



XOMA 358

P. Rubin

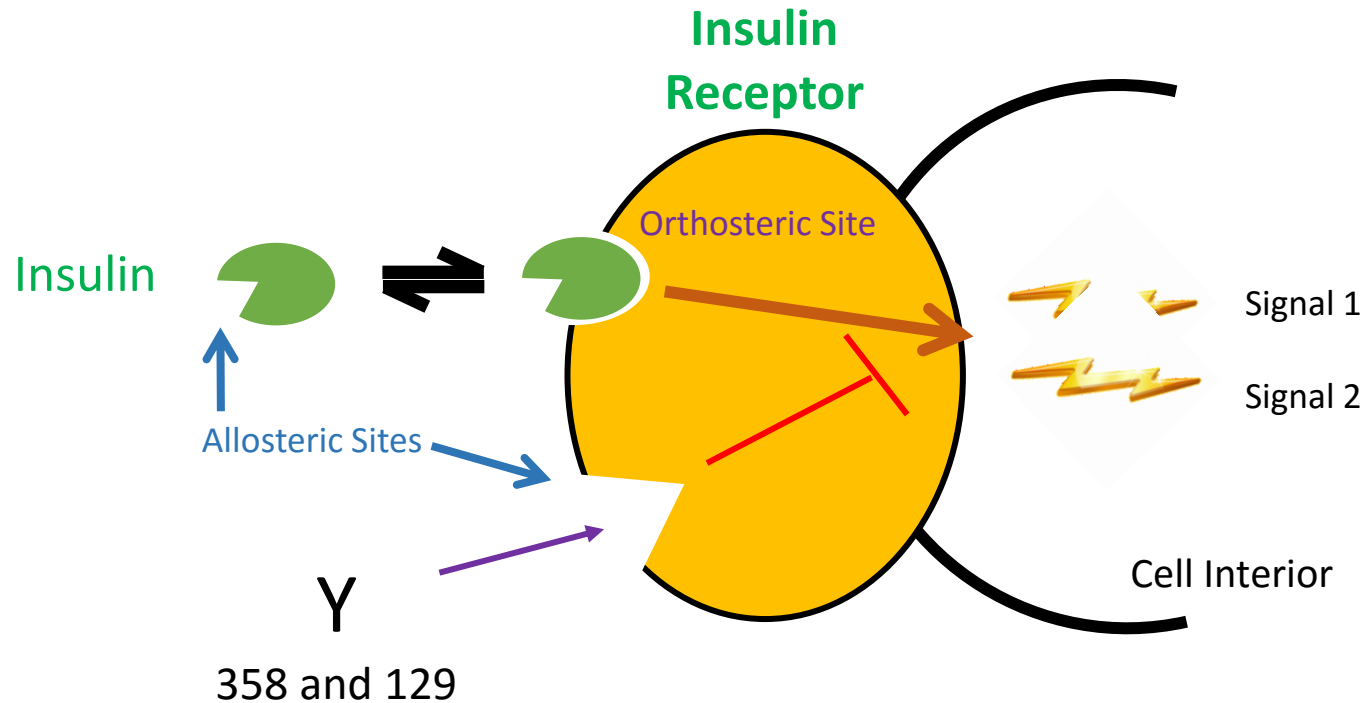
Congenital Hyperinsulinism

- Inappropriately high insulins at times of low blood sugar
 - Can result in significant symptoms and permanent neurological deficit
- Two major therapeutic needs
 - Better tolerated therapies to prevent hypoglycemic episodes
 - Can ultimately delay or prevent need for pancreatectomy
 - Significantly reduce side-effects
 - Easily administered and effective therapies to rapidly reverse hypoglycemia
 - No need for reconstitution
 - No dependence on nutritional state and need for gluconeogenesis
 - Longer duration avoiding need for multiple doses

XOMA 358: Overall Status

- **First-in-class, fully human, monoclonal antibody**
- **Allosterically binds to insulin receptor (INSR) and reduces INSR activity**
 - Shifts insulin response curve up to 100-fold in vitro
- **Effects can be reversed with the addition of insulin**
- **In Phase 2 clinical trials at multiple sites**

