MON 056

Activity of Xoma 358, an Inhibitor of Insulin Action Following Short-Term Administration to Congenital Hyperinsulinism Patients

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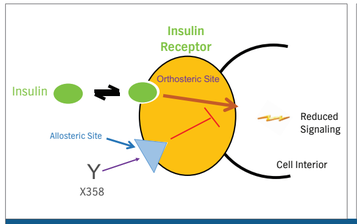
BACKGROUND

XOMA 358: Targets an Allosteric Site on the Insulin Receptor to Decrease Insulin Receptor Signaling



Mechanism of Action

- IgG2 monoclonal antibody that is a Negative Allosteric Modulator (NAM) of the Insulin Receptor (INSR)
- Inhibits INSR auto-phosphorylation and signaling via Akt
- Binds to both forms of INSR (A and B)
- Selective to insulin receptor and does not bind to the homologous IGF-1 receptor

Desired mechanism of action of XOMA 358 is to create insulin resistance in hyperinsulinemic patients

We are Developing X358 for Hyperinsulinemic Hypoglycemic Conditions with Severe Medical Consequences and Serious Unmet Needs

Congenital Hyperinsulinism (CHI)	Post-Bariatric Surgery (PBS)
▪ Mutations regulating insulin secretion in >1:50,000 births ▪ Neonatal and infant severe hypoglycemia due to dysregulated insulin secretion in the pancreas which can result in neurocognitive damage ▪ Approx. half are focal and can be PET-localized and surgically corrected, but only at a few centers in the world. The remainder are diffuse and are pharmacologically treated, but some mutations are not responsive and many patients are not adequately controlled by existing pharmacotherapies ▪ Many children have near-total pancreatectomy to limit the hypoglycemia and then become diabetic ▪ Between-meal and overnight glycemic control are major challenges in this condition	▪ Chronic PBS hypoglycemia is particularly prominent after the most effective Roux-en-Y surgical procedure ▪ 1/3 of ~200,000 bariatric surgeries (U.S.) are RnY and ~10% of those subjects have HH complications[4] ▪ 80-90% are mid-aged females ▪ Post-meal insulin secretions are multi-fold elevated beyond normal and lead to hypoglycemic crashes ~2 hr later ▪ Quality of life is severely impacted ▪ There are no approved or generally-recognized beneficial pharmacotherapies

CHI Disease Burden is Significant in Neonatal and Pediatric Population

Disease Burden

- Major emotional burden on families
- Parents in constant fear of hypoglycemic attacks
  - Constant monitoring of blood glucose
  - Irreversible brain damage and permanent developmental issues may result

Economic Burden

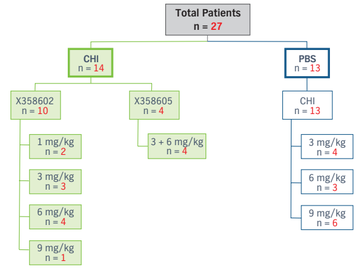
- Medical Treatment: **$150,000 / year**
- Cost of Nursing Care: **$200,000 / year**
- In event of pancreatectomy: **$1,000,000**
  - Type 1 diabetics post-pancreatectomy

Healthcare System Burden

- Patients may require medical treatment for many years
- Significant costs incurred over patient's lifetime
- Long-term care requirements: epilepsy, permanent brain damage
- CHI centers of excellence: 5 in U.S., 8 outside U.S.

Source: Arnoux, Jean-Baptiste. Congenital Hyperinsulinism: Current Trends in Diagnosis and Therapy. Orphanet Journal of Rare Diseases. 10/03/2011. http://www.ojrd.com/content/6/1/63 McLaughlin, Tracey.

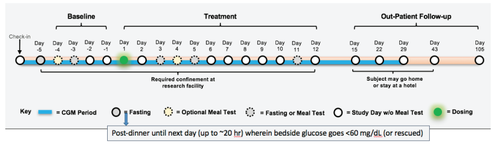
Phase 2 XOMA 358 Data from 27 Hyperinsulinemic Hypoglycemic Patients



Study Objective

- The objective of this study is to evaluate the safety and clinical pharmacology of a single dose of XOMA 358 in subjects with hypoglycemia associated with congenital hyperinsulinism.

