LBS-104

XOMA 358, a Novel Treatment for Hyperinsulinemic Hypoglycemia: Safety and Clinical Pharmacology from the First in Human Trial

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Abstract

Hyperinsulinemic hypoglycemia (HH), a complication of non-resectable insulinomas and Congenital Hyperinsulinism, remains a serious medical concern with limited therapeutic options. We recently described a fully human IgG2 monoclonal antibody XOMA 358 to the human insulin receptor (InsR) that allosterically inhibits insulin action both in vitro and in HH mice (*mAbs 6:262,* 2014). We herein report results from a **Phase 1, Double-blind, Placebo-controlled, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of intravenous doses of XOMA 358 in Healthy Adult Male Subjects**. 4 subjects in the sentinel cohort were to receive 4 active drug and 2 were to receive placebo; 3 subjects in subsequent cohorts were to receive active drug and one was to receive placebo. Doses of 0.1, 0.3, 1, 3, 6 and 9 mg/kg were scheduled for administration in sequential cohorts, with dose escalation based on safety and pharmacokinetic (PK) review. Serum insulin, glucose, β-hydroxy butyrate, C-peptide and glucagon levels were monitored as potential biomarkers. Mixed meal tests (MMTs) were scheduled pre-dose at day -1 and post-dose at days 1, 2, 3 and 6. Once changes in insulin and glucose consistent with induced insulin resistance were observed in a cohort, a 15 minute insulin tolerance test (ITT) was performed in subsequent cohort(s) pre-dose on day-1 and post-dose on days 1, 2, 3 and 5 to assess insulin sensitivity. Subjects remained in-patient from day -1 or day -2 (cohorts with ITT) until day 7 after drug administration. Dosing was stopped at cohort 4 (3 mg/kg) after observation of pharmacologic effects consistent with drug-induced insulin resistance; overall, 14 active and 5 placebo doses were administered to a total of 19 subjects. XOMA 358 appeared to be well-tolerated; there were no serious adverse events or severe adverse events. 11/14 subjects experienced adverse events. All drug-related adverse events were mild (43/46) or moderate (3/46), and none required either concomitant medication or invasive procedures for management. The PK was linear with a drug half-life of approximately 14 days. Dose-related increases in post-prandial glucose levels as measured in the MMTs were observed through day 6 following drug infusion, with the Day 3 glucose AUC nearly 80% greater than placebo at the 1 mg/kg dose level. Fasting HOMA-IR values, a measure of XOMA 358-induced insulin resistance, were likewise elevated by XOMA 358 in a dose-dependent manner and at peak time points, ranged from 2 to 9-fold over baseline for 0.1 to 3 mg/kg doses, respectively. A marked reduction in insulin sensitivity was verified via the ITT procedure at the 3 mg/kg dose level; markedly reduced K_{ITT} values in the XOMA 358-treated subjects were observed relative to either placebo or baseline values. The safety and clinical pharmacology of XOMA 358 may justify further exploration in patient population(s) with HH.
Disclosure: RN, KWJ, JMR, KD, ACN, PR, IDG: Employees, XOMA LLC.

Background

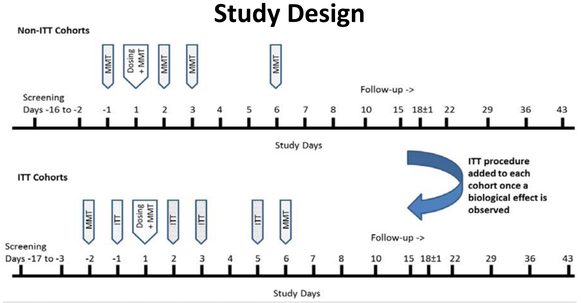
- XOMA 358 is a fully human monoclonal antibody to the human insulin receptor that is an allosteric down-modulator of insulin action (Corbin et al., 2014).
- Its activity profile includes some dissociation of binding and reduced clearance of insulin.
- XOMA 358 treatment normalizes blood glucose in a mouse model of CHI (*SUR1* knockout mice) and reverses hypoglycemia in hyperinsulinemic mice and rats at doses ≥ 3 mg/kg.
- A biomarker of XOMA 358 action in animals is an increase in circulating insulin (but sustained inhibition of insulin action).
- XOMA 358-induced hyperglycemia in normal animals can be reversed with insulin administration.
- Safety pharmacology and toxicology evaluations enable doses in human higher than that utilized in this first-in-human clinical trial.