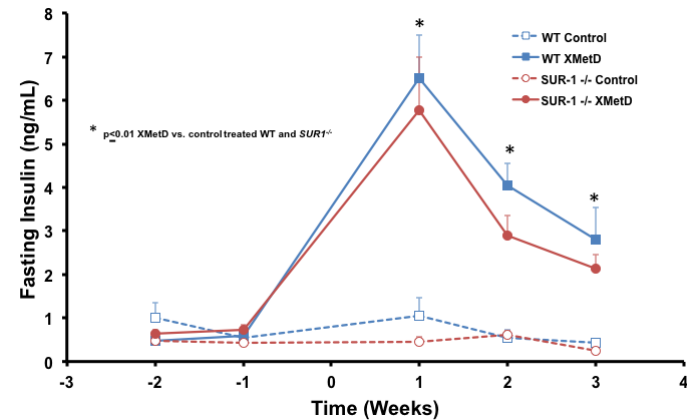
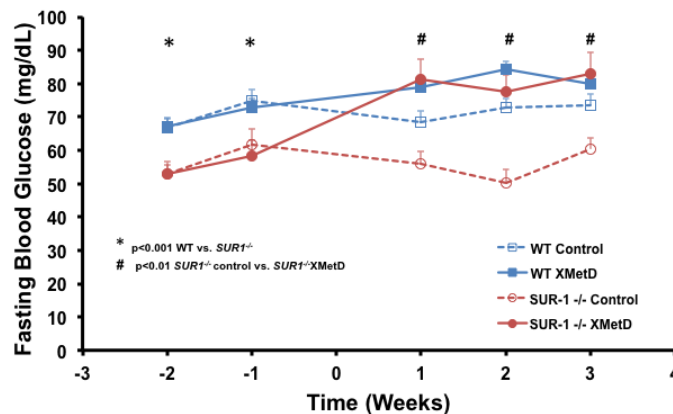
XOMA 358 and XOMA 129 are Negative Allosteric Modulators of Insulin Action



Has the potential to normalize insulin signaling in the presence of high insulin levels

Should infer benefit independently of CHI genotype

XOMA358 Increases Fasting Blood Glucose in *SUR1*^{-/-} mice



In this model of CHI XOMA-358 shows the potential to prevent hypoglycemic

XOMA 358: Phase 1 Human Study Highlights

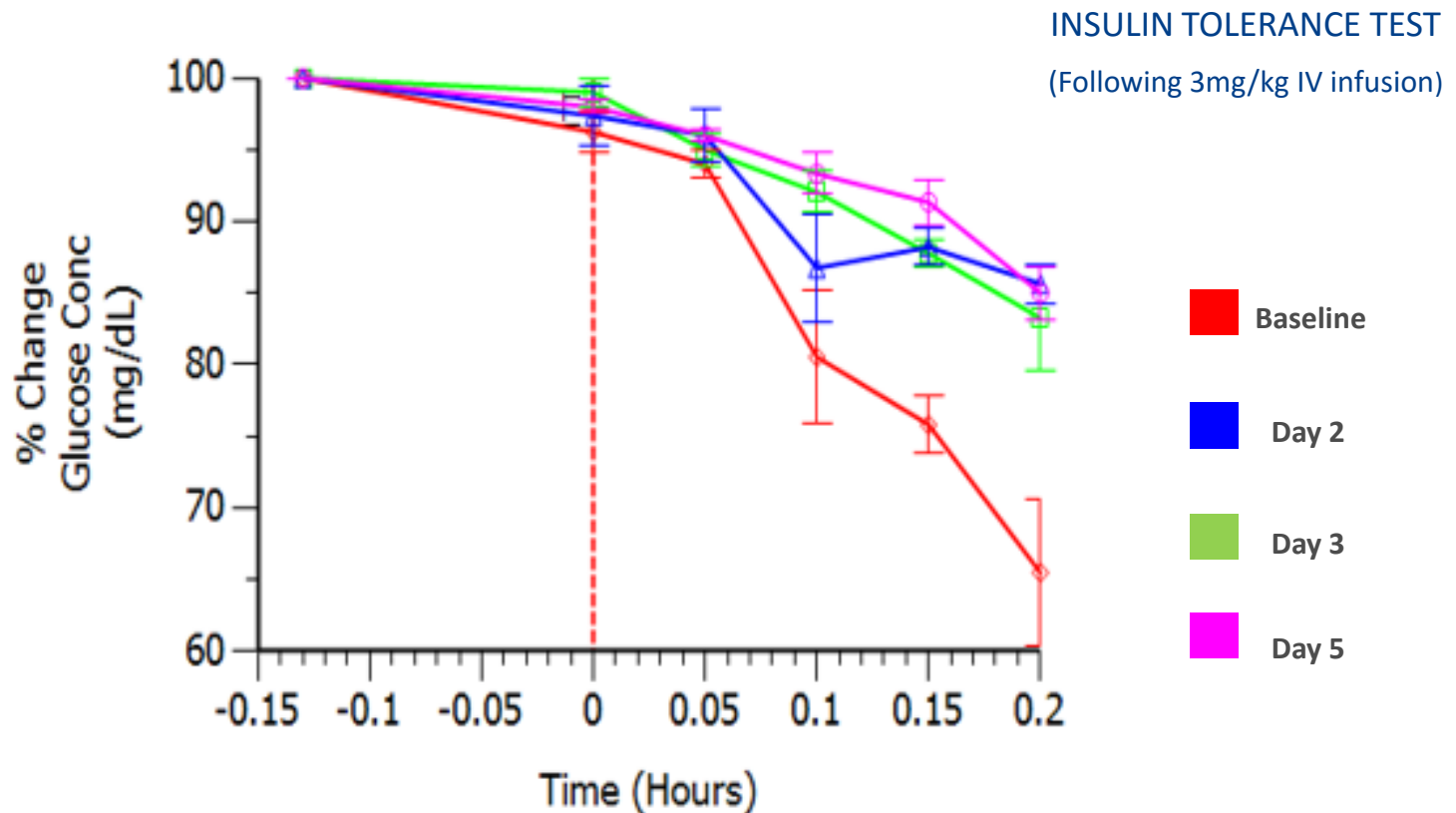
■ Phase 1 Study results presented at ENDO 2015 demonstrated:

- Dose-dependent increase in post-meal glucose
- Dose-dependent decrease in insulin signaling
- Dose-proportional PK profile longer than expected for a surface receptor-targeted mAb
 - Reduced insulin sensitivity from Day 2 through at least Day 5
- Extended duration of therapy while also improving insulin tolerance
 - Duration of therapy (~15-26 day half life) offers differentiation over current treatment options
 - May need to be delivered only once or twice a month
- Dose dependent decrease in insulin clearance resulting in increase insulin levels
 - Same phenomenon seen in animals
 - Effect seems to plateau and drug-effect overcomes in healthy subjects

■ Well-tolerated with no Serious Adverse Events

- No active intervention was needed
- Most events were mild; no patients were removed from study

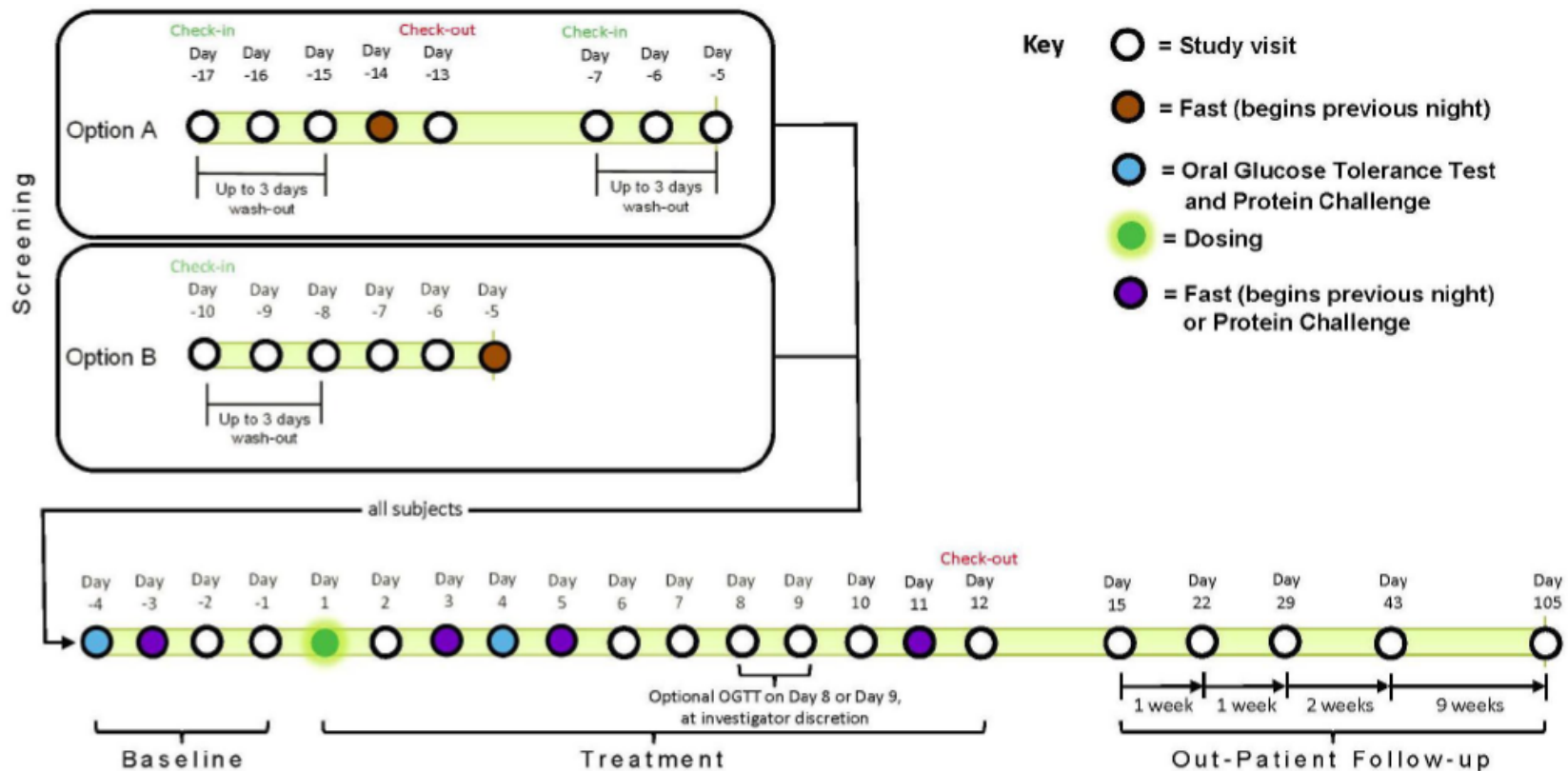
Effect of XOMA358 on insulin-induced hypoglycemia in normal volunteers



