XOMA Overview
XOMA background

- Established 1981
- Headquarters: Berkeley, CA
- Publicly traded
  - NASDAQ: XOMA
- ~ 170 employees
To be a leading bio-pharmaceutical company by

- **discovering** unique therapeutic antibodies using our world class expertise
- **developing** innovative products which improve patients’ lives
- **commercializing** to specialty markets

Achieving this vision will provide significant returns for our stakeholders and rewarding opportunities for our employees
XOMA’s Business Strategy

1. Advance gevokizumab in collaboration with Servier
   • XOMA retains all rights in U.S. and Japan for all indications except cardiovascular and diabetes with option rights to these
   • Phase 3 NIU program initiated Q2 2012
   • Multiple Phase 2 POC program to identify next Phase 3 program, expected to be developed jointly

2. Commercialize gevokizumab and future products in the U.S. to Specialty markets and for orphan indications to capture greater value

3. Invest in differentiating discovery & development capabilities for pipeline and partnering
## Current Pipeline

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<th>Compound</th>
<th>Indication</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<td>Gevokizumab</td>
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XOMA’s Ab Platform Includes Multiple Technologies that are ADAPTed to Specific Antibody Design Goals

- XOMA mAb discovery program capable of rapid interrogation of receptors and discovery of novel allosteric binder

Integrated Display

adapt™

Technology for identifying modulating mAbs

modulx™

Technologies for optimization of biophysical properties of mAbs

optimx™
XOMA mAb Discovery: XMet Program

- The XMet program uncovered three apparently novel classes of insulin receptor allosteric binders
  - Activators of the INSR (e.g. XMetA)
  - Enhancers of the insulin-receptor complex (e.g. XMetS)
  - Deactivators of the INSR (e.g. XMetD)

- **XMetA and XMetS programs are in research**
  - XOMA intends to seek collaboration partners for global development for XMetA and XMetS

- **Within XMetD class molecules, a lead has been identified for development by XOMA to treat CHI and potentially other hyperinsulinemic hypoglycemic conditions**
XMetD Rationale
XMetD mechanics

- Allosteric antagonist that inhibits insulin dependent activation of the INSR

\[ \text{Insulin} \rightarrow \text{GLUCOSE UPTAKE} \]
XMetD In Vitro Profile
XMetD In Vitro Profile

Antagonism
- Inhibits binding of insulin to the INSR
- Inhibition of INSR auto-phosphorylation
- Inhibition of INSR signaling via Akt

Specificity
- Does not affect IGF-1R mediated Akt signaling
Assay to analyze inhibition of binding of insulin to the INSR

- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of insulin
- Biotinylated insulin binding to INSR measured by FACS

- XMetD appears to inhibits the binding of insulin to the INSR by ~3x
Assay to analyze attenuation of INSR autophosphorylation

- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of insulin
- INSR autophosphorylation was determined by ELISA

- XMetD appears to attenuate autophosphorylation of the INSR in the presence of insulin by ~40x
Assay to analyze attenuation of INSR signaling via Akt

- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of insulin
- Phosphorylation of Akt determined by electrochemiluminescence

Akt signaling via INSR appears to be effectively attenuated in the presence of XMetD by ~100x
Assay to demonstrate lack of antagonism of IGF-1R via Akt

- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of IGF-1
- Phosphorylation of Akt determined by electrochemiluminescence

- XMetD is selective for the INSR and does not appear to affect Akt signaling via the IGF-1R
- Theoretically should permit normal IGF-1 response
XMetD In Vitro Summary

- XMetD antagonism can be measured via insulin binding inhibition, INSR autophosphorylation, and Akt signaling.
- Antagonist activity of XMetD is selective for the INSR.
XMetD Pharmacology
Pharmacology models and studies

- Objective for pharmacology models to use XMetD to restore FBG in hypoglycemic animal models
- XMetD was tested in rodent models of hyperinsulinemia-induced hypoglycemia:
  - Rat model of hyperinsulinemic hypoglycemia
  - Mouse model of hyperinsulinemic hypoglycemia
  - Sur1-/- mouse model (Deleon @ CHoP)

• **Primary PD endpoints for efficacy evaluation**
  • Fasting and fed glucose levels
  • Fasting and fed insulin levels
Single dose, rat hyperinsulinemic model to demonstrate efficacy on FBG

- XMetD has a dose dependent effect on hypoglycemia in a single dose study
- At higher doses, duration extends through Day 28
Single dose, **mouse** hyperinsulinemic model to demonstrate efficacy on FBG

- XMetD restores FBG in mice with elevated insulin levels

![Graph showing fasting blood glucose levels](image)

- Untreated control mice
- Control/cIgG
- Hyperinsulinemic/cIgG
- Hyperinsulinemic/XMetD

*P < 0.05 (compared to untreated control)
**P < 0.05 (compared to hyperinsulinemic/cIgG)
Demonstration of prolonged FBG control with a repeat dosing in a rat hyperinsulinemic model

WinNonLin Simulation of biwk x 7

- Data from Study 1 along with PK and TK data generated from prior studies were used to generate a dosing model for producing a euglycemic state
- Data derived from the model was used to design a multi-dose study
- Repeat study dosing study was done in the rat hyperinsulinemic model
Demonstration of prolonged FBG control with a repeat dosing in a rat hyperinsulinemic model (contd.)

- Preliminary data from Day 24
- Model accurate at predicting pharmacological dose response
Demonstration of efficacy in $K_{ATP}$ CHI with Sur1 -/- mouse model

- $K_{ATP}$ hyperinsulinism is a rare but devastating disease characterized by defects in the islet $K_{ATP}$ channel
  - The Sur1 -/- mouse model simulates one the most severe forms of this disease

- Developed and run by Diva Deleon at CHoP
  - XMetD experiments are run in collaboration with XOMA
Demonstration of efficacy in $K_{\text{ATP}}$ CHI with Sur1 -/- mouse model (contd.)

- The Sur1 -/- model is characterized by lower FBG in relation to WT
- The ratio of circulating insulin to FBG is significantly higher in the Sur1 -/- mouse
Demonstration of efficacy in $K_{ATP}$ CHI with Sur1-/- mouse model (contd.)

Efficacy and duration of 4 doses at 30mgs/Kg over a 28 days study

Fasting Blood Glucose (mg/dL)

Days

Baseline

-11  1  4  8  11  27

TA  TA  TA  TA  TA

**<0.01  ***<0.001

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**<0.05

SUR-1-/- Control

SUR-1-/- XPA.15.247

F<0.001

*<0.05

**<0.01

***<0.001
Pharmacology Summary

- XOMA247 demonstrates the ability to normalize fasting glucose levels in both a hyperinsulinemic hypoglycemia and a CHI model of hypoglycemia in rodent models.
XMetD Clinical Plans
Ph1: Study Design

• **Phase 1**
  • Design
    • Adult patients with CHI
    • Ascending single doses
  • Objectives
    • Safety
    • Pharmacokinetics
    • PK/PD relationship regarding hypoglycemia after a prolonged fast
    • Duration of activity
    • Optimal dose and dosing schedule