We are developing XOMA 358 as a first-in-class therapeutic for conditions of hyperinsulinemic hypoglycemia.

Study Objective

To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending intravenous doses of **XOMA 358** in healthy adult male subjects

Study Design



- PD markers: insulin, glucose, C-peptide
- **Mixed Meal Tolerance (MMT)** test for postprandial glucose, C-peptide, & insulin
- Assessment of insulin sensitivity using a 15-min **Insulin Tolerance Test (ITT)** (Bonara et al., 1989)
- Ascending doses of 0.1 / 0.3 / 1 / 3 / 6 / 9 mg/kg planned
  - *Study stopped after cohort 4 (3 mg/kg) based upon PD effects consistent with predicted treatment-related insulin resistance*
- Single clinical site: Celerion, Tempe, AZ

Results - Safety

XOMA 358 Appeared to be Well-tolerated

- 14 Subjects received Active treatment with XOMA 358, of which 13 Subjects reported adverse events (AEs); 5 Subjects received Placebo, of which 4 Subjects reported AEs.
- No Serious Adverse Events (SAEs) were reported
- Most AEs (94.6%, 88/93) were mild in severity, with a few AEs moderate in severity (5.4%, 5/93); there were no severe AEs.
- All AEs resolved; none of the subjects required either concomitant medication or invasive procedures for management of AE's.

TABLE 1: Summary of AEs by Treatment Group

Treatment	Total # of Subjects	# of Subjects with AEs	Total # of AEs	# mild AEs	# moderate AEs	# severe AEs
Placebo	**5**	**4/5**	**27**	**26**	**1**	**0**
0.1mg/kg	4	3/4	13	13	0	0
0.3mg/kg	3	3/3	5	5	0	0
1 mg/kg	3	3/3	14	13	1	0
3 mg/kg	4	4/4	34	31	3	0
Total Active	**14**	**13/14**	**66**	**62**	**4**	**0**
Overall	**19**	**17/19**	**93**	**88**	**5**	**0**

TABLE 2: Summary of Treatment-emergent AEs in Subjects on XOMA 358 (N=66)

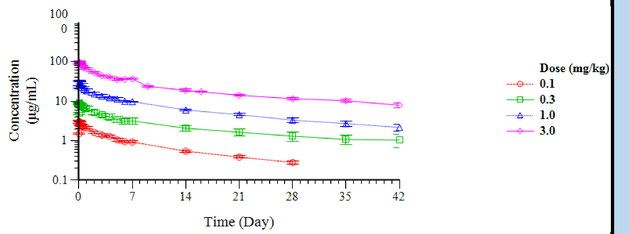
TEAEs by Body System (System Organ Class) ≥ 5% Preferred Term (PT) ≥ 5%	Frequency of AEs	Severity of AEs	Study Drug Relationship
General disorders & administration site conditions Catheter site reactions 38% (25)	46% (30)	Mild	6% (4) Related
Nervous system disorders Headache 5% (3)	20% (13)	Mild	17% (11) Related
Skin and subcutaneous tissue disorders Hyperhidrosis 8% (5)	11% (7)	Mild	6% (4) Related
Musculoskeletal and connective tissue disorders Muscle Spasm 8% (5)	11% (7)	Mild	9% (6) Related
Gastrointestinal Disorders Abdominal Pain 6% (4)	9% (6)	Mild	8% (5) Related

Note: All percentages rounded up

Results - PK

XOMA 358 Human Pharmacokinetics Were Better Than Predicted:

- Dose-proportional PK and an elimination half-life longer than expected for a surface receptor-targeted monoclonal antibody



Dose Level (mg/kg)	Cmax (µg/mL)	AUCinf (Day*µg/mL)	Half Life (Day)
0.1	3.14	27.3	15.5
0.3	9.00	120	21.2
1.0	29.4	338	23.7
3.0	100	1150	24.9

Results - PD

XOMA 358 Treatment Induced Insulin Resistance

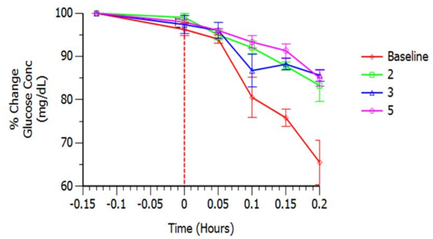
- Indicated by a dose-related increase in magnitude and duration of AM fasting HOMA-IR
- Peak insulin resistance observed at 1 mg/kg and sustained at a severe to moderate level for over a week at 3 mg/kg