Study Design for Single IV XOMA 358 Administration to CHI Patients



- In general, the challenge days were prolonged fasts on Days -5 and -3 and Days 3, 5, 11
- CGM was implemented from Baseline through the Post-dose interval
- Glucose measurements included bedside glucometer, clinical lab. serum glucose, and interstitial glucose by CGM
- A parallel study in Germany allows a first dose at 3 mg/kg followed by a second dose at 6 mg/kg 3-4 days later. Otherwise, safety and activity measurements are similar

CHI Patient Demographics Are Consistent with Disease Population (aged 12 & up)

Subject ID	X358 Dose mg/kg	Age	Gender	BW (kg)	Mutation	Pre-trial Treatment and Drug Washout
1002 (US)	1	24	Female	75	GDH (GLUD1)	Diazoxide
1003 (US)	1	21	Female	68	GLUD1	Diazoxide
1005 (US)	3	24	Male	104	K-ATP	
1008 (US)	3	35	Male	57	GLUD1	
2001 (UK)	3	12	Male	30	K-ATP	Lanreotide
1009 (US)	6	18	Female	87	K-ATP	Diazoxide
1010 (US)	6	30	Female	89	K-ATP	Diazoxide/Octreotide
1011 (US)	6	23	Female	84	K-ATP	Diazoxide
3001 (UK)	6	12	Male	47	Unknown mutation	Octreotide
3002 (UK)	9	32	Male	57	Unknown mutation	Diazoxide
9001 (DE)	3+6	12	Female	61	K-ATP	
9002 (DE)	3+6	36	Male	78.9	GLUD1	Diazoxide
9003 (DE)	3+6	37	Male	69	Glucokinase	Diazoxide
9004 (DE)	3+6	13	Male	44	K-ATP	Diazoxide

Mutations and their Percentiles in CHI — Our patient population consistent with disease population

Mutation	Approximate Global Percentile	XOMA's set
K_{ATP} channel (ABCC8, KCNJ11)	50%	50%
Glutamate HD (GLUD1)	7%	29%
Glucokinase (GK)	3%	7%
UCP, HNFs, other rare known	5%	–
Novel or Not determined	35%	14%

Low Blood Sugar is the Major Problem *and* Unmet Need in these Hyperinsulinemic Disorders

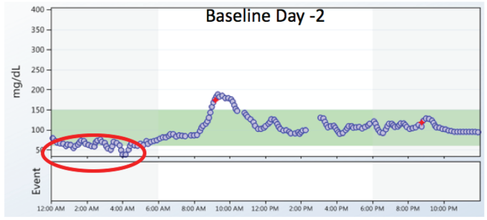
- Hypoglycemia is commonly defined as glucose values <70 mg/dL
- Glucose levels were monitored, often in parallel, by:
  - bedside glucometer
  - serum laboratory
  - Continuous Glucose Monitoring (CGM)

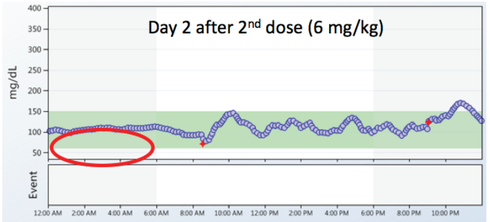
By CGM:

- CGM durations of blood glucose below 70 mg/dL for >2 hr/day is abnormal[1]
- An improvement of ~50% is considered "clinically meaningful"[2]

1. *Accuracy of Continuous Glucose Monitoring Measurements in Normo-Glycemic Individuals. PLOS One October 7, 1-13, 2015. JDRF, Diabetes Care 33:1297, 2010. Brynes AE, Brit JAkintola, A.A. Accuracy of Continuous Glucose Monitoring Measurements Nutr 93:179, 2005*
2. *CHI Key Opinion Leaders and Principal Investigators*

