

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

Rajneesh Nath^{1*}, Kirk W Johnson^{2*}, Julie M Roessig^{1*}, Ken Der^{2*}, Ann C Neale^{3*}, Paul Rubin, M^{4*} and Ira D Goldfine, MD^{4*}

¹Clinical Science, XOMA (US) LLC, Berkeley, CA; ²Preclinical Development, XOMA (US) LLC, Berkeley, CA; ³XOMA (US) LLC, Danville, CA; ⁴Dept. of Research and Development, XOMA Corp., Berkeley, CA. *Potential conflict of interest may exist. Refer to the Abstract.

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

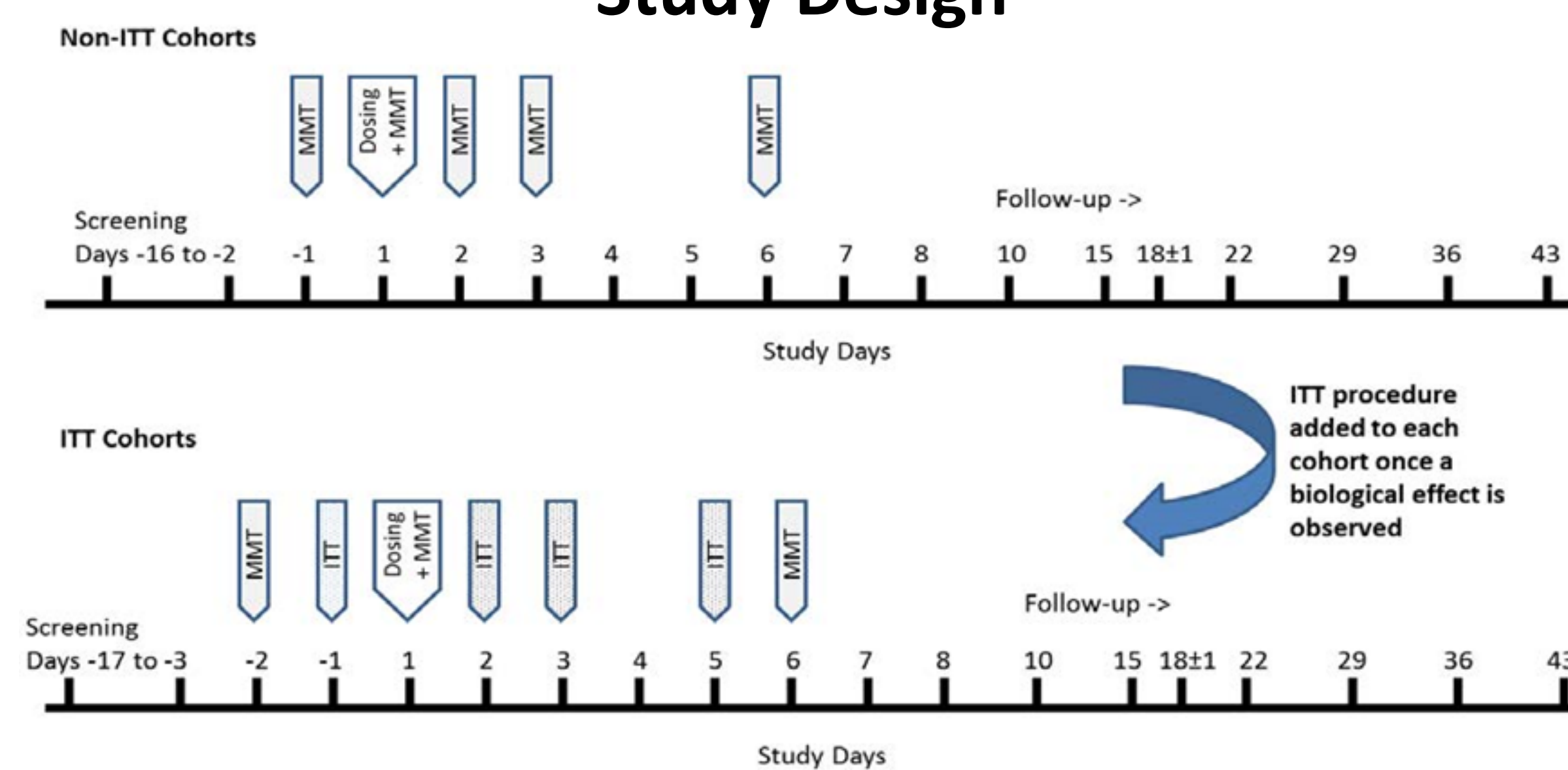
- XOMA 358 is a fully human monoclonal antibody to the human insulin receptor that is an allosteric down-modulator of insulin action (Corbin et al., 2014).
- Its activity profile includes some dissociation of binding and reduced clearance of insulin.
- XOMA 358 treatment normalizes blood glucose in a 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)

