

Safety and Pharmacodynamics of IMO-3100, a Novel Toll-like Receptor Antagonist for Autoimmune and Inflammatory Diseases, in a Rising Single-Dose Phase 1 Clinical Trial

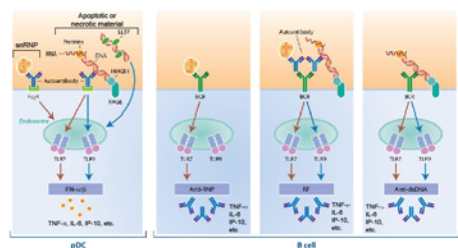
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INTRODUCTION

IMO-3100 is a modified oligonucleotide designed as an antagonist of both TLR7 and TLR9. Growing evidence suggests that in many autoimmune diseases, autoimmune complexes induce pro-inflammatory responses mediated through TLR7 and TLR9. Therefore, an antagonist of TLR7 and TLR9 should suppress inflammation in these autoimmune diseases. Consistent with this concept, IMO-3100 has shown potent activity in reducing immunologic and pathologic manifestations in preclinical disease models of lupus, rheumatoid arthritis, psoriasis, and hyperlipidemia. The first-in-human clinical trial evaluated the safety of IMO-3100 and the pharmacodynamic mechanism of action in peripheral blood mononuclear cells (PBMCs).

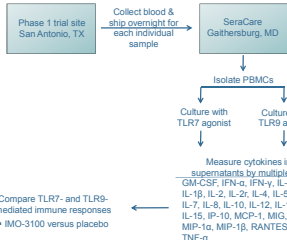
Rationale for Use of TLR Antagonist in Autoimmune Diseases



IMO-3100 Phase 1 Single Ascending Dose Trial Design

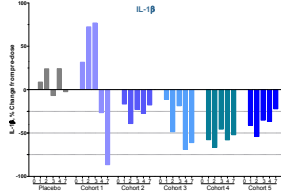
- Subcutaneous single dose in healthy subjects
 - Objectives:
 - Safety and tolerability
 - Demonstrate target engagement via ex vivo PD study
 - PK
- Six cohorts enrolled sequentially, N=6
 - 0.04, 0.08, 0.16, 0.32, and 0.64 mg/kg, placebo
- Study schedule
 - Screening visit within 3 weeks prior to study drug administration
 - Admission 1 day prior to study drug administration
 - In residence for 24 hours post-study drug administration
 - Daily outpatient visits days 3-5
 - Outpatient visits days 8 and 30

IMO-3100 Phase 1 Trial Ex Vivo PD Study Methods

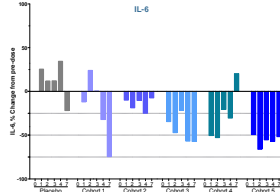


Compare TLR7- and TLR9-mediated immune responses
• IMO-3100 versus placebo

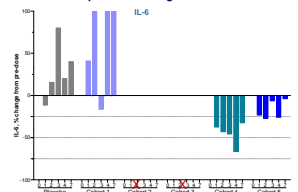
IMO-3100: Impact on TLR7 Agonist-Induced IL-1β Levels



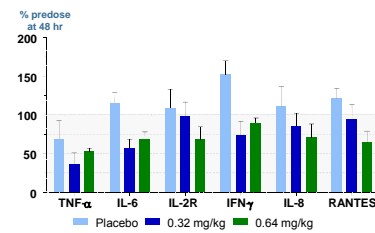
IMO-3100: Impact on TLR7 Agonist-Induced IL-6 Levels



IMO-3100: Impact on TLR9 Agonist-Induced IL-6 Levels

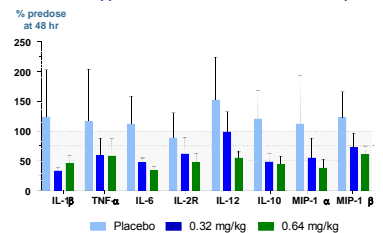


IMO-3100 Suppressed TLR9-Mediated Immune Response



Unaudited data. N=6 except one outlier excluded from analysis for IL-6 in 0.32 mg/kg groups.