Group (mg/kg)	Mean AM Fasting HOMA-IR				
	Baseline	Day 1	Day 3	Day 5	Day 7
All	1.4	-			
Placebo	1.6	1.8	1.7	1.6	1.6
0.1	1.0	3.1	1.9	1.2	1.0
0.3	1.4	5.0	3.7	3.6	3.3
1	2.0	10.8	5.7	2.3	3.7
3	1.4	10.6	6.2	5.0	3.8

Moderate Insulin Resistance (HOMA-IR ≥ 3)
Severe Insulin Resistance (HOMA-IR ≥ 5)

XOMA 358 Treatment Reduced Insulin Sensitivity

- Utility of a 15 minute ITT confirmed insulin resistance, that was fully evident by Day 2, and persisted for at least 5 days.

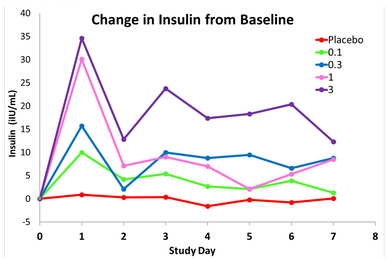


Treatment Grp	K_{ITT} Value			
	Baseline	Day 2	Day 3	Day 5
Placebo (N=1)	2.1	1.8	1.7	1.4
3.0 mg/kg (N=4)	2	0.86	0.68	0.67

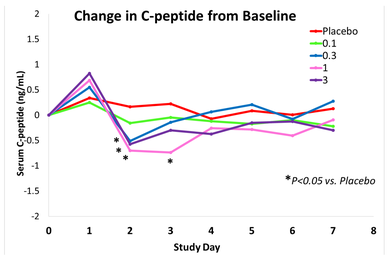
Results - PD

XOMA 358 Treatment Resulted In Dose-dependent Elevation Of AM Fasting Serum Insulin Without Significant C-peptide Modulation:

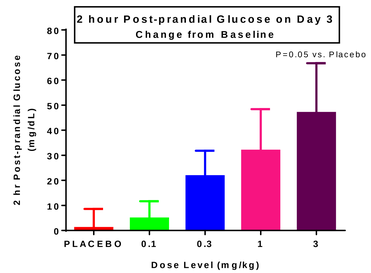
- **Changes in Serum Insulin Levels Post-XOMA 358 Dosing Identified as a Biomarker of XOMA 358 Exposure, Likely Related to Reduced Insulin Clearance**

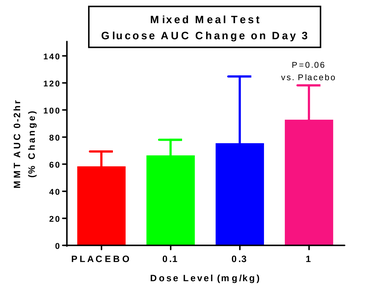


Note: nearly every XOMA 358 treatment group data point above is p<0.05 vs. Placebo but is not depicted for clarity.



XOMA 358 Treatment Induced Dose-related, Sustained Increases In Post-prandial Glucose





Summary & Conclusions

Final Cohorts & Key Outcomes:

Group #	Placebo N	XOMA 358 Dose (mg/kg)	XOMA 358 N	Biomarker Activity Observed	Insulin Resistance Observed
1	2	0.1	4	+	-
2	1	0.3	3	++	+
3	1	1.0	3	++	+
4	1	3.0	4	++	++
	Total = 5		Total = 14		

- XOMA 358 was well-tolerated with no serious adverse events observed.
  - TEAEs: No severe events, all events were mild (88/93) to moderate (5/93).
  - No active intervention was needed.
- Pharmacokinetics in humans were better than anticipated with a half-life ranging 15-26 days.
- XOMA 358 is active and potent in humans:
  - Circulating insulin levels, considered as a biomarker, are affected at the lowest tested dose (0.1 mg/kg).
  - Increases in post-prandial glucose are evident at 0.3 mg/kg and above.
  - Drug-induced severe insulin resistance, as measured by AM fasting HOMA-IR, is evident at 0.3 mg/kg and above.
  - Utilization of an ITT confirms XOMA 358-induced insulin resistance is evident within two days of IV infusion and sustained for at least 5 days.

The data indicate that treatment with XOMA 358, a first-in-class fully human allosteric monoclonal antibody to the human InsR, may be a safe and effective novel approach for the control of hypoglycemia in hyperinsulinemic conditions.

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