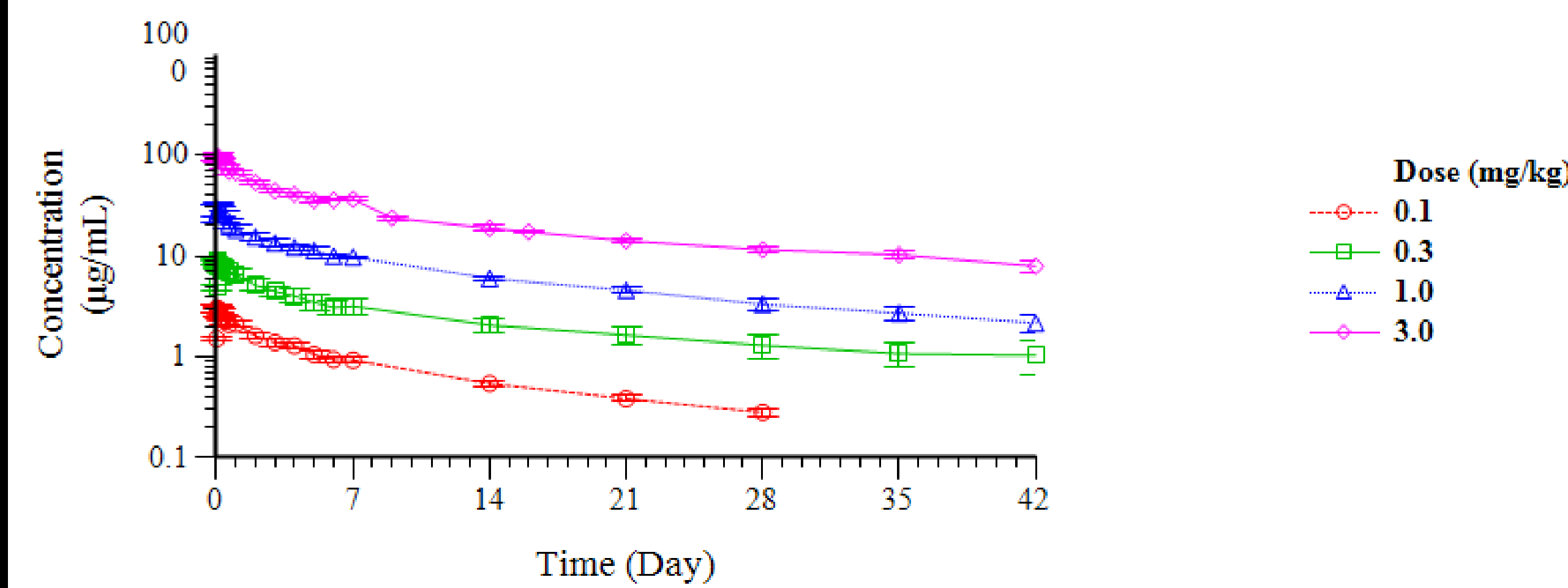
TEAEs by Body System (System Organ Class) ≥ 5% Preferred Term (PT) ≥ 5%	Frequency of AEs	Severity of AEs	Study Drug Relationship
General disorders & administration site conditions Catheter site reactions 38% (25)	46% (30)	Mild	6% (4) Related
Nervous system disorders Headache 5% (3)	20% (13)	Mild	17% (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