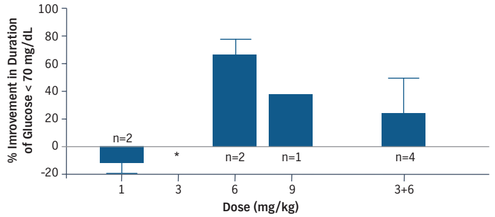
Normalization of Glycemia in a 12-year-old CHI Patient (#9001) Following XOMA 358 Infusion(s) — 24 hr CGM Profiles





358 Reduced Duration of Hypoglycemia by 25% - 70%

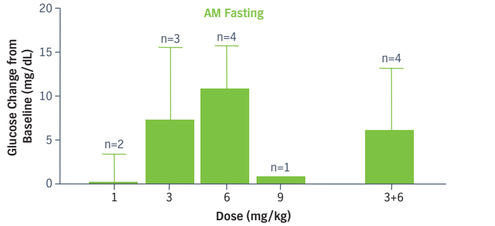
9/14 Patients with baseline durations of 24hr CGM <70 mg/dL for >120 min
Change in Post-358 Days 2,4,6 vs Non-challenge Baseline Days -2 & -1



** Excluded from analysis as they did not meet this CGM criteria*

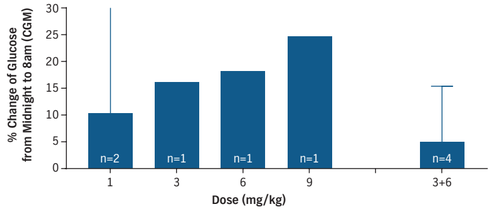
358 Treatment Increased AM Fasting Glucose Levels in CHI Patients

Change Post-358 on Days 2,4,6 vs Baseline Days -2 & -1 (mean bedside glucose, all patients)



In CHI Patients with Low Mean Nightly Glucose Levels, XOMA 358 Treatment Dose-dependently Improves Mean Nighttime Glucose (midnight to 8 am, via CGM)

Change Post-358 on non-challenge Days 2,4,6# vs Baseline Days -2 & -1
*Majority subset of all patients with baseline mean glucose through the night below a normal average**



Sustained drug activity through a potentially risky period
#For 3+6 group it is Days 2&4 post 6 mg/kg vs Baseline
**Normal means through this period are typically > 90 mg/dL (Ref. 1)*

SAFETY SUMMARY

Across both Phase 2 Trials 358 was determined to be generally safe and well-tolerated

In the CHI and PBS studies (N=27)

- All patients completed studies. No deaths. 2 serious adverse events unrelated to study drug. 1 serious adverse event related to study drug but consistent with pre-trial history.
- No clear positive anti-drug antibody titers seen
- No clinically significant changes in laboratory parameters, ECGs, physical examinations or vital signs.

NEXT STEPS

- Open-label multi-dose XOMA 358 Phase 2 study in CHI patients ages 2 & up underway in EU testing XOMA 358 in different doses over 3 months.
- XOMA 358 can be dosed on top of Standard-of-Care or stand alone.
- This study will be informative for upcoming pivotal studies in CHI

SUMMARY AND CONCLUSION OF RESULTS IN CHI PATIENTS

- XOMA 358 single-administration at doses ≥3 mg/kg yields increases in fasting and postprandial glucose levels.
- In patients with daily hypoglycemia, XOMA 358 administration improves glycemic control
- Patients with baseline durations below 70 mg/dL for >120 min are reduced by nearly 50% following XOMA 358 administration
- # episodes <60 mg/dL are reduced in the 3-9 mg/kg subset with at least 2/day
- In patients with nighttime average glucose levels from midnight to 8am below normal, XOMA 358 administration dose-dependently increases glucose levels at 3-9 mg/kg
- The improvement is sustained into the 2nd week post-dose at these dose levels
- Study objectives were met including validation of safety & PK, and initial proof-of-concept
- Consistency and potentially magnitude of effect should be improved with multiple dosing and sustained steady-state drug exposure
- Target serum drug AUC's are achievable with ≥3 mg/kg repeat-dosing regimens