A Randomized, Double-Blinded, Placebo-Controlled, Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of XmAb®7195

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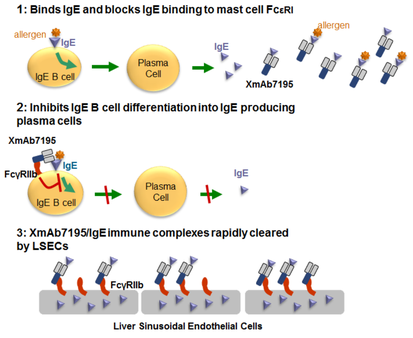
INTRODUCTION

- The clinical utility of blocking the interaction of IgE with basophils and mast cells has been well established in moderate to severe allergic asthma.
- Data from omalizumab controlled clinical studies have demonstrated a correlation between free IgE levels and asthma symptom control suggesting that greater suppression of free IgE may result in better clinical outcomes[1].
- XmAb®7195 is a humanized, Fc-engineered, anti-IgE mAb with enhanced Fc binding to the Fcγ receptor IIb (FcγRIIb) being developed for the treatment of allergic asthma and other IgE-mediated diseases.
- The antibody variable region has been engineered to increase affinity for human IgE relative to the murine antibody MaE11 (parent of omalizumab), while the Fc is engineered to increase affinity for the inhibitory Fc receptor FcγRIIb 200-400 fold relative to native IgG1 Fc.
- In nonclinical testing, XmAb7195 has been demonstrated to prevent IgE binding to mast cells and to inhibit the differentiation of IgE bearing B-cells[2].

XmAb7195 has three main mechanisms of action:

1. XmAb7195 binds to circulating IgE, blocking its ability to interact with the FcεRI receptors on mast cells and basophils.
2. XmAb7195, by coengagement of FcγRIIb and the B cell receptor on IgE expressing B cells, inhibits allergen activation of B cells, down-regulating their differentiation into plasma cells and subsequent IgE production.
3. FcγRIIb mediates accelerated clearance of XmAb7195:IgE immune complexes resulting in rapid and persistent reductions in both total and free IgE levels, unlike omalizumab which only reduces free IgE levels.

Figure 1: XmAb7195 Mechanisms of Action



METHODS

STUDY DESIGN

First-in-human, randomized, double-blinded, placebo-controlled, ascending-dose safety, tolerability and pharmacokinetic study

- Part 1: single ascending IV dose in adult healthy subjects; planned doses of 0.3, 1.0, 3.0, 6.0 and 10.0 mg/kg; 8 subjects per cohort; randomized 6:2 (XmAb7195:placebo).
- Part 2: single ascending IV dose in otherwise healthy adult subjects with a history of allergic rhinitis and/or conjunctivitis and/or atopic dermatitis with elevated serum IgE (300 – 3000 IU/mL); planned doses of 0.6, 2.0 and 5.0 mg/kg; 8 subjects per cohort; randomized 6:2 (XmAb7195:placebo).
- Part 3: two sequential IV doses (D1 priming dose and D8 2nd ascending dose) in adult healthy subjects; planned doses on D1/D8 of 0.3/0.3, 0.3/1.0, 0.3/2.0 mg/kg; 8 subjects per cohort; randomized 6:2 (XmAb7195:placebo)
- All subjects were followed for at least 28 days following XmAb7195 administration.

SUBJECTS

Major Inclusion Criteria	Major Exclusion Criteria
• Adult males and females 18 to 50 years of age, weight 50.0 to 100.0 kg, BMI 19.0 to 32.0 kg/m^2; • Part 1 and Part 3: Healthy as assessed by the PI with no clinically significant disease/disorder that would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion; • Part 2: Otherwise healthy male and female subjects with a history of allergic rhinitis and/or allergic conjunctivitis and/or atopic dermatitis with an elevated serum IgE of 300 – 3000 IU/mL inclusive on screening; • Subjects who are willing to forego other forms of experimental treatment during the study	• Subjects who have a clinically significant disease/disorder (other than allergic rhinitis and/or allergic conjunctivitis and/or atopic dermatitis in Part 2) that would pose a significant risk to subject safety or significantly interfere with the study evaluation, procedures, or completion as assessed by the PI; • Subjects with a history of asthma (subjects with a history of childhood asthma and no asthma symptoms for at least 10 years are eligible); • Subjects with prior exposure to a monoclonal antibody; • Subjects with a history of anaphylaxis; • Subjects who have a platelet count <150 k/μL within 1 day of dosing