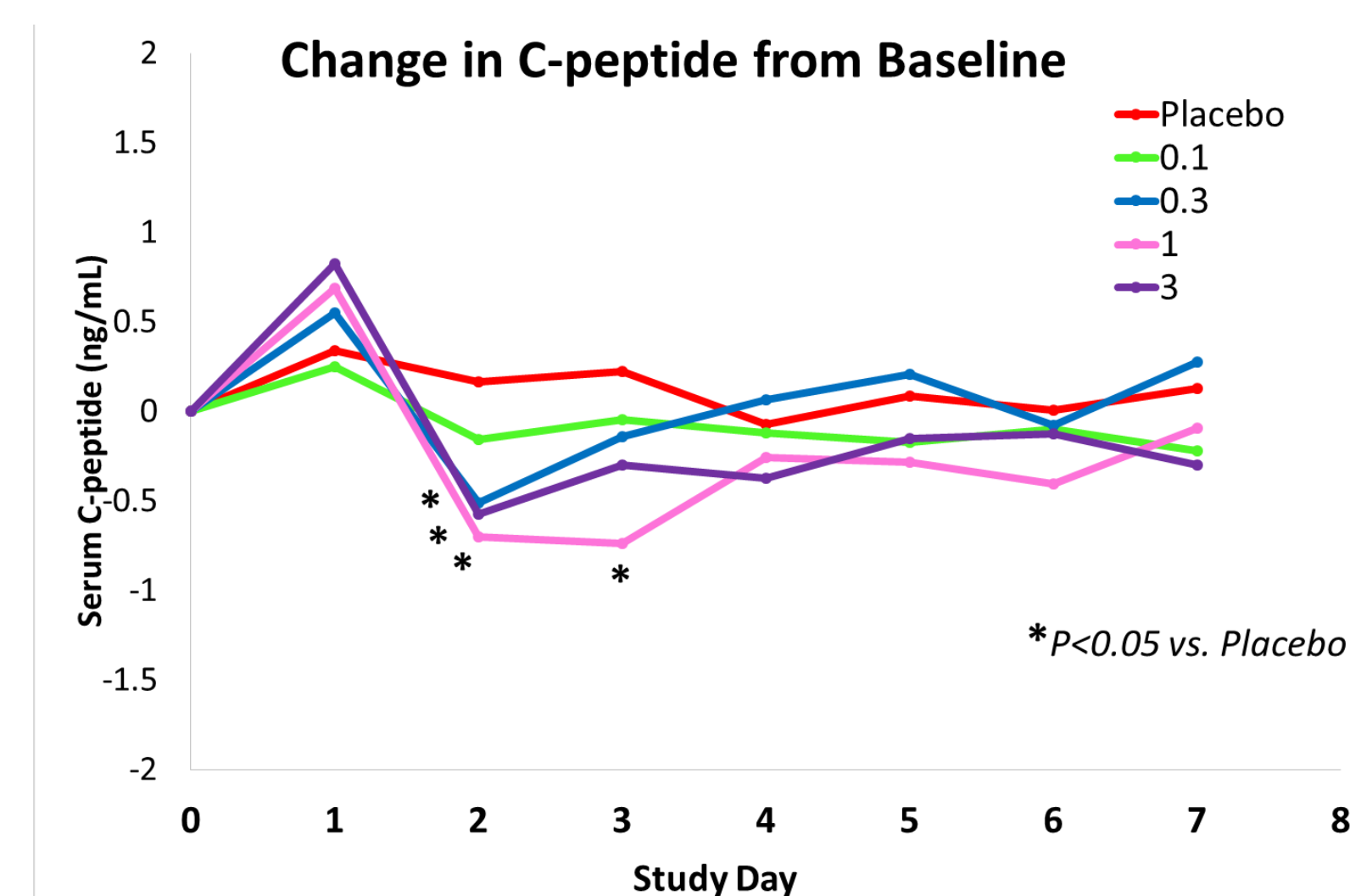
