatment discontinuations
  - No changes in vital signs
  - No patterns of changes in safety laboratory parameters
- Injection site reactions (ISRs) were the most common treatment-related AEs
  - Asymptomatic mild erythema in 15 of 30 IMO-8400 subjects
  - Other ISRs were tenderness (N=4), pruritus (N=2), and induration (N=2)
- Other AEs seen in >1 subject occurred similarly in treated and placebo groups

Pharmacodynamics (PD)

- PD of IMO-8400 was evaluated in the single dose cohorts (IMO-8400 0.3 or 0.6 mg/kg, or placebo)
- Peripheral blood mononuclear cells (PBMCs) were isolated from the whole blood collected pre-dose (Day 1) and post-dose (Day 3 and Day 7) and cultured with TLRs 7, 8, and 9 agonist[5]
- Supernatants were harvested after 24 hours and assayed for cytokines using multiplex antibody beads (Luminex, Invitrogen)
- Inhibition of cytokine induction was assessed by comparing cytokine levels pre- and post-treatment in treated and placebo subjects

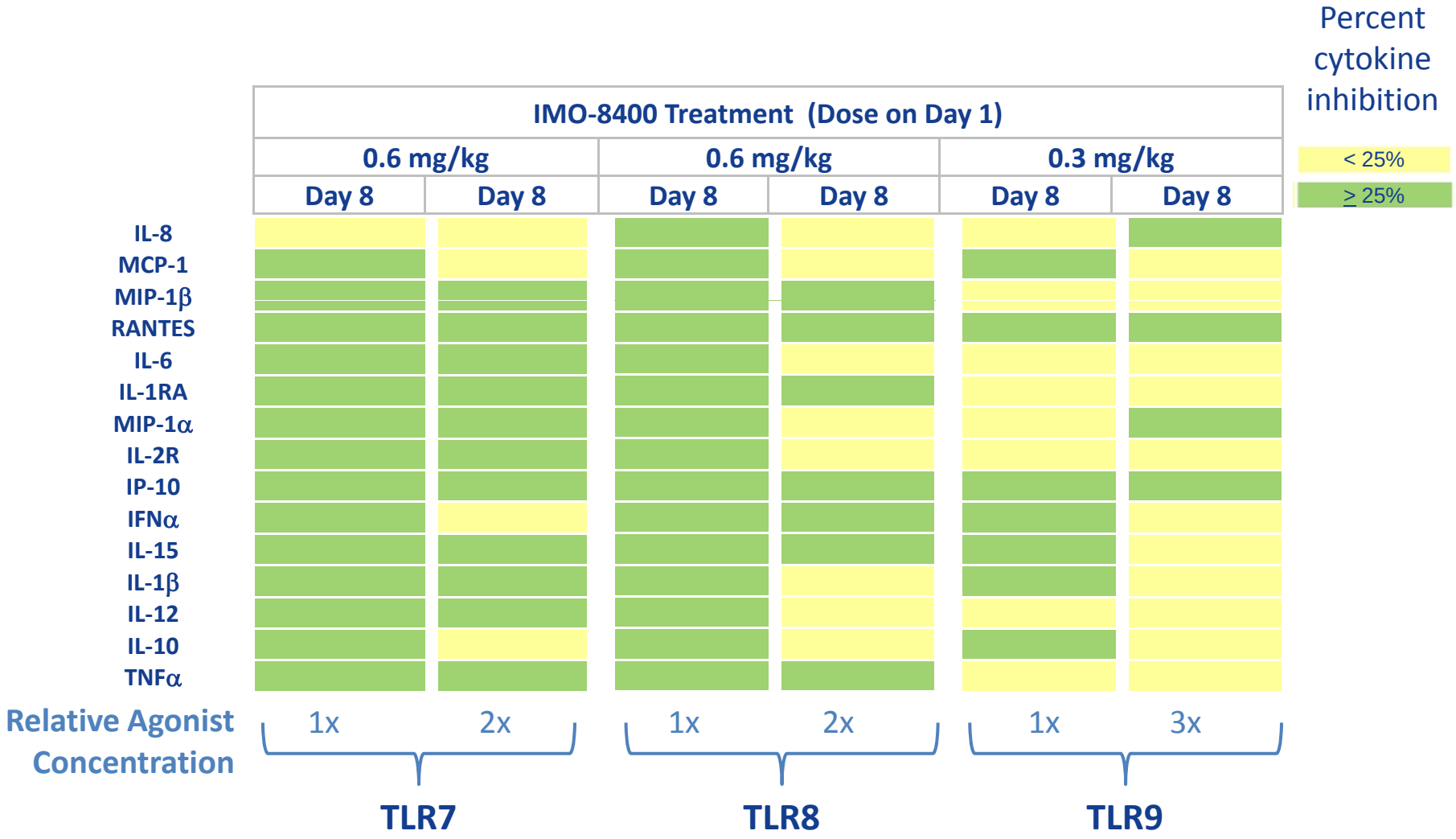
Overview of PD Procedures





Pharmacodynamics (PD)

- Compared to placebo, subjects treated with IMO-8400 showed inhibition of multiple cytokines induced by TLRs 7, 8, and 9 agonists
- Following a single dose administration, inhibition of cytokines was sustained through Day 8
- Inhibition of cytokine induction was dose-dependent, with 0.6 mg/kg dose resulting in more extensive and sustained inhibition than 0.3 mg/kg dose



Pharmacodynamics (PD)

- Inhibition of cytokines by IMO-8400 is also dependent on the dose of agonist. Cytokine inhibition was decreased at 2x or 3x higher concentrations of TLR agonist.
- In autoimmune diseases, the concentration of the self nucleic acid complexes is significantly less than the agonist dose in the ex vivo PD assay.

Pharmacokinetics (PK)

- IMO-8400 was rapidly cleared from the plasma
- Systemic exposure to IMO-8400 following escalating single and repeated subcutaneous doses increased approximately dose proportionately
- There was no accumulation in plasma following repeated doses: systemic exposure was similar after the 1st and 4th doses