No decrease in effect five days after a single dose

Ongoing Phase 2 Study Design In Patients With Congenital Hyperinsulinism

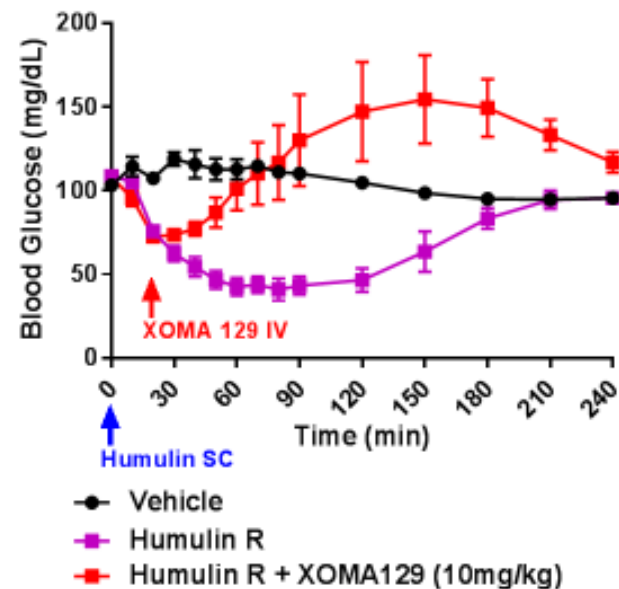
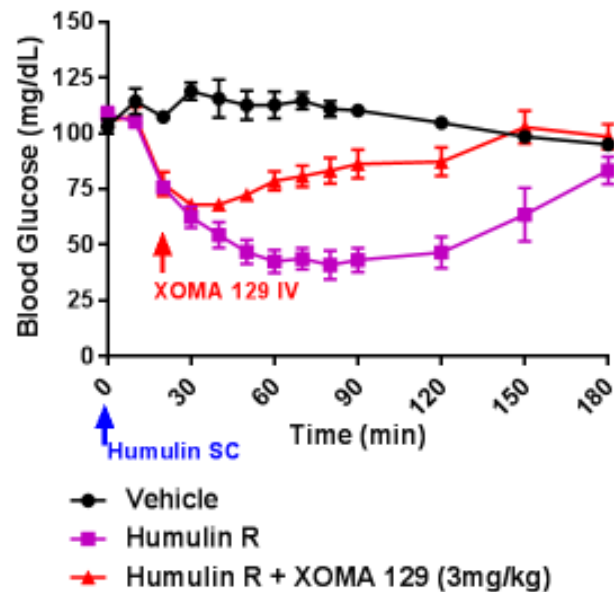
Experimental Paradigm