OBJECTIVES

Primary Objective: To determine the safety and tolerability profile of IV administration of XmAb7195

Secondary Objective: To characterize PK and immunogenicity of IV administration of XmAb7195

Exploratory Objectives: To characterize the relationship between XmAb7195 dose and serum total IgE, serum free IgE, basophil surface-bound IgE and basophil FcεRI expression levels over time. To evaluate the effects of FcγRIIa and FcγRIIb gene polymorphisms on XmAb7195 PK and PD

STATISTICAL ANALYSIS

- Safety population consisted of all subjects that received XmAb7195 (or placebo)
- All treatment emergent adverse events (TEAEs), i.e. those reported after the start of infusion on Day 1, were included in the analysis
- PK and PD population consisted of all subjects that received XmAb7195 (or placebo) and had PK and PD data considered to be sufficient and interpretable
- PK parameters were computed using non-compartmental methods appropriate for a constant rate infusion performed using WinNonlin V 6.3

RESULTS

DISPOSITION

- Part 1: 40 healthy subjects; single IV administrations of XmAb7195 (or placebo) of 0.3, 1.0, 3.0, 0.75 and 0.75 mg/kg were investigated in Cohorts 1, 2, 3, 4 and 5, respectively
- Part 2: 16 atopic subjects with elevated total IgE; single IV administrations of XmAb7195 (or placebo) of 0.6 mg/kg and 2.0 mg/kg (reduced to 1.5 mg/kg and further reduced to 1.0 mg/kg) were investigated in Cohorts 6 and 7 respectively
- Part 3: 16 healthy subjects; two sequential IV doses of XmAb7195 (or placebo) were administered on Day 1 and Day 8. Cohort 9: 0.3 mg/kg on Day 1 and 0.3 mg/kg on Day 8. Cohort 10: 0.3 mg/kg on Day 1 and 1.0 mg/kg on Day 8

Table 1: Subject Disposition

	Placebo	Part 1 XmAb7195	Part 2 XmAb7195	Part 3 XmAb7195	Total XmAb7195
Enrolled	18 (100%)	31 (100%)	13 (100%)	12 (100%)	56 (100%)
Dosed	18 (100%)	30* (96.8%)	12* (92.3%)	12 (100%)	54 (96.4%)
Completed	18 (100%)	30 (96.8%)	11 (84.6%)	12 (100%)	53 (94.6%)

*1 subject in Part 1 and 1 subject in Part 2 discontinued prior to dosing

Baseline characteristics with the exception of total and free IgE levels were similar across the 3 parts of the study

Table 2: Subject Demographics and Baseline Characteristics

	Placebo	Part 1 XmAb7195	Part 2 XmAb7195	Part 3 XmAb7195	Total XmAb7195
Mean Age, years (range)	31.4 (18-45)	31.1 (19-49)	28.5 (21-46)	33.3 (19-49)	31.0 (19-49)
Female (%)	9 (50.0%)	22 (73.3%)	4 (33.3%)	6 (50.0%)	32 (59.3%)
Black or African American (%)	16 (88.9%)	24 (80.0%)	10 (83.3%)	9 (75.0%)	43 (79.6%)
White	2 (11.1%)	6 (20.0%)	1 (8.3%)	3 (25.0%)	10 (18.5%)
Mean Weight, Kg (range)	79.0 (55.1-99.0)	73.6 (53.3-90.7)	76.4 (62.0-84.9)	75.8 (61.5-86.9)	74.7 (53.3-90.7)
Median Total IgE, IU/mL (range)	82.6 (1.0-963)	34.7 (7.1-480)	489.5 (327-1120)	65.5 (3.1-176)	59.1 (3.1-1120)
Median Free IgE, ng/mL (range)	77.2 (4.8-1609)	42.7 (4.8-907)	710 (424-1777)	87.8 (4.8-316)	74.0 (4.8-1777)