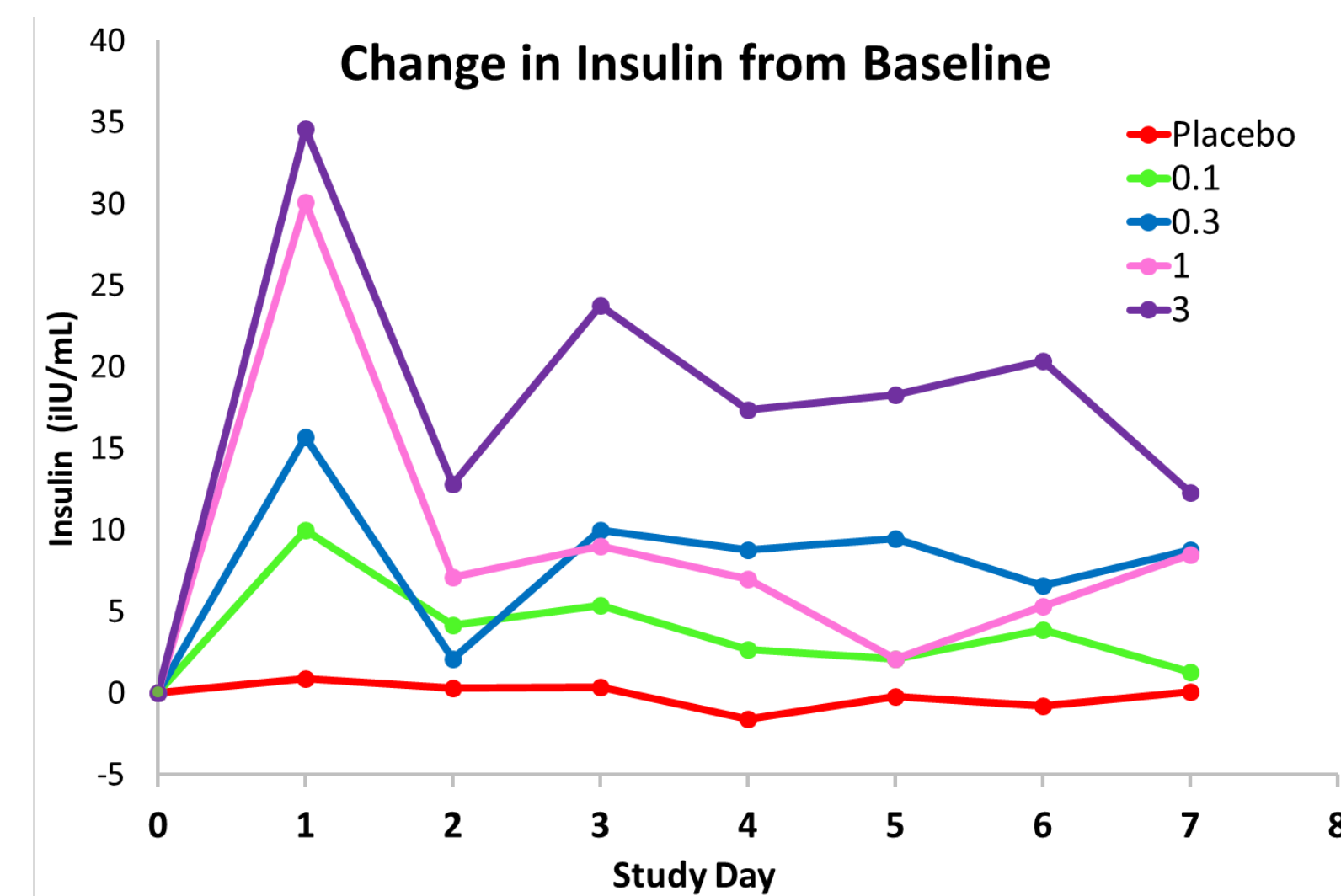