- Between-subject variability in systemic exposure to IMO-8400 was moderate to low (CV of C_{max} and $AUC_{0\text{-}12h}$ geometric means were 11 to 38%)
- Median T_{max} was 2 hr (range: 1 to 4 hr), with no apparent relationship to dose level or single versus multiple doses

Pharmacokinetics (PK)

	Single-dose		
	0.1 mg/kg	0.3 mg/kg	0.6 mg/kg
Cmax (µg/mL)	0.324	0.651	1.49
$AUC_{0\text{-}12h}$ (µg-h/mL)	1.01	3.52	8.86

	Multiple-dose			
	0.3 mg/kg/week		0.6 mg/kg/week	
	Dose 1	Dose 4	Dose 1	Dose 4
Cmax (µg/mL)	0.575	0.609	1.29	1.60
$AUC_{0\text{-}12h}$ (µg-h/mL)	3.49	3.67	7.26	7.72

Comparing Pharmacodynamics and Pharmacokinetics

- Compared to PK data, PD data is more informative about duration of activity.
  - Following subcutaneous injection in humans, IMO-8400 was not detected in the plasma beyond 12 hours, whereas, in the same subjects, the *ex vivo* PD assay demonstrated sustained inhibition of TLR 7, 8, and 9-mediated cytokine induction for up to seven days.
- PD data may also be more informative regarding dose selection.
  - For the clinical proof of concept study using IMO-3100 in patients with moderate to severe plaque psoriasis, dose levels were selected based on PD data, which correlated well with clinical activity.

Summary and Conclusions

- IMO-8400 is a first-in-class antagonist of TLRs 7, 8, and 9.
- Single and multiple doses of IMO-8400 were well tolerated in healthy subjects at all dose levels administered in a placebo-controlled, double-blind, randomized Phase 1 clinical trial.
- PD studies show that following administration of IMO-8400 the induction of multiple cytokines is inhibited in response to agonists of TLRs 7, 8, and 9
    - Inhibition of cytokine induction was maintained for up to seven days post-dosing.
- IMO-8400 plasma PK showed rapid clearance, with no accumulation after four weekly doses.
- A Phase 2 trial of IMO-8400 in patients with moderate to severe plaque psoriasis is in progress.

References

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