SAFETY

Table 3: Summary of TEAEs (Safety Population)

	Placebo	XmAb7195			
		Total Part 1	Total Part 2	Total Part 3	Parts 1 to 3
	N = 18 n (%) E	N = 30 n (%) E	N = 12 n (%) E	N = 12 n (%) E	N = 54 n (%) E
TEAEs	7 (38.9) 12	17 (56.7) 30	9 (75.0) 25	6 (50.0) 11	32 (59.3) 66
Related TEAEs	0	11 (36.7) 16	7 (58.3) 18	3 (25.0) 3	21 (38.9) 37
Mild TEAEs	6 (33.3) 11	11 (36.7) 17	9 (75.0) 21	5 (41.7) 8	25 (46.3) 46
Moderate TEAEs	1 (5.6) 1	11 (36.7) 13	2 (16.7) 3	2 (16.7) 3	15 (27.8) 19
Severe TEAEs	0	0	1 (8.3) 1	0	1 (1.9) 1
Life-threatening TEAEs	0	0	0	0	0
Fatal TEAEs	0	0	0	0	0
Serious TEAEs	0	0	1 (8.3) 1	0	1 (1.9) 1
TEAEs leading to withdrawal	0	0	0	0	0

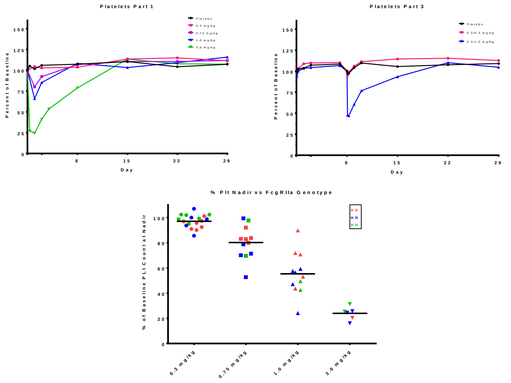
Table 4: TEAEs by Preferred Term and Treatment – Related to IMP- In > 1 Subject (Safety Population)

	Placebo	Part 1 XmAb7195				Placebo	Part 2 XmAb7195				Placebo	Part 3 XmAb7195	
Preferred Term	N = 10 n (%) E	0.3 mg/kg N = 6 n (%) E	0.75 mg/kg N = 12 n (%) E	1.0 mg/kg N = 6 n (%) E	3.0 mg/kg N = 6 n (%) E	N = 4 n (%) E	0.6 mg/kg N = 6 n (%) E	1.0 mg/kg N = 4 n (%) E	1.5 mg/kg N = 1 n (%) E	2.0 mg/kg N = 1 n (%) E	N = 4 n (%) E	0.3/0.3 mg/kg N = 6 n (%) E	0.3/1.0 mg/kg N = 6 n (%) E
Thrombocytopenia	0	0	0	0	6 (100) 6	0	0	0	0	1 (100) 1	0	0	0
Nasal congestion	0	0	0	0	0	0	0	1 (25.0)	0	1 (100) 1	0	0	0
Rhinorrhoea	0	0	0	0	0	0	1 (16.7) 1	2 (50.0) 1	0	0	0	0	0
Pruritus	0	0	0	0	1 (16.7)	0	1 (16.7) 1	1 (25.0) 1	0	0	0	0	0
Urticaria	0	0	2 (16.7) 2	2 (33.3) 2	3 (50.0) 3	0	0	1 (25.0) 1	0	0	0	1 (16.7) 1	1 (16.7) 1