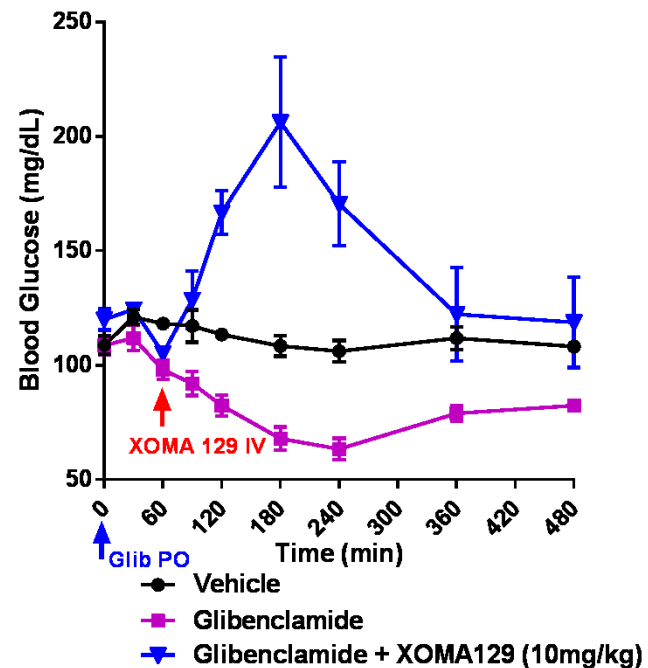
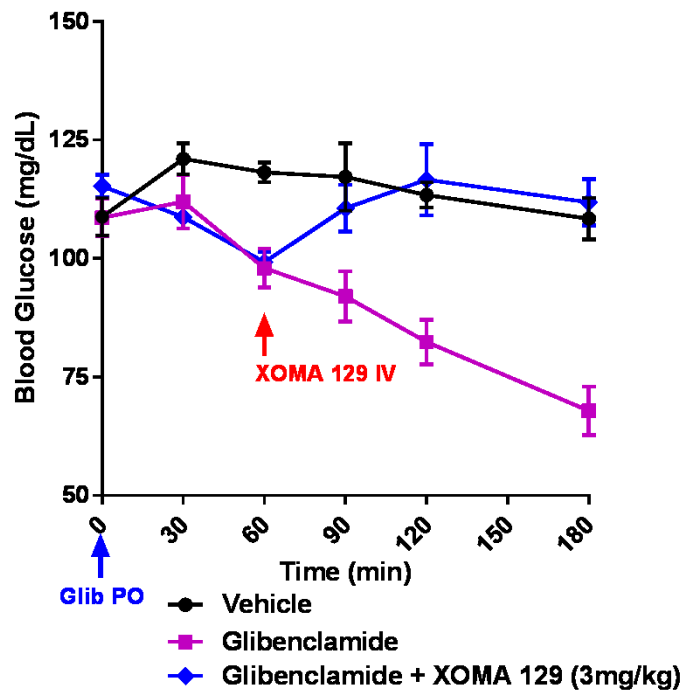
XOMA 358: Phase 2 Study in Congenital Hyperinsulinism (CHI)

- **Study ongoing at**
 - Children's Hospital of Philadelphia (CHOP)
 - Dr. Diva DeLeon
 - Great Ormond Street Hospital in London (GOSH)
 - Dr. Khalid Hussain
- **Similar trial will commence at Otto-von-Guericke Universität, Universitätskinderklinik, Magedburg, Germany**
 - Dr. Klaus Mohnike (June)
- **Study will include from up to 18 CHI patients in 2-3 cohorts**
 - Patients act as their own control
 - Single dose study which may adapt to multi-dose
 - Cohort 1 is complete and Cohort 2 patients will receive a higher dose
- **Once dose is defined we will move to multidose evaluation**

XOMA 129 | Dose-dependently rapidly stabilizes glycemia or reverses hypoglycemia in bolus insulin-treated rats



XOMA 129 | Potent and has a fast onset in reversing sulfonylurea-induced hypoglycemia in rats



XOMA-129 a rapid acting, short duration inhibitor of insulin signaling

- Fab derived from XOMA 358
 - Smaller molecule more potent
 - Rapid penetration and effect
 - Chemically stable in solution
 - Fab confers relatively short duration (3 hours)
 - Dose dependent
 - No need for reconstitution
 - Should be easier to administer
 - Not dependent on liver to make glucose

Conclusions

- **Allosteric inhibition of the insulin receptor with XOMA 358 can prevent hypoglycemia as demonstrated in animal and human studies**
- **Allosteric inhibition with XOMA 129 can reverse existing hypoglycemia induced by insulin or oral hypoglycemic agents**
- **Ongoing trial to evaluate the effect of a single dose of XOMA 358 on glucose metabolism of individuals with congenital hyperinsulinism**
- **XOMA is initiating activity to support human clinical trials in hypoglycemia reversal with XOMA 129**