Dose Level (mg/kg)	Cmax (µg/mL)	AUCinf (Day*µg/mL)	Half Life (Day)
0.1	3.14	27.3	15.5
0.3	9.00	120	21.2
1.0	29.4	338	23.7
3.0	100	1150	24.9

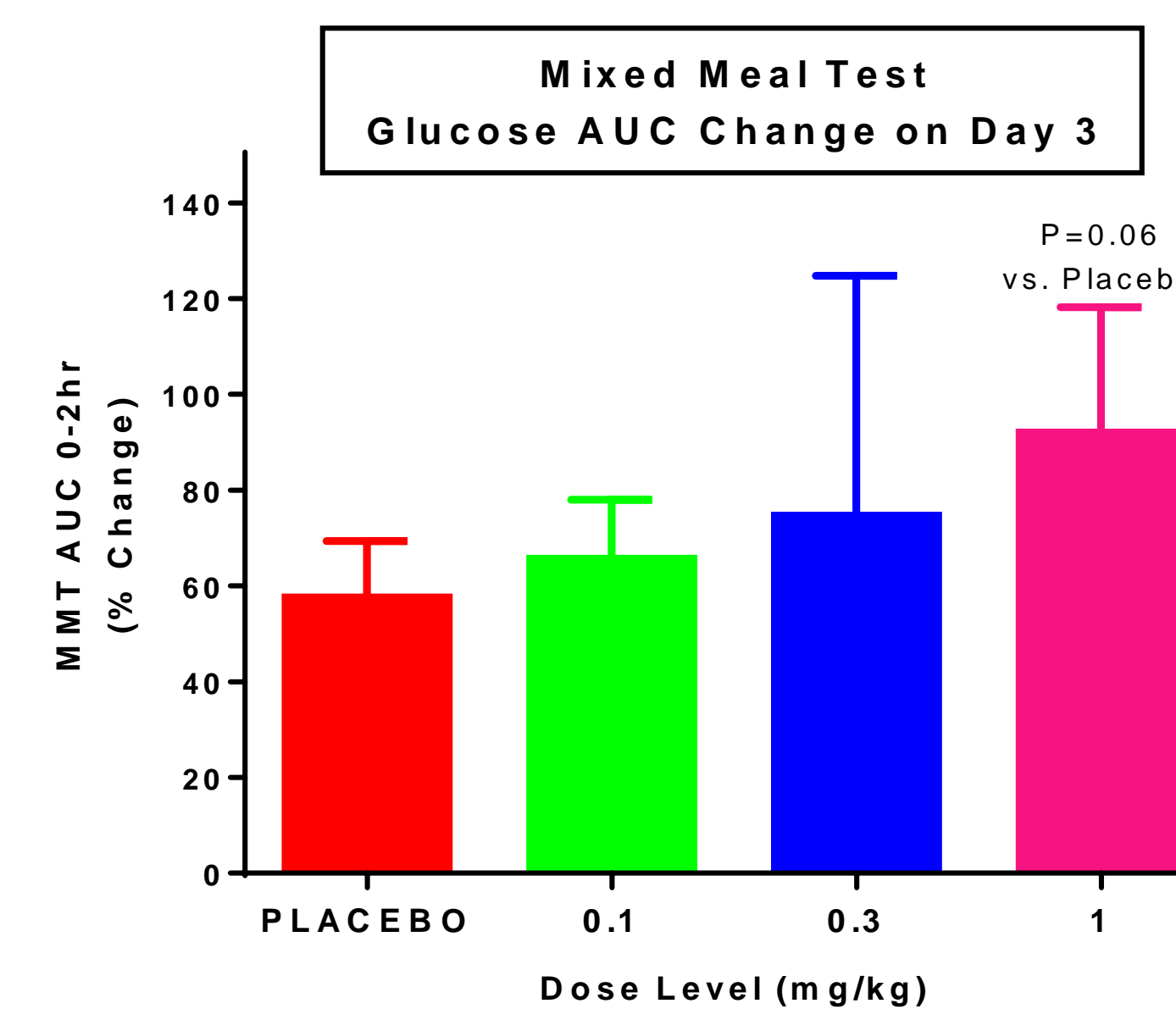
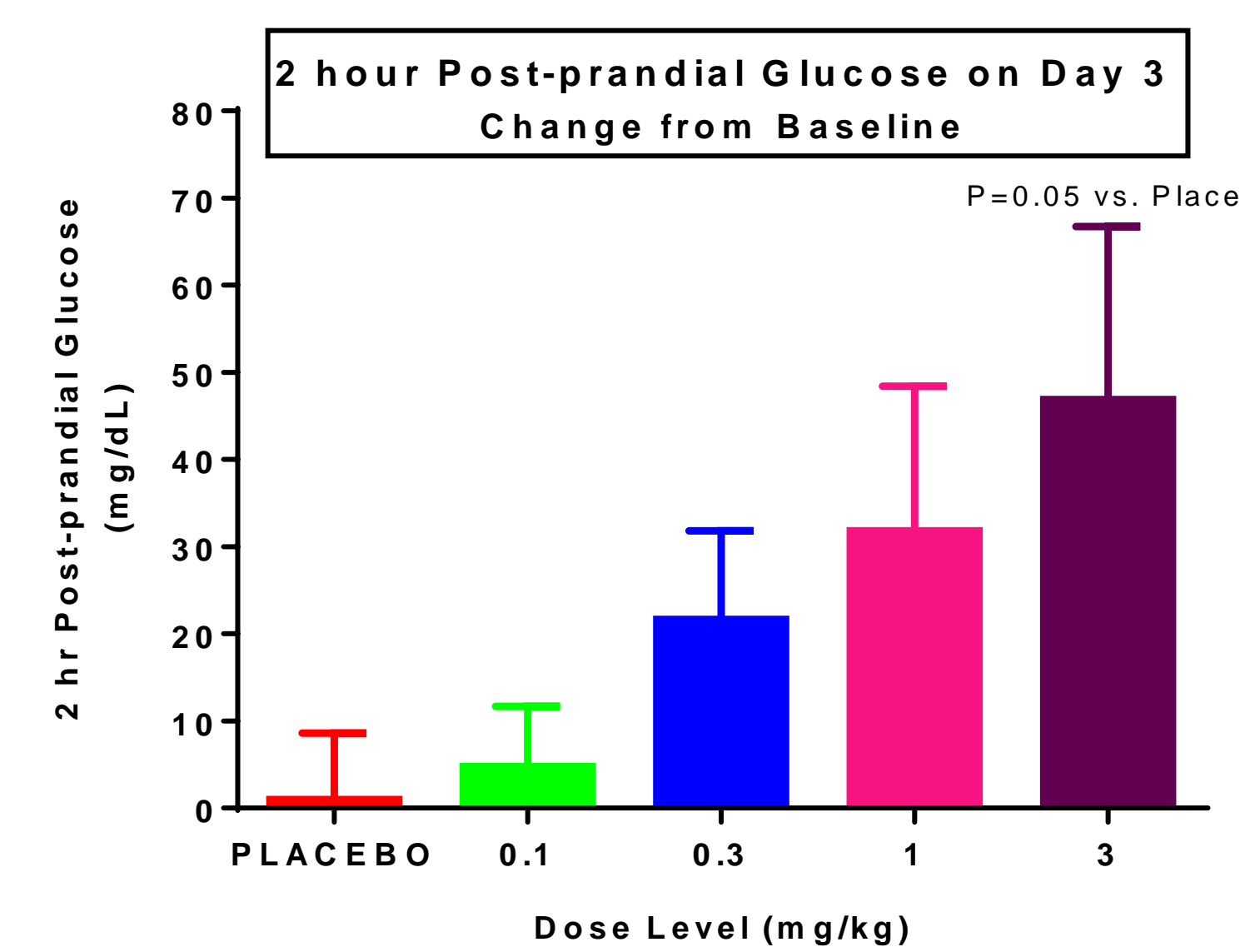
Results - PD