The 2 most common drug-related TEAEs were thrombocytopenia and urticaria

Thrombocytopenia

- Dose-dependent reductions in platelet counts were observed in subjects that received ≥0.75 mg/kg XmAb7195
- Thrombocytopenia was reported in all subjects that received ≥2 mg/kg XmAb7195
- Transient with nadir by 24 hours and recovering beginning by 48 hours after infusion
- Asymptomatic; no evidence of bleeding or bruising
- In Part 3, decreases in platelet count were seen after the 1.0 mg/kg dose level even in subjects with free IgE BLQ (<9.59 ng/ml) following the 0.3 mg/kg priming dose
- No apparent association with FcγRIIa R131H genotype



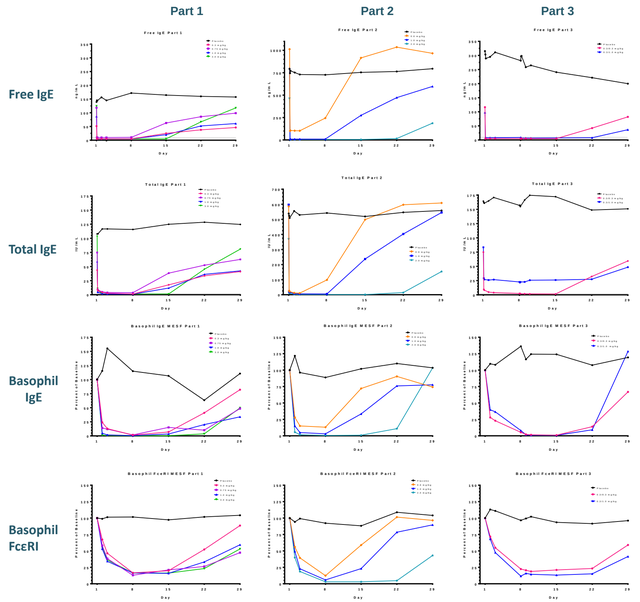
Urticaria

- Urticaria (pruritus and hives) occurred in 10 subjects with onset during the infusion
- Easily treated with oral antihistamines; no interruption of the infusion was required
- Two subjects that experienced urticaria during the first dose in Part 3 did not have recurrence during or after the second dose.

Serious Adverse Events

- One atopic subject with a history of perennial and seasonal allergies experienced severe bronchospasm 25 minutes after the start of the XmAb7195 infusion
- The event responded quickly to discontinuation of the infusion and medical intervention
- There were no other clinical signs and/or symptoms of anaphylaxis in the subject per the Sampson criteria[3]

PHARMACODYNAMICS



PHARMACOKINETICS/IMMUNOGENICITY

- XmAb7195 exposure increased in a slightly greater than proportional manner with doses between 0.3-3.0 mg/kg
- Clearance (19.34 ± 7.37 mL/day/kg), volume of distribution (73.90 ± 32.55 mL/kg) and half-life (3.85 ± 3.93 days) showed little if any dependence on dose level
- There were no significant differences in clearance, volume of distribution or half-life between subjects with FcγR2A (R131H) or FcγR2B (I232T) isoforms
- Only 1 of 54 (1.9%) XmAb7195 treated subjects was observed to have a confirmed positive ADA result

CONCLUSIONS

- XmAb7195 was generally well tolerated when administered as a single IV infusion with transient, asymptomatic thrombocytopenia occurring at doses ≥2.0 mg/kg
- XmAb7195 induced rapid and extensive depletion of serum free IgE, serum total IgE, basophil surface IgE and basophil FcεRI expression levels at all doses tested
- Across all dose levels tested, 93% of healthy adults (Part 1) and 75% of atopic subjects with predose total IgE of >300 IU/ml (Part 2) had reduction of free IgE levels to BLQ (<9.59 ng/ml) following a single dose of XmAb7195
- The results of this study support further development in a multiple ascending dose study with subcutaneous administration

REFERENCES

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3. Sampson et al. J Allergy Clin Immunol 2006;117:391-397

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