IMO-3100 Suppressed TLR7-Mediated Immune Response



Unaudited data. N=6 except one outlier excluded from analysis for IL-6 in 0.32 mg/kg group.

Design of TLR Antagonist

Synthetic oligonucleotides containing unmethylated CpG motifs or synthetic dinucleotide motifs, referred to as immune stimulatory motifs, are shown to act as agonists of TLR9 (1-3). For an oligonucleotide to be active as an agonist of TLR9, 5'-accessibility is required and oligonucleotides containing two 5'-ends are shown to act as more potent TLR9 agonists (4-6). When 2'-O-substituted modifications, referred to as immune regulatory motifs, are incorporated adjacent to immune stimulatory motif on the 5'-side, they are shown to act as antagonists of TLR9 (7,8).

Based on structure-activity relationship studies, we have designed synthetic oligonucleotides which act as antagonists of TLR7 and TLR9 and selected a lead candidate, referred to as IMO-3100.

Following is an example of general structure of an antagonist.



Injection Site Reactions in IMO-3100 Single Dose Study

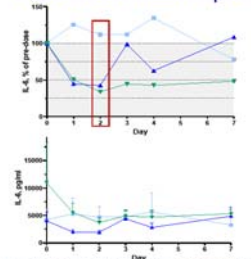
	IMO-3100 (mg/kg)						All IMO	Placebo
	0.04	0.08	0.16	0.32	0.64	n=31		
Any injection site reaction	4	3	3	5	5	20 (65%)	1	
Injection site erythema	3	2	3	4	5	17 (55%)		
Injection site induration	1	3	2	3	2	11 (35%)	1	
Injection site pain				3	2	5 (16%)		
Injection site pruritus	2					2 (6%)		
Injection site excoriation		1				1 (3%)		

Adverse Events in IMO-3100 Single Dose Study

Any AE	IMO-3100 (mg/kg)						All IMO	Placebo
	0.04	0.08	0.16	0.32	0.64	n=31		
Headache	1	1	1	0	3	3 (10%)	0	
Lymphadenopathy*		2	1			3 (10%)		
Excoriation	1				1	2 (6%)		
Oropharyngeal pain	1					1 (3%)		
Joint stiffness	1					1 (3%)		
Fever		1				1 (3%)		
Allergic rhinitis						1 (3%)		
Pruritus		1				1 (3%)		
Abdominal distension					1	1 (3%)		
Diarrhea					1	1 (3%)		
Nausea					1	1 (3%)		
Cough					1	1 (3%)		

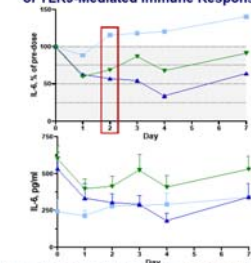
* the 2 cases at 0.08 were attributed to injection site (draining lymph nodes)

Example Time Course of IMO-3100 Suppression of TLR7-Mediated Immune Response



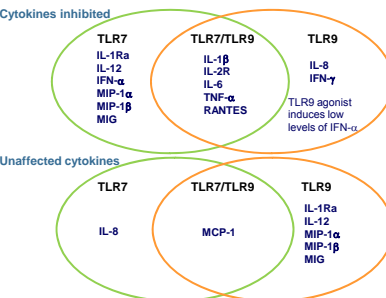
Unaudited data. N=6 except one outlier excluded from analysis for 0.32 mg/kg group.

Example Time Course of IMO-3100 Suppression of TLR9-Mediated Immune Response



Unaudited data. N=6 except one outlier excluded from analysis for 0.32 mg/kg group.

IMO-3100 Phase 1 Single-dose Trial: PD Summary



- ### IMO-3100 Phase 1 Single-dose Trial Summary
- Well-tolerated at all dose levels, no SAEs
 - All adverse events were grade 1
 - Injection site reactions most frequent (65%)
 - No TLR agonist activity
 - Proof of target engagement
 - Sustained inhibition of TLR7- and TLR9-mediated cytokine induction in PBMCs isolated after IMO-3100 treatment
 - Kinetics of inhibition vary between different cytokines
 - PBMCs from placebo-treated subjects showed no consistent differences in post-dose cytokine responses
 - Model successfully demonstrates pharmacodynamic effect

References

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