XOMA 358 Treatment 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



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



Results - PD

XOMA 358 Treatment Induced Insulin Resistance

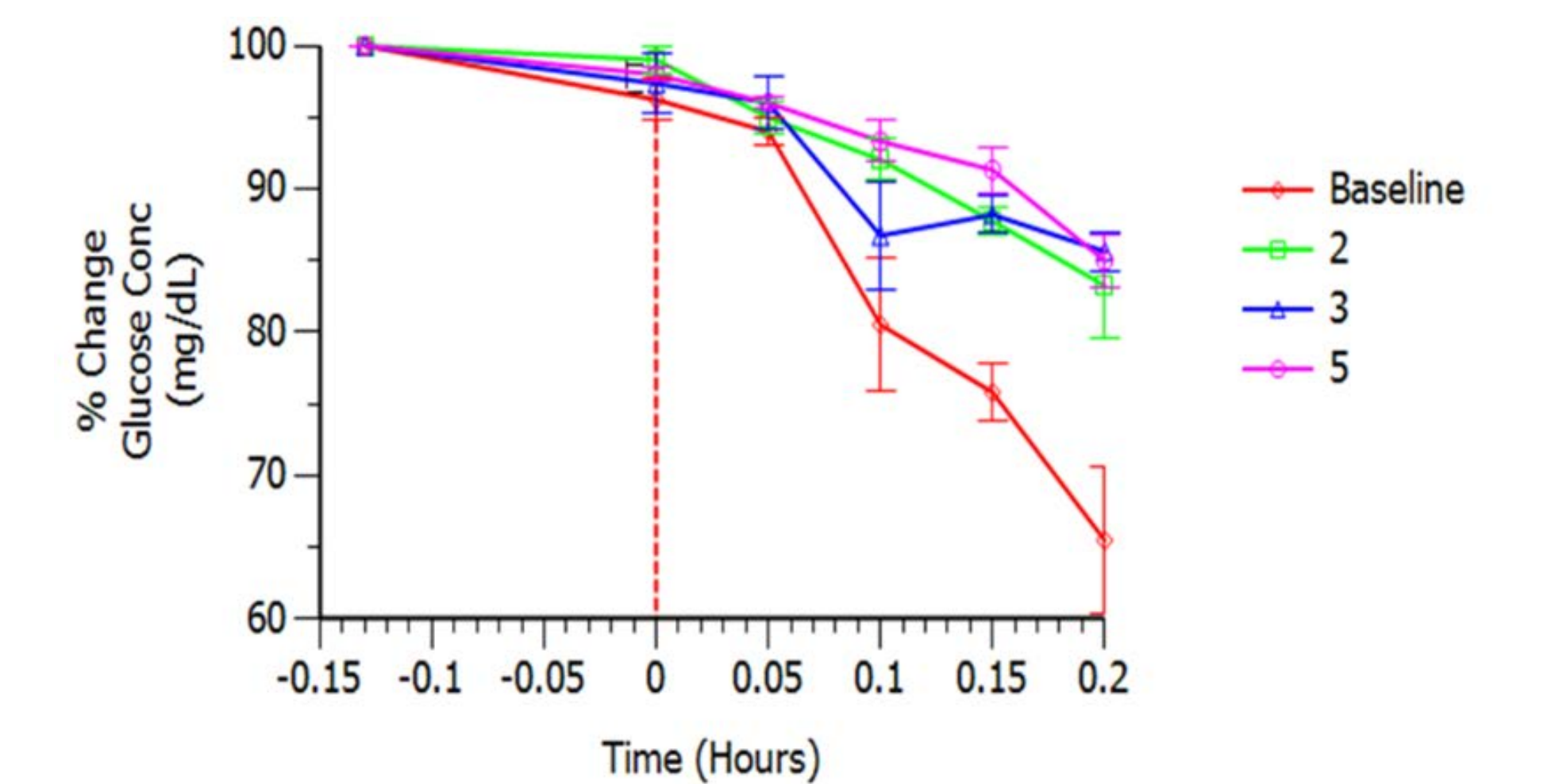
- Indicated by a dose-related increase in magnitude and duration of AM fasting HOMA-IR
- Peak insulin resistance observed at 1 mg/kg and sustained at a severe to moderate level for over a week at 3 mg/kg

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

Summary & Conclusions

Final Cohorts & Key Outcomes:

Group #	Placebo N	XOMA 358 Dose (mg/kg)	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.

References

Bonora E, Moghetti P, Zancanaro C, Cigolini M, Querena M, Cacciatori V, Corgnati A, Muggeo M. Estimates of in vivo insulin action in man: comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. *J Clin Endocrinol Metab.* 1989 68(2):374-378.
Corbin JA, Bhaskar V, Goldfine ID, Issafras H, Bedinger DH, Lau A, et al. Inhibition of insulin receptor function by a human, allosteric monoclonal antibody: a potential new approach for the treatment of hyperinsulinemic hypoglycemia. *mAbs* 2014; 6(1):262-272.