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Challenge Your Thinking

CLYM116, a Novel 'Sweeper' Anti-APRIL mAb: Extrapolation of PK and Ig Suppression from NHPs to Healthy Volunteers and Initial Phase 1 Data

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INTRODUCTION

IgAN is the most common primary glomerulonephritis worldwide, and a substantial proportion of patients progress to kidney failure despite recent therapeutic advances.[1]

APRIL is a key driver of IgAN pathogenesis, promoting production of Gd-IgA1 that form immune complexes with anti-glycan antibodies and deposits in the glomeruli, triggering immune complex formation and progressive loss of kidney function.[1]

CLYM116 (also known as MIL116) is an investigational, novel **'sweeper' anti-APRIL mAb** engineered with **pH-dependent antigen binding** to enhance APRIL degradation and antibody recycling, **and with Fc mutations** to extend half-life and reduce effector function.

AIMS

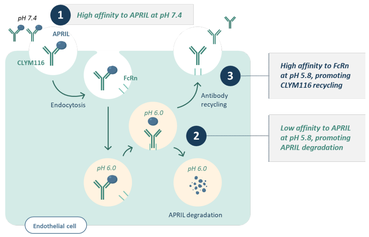
- Develop a translational PK/PD model of CLYM116 from pooled NHP data
- Project human PK and IgA suppression following SC administration to support Phase 1 dose selection
- Explore correlation of published IgA reductions following treatment in NHP vs. HV

METHODS

- Pooled data from 4 SAD and MAD NHP studies (0.5−100 mg/kg SC, 6 mg/kg IV).
- Constructed the following models:
  1. Two-compartment PK model with linear and saturable (TMDD) clearance.
  2. Indirect-response PD models with saturable inhibition of Ig production.
- Used allometric scaling to humans with exponents optimized for Fc-engineered, half-life-extended mAbs; Ig suppressions scaled accounting for species differences in Ig half-life.

CLYM116 'SWEEPER' MOA

Enhanced APRIL Clearance, CLYM116 Recycling



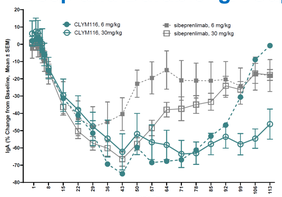
pH-dependent binding to APRIL provides potential for enhanced APRIL elimination through **both**:

1. potent **blocking of APRIL binding to its receptors *and***
2. **promotion of APRIL degradation** in the lysosome

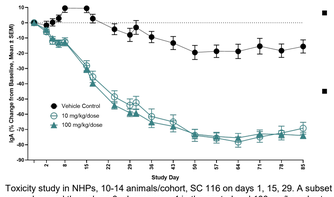
Efficient antibody recycling 3 reduces clearance of CLYM116, resulting in potentially longer half-life

CLYM116 NHP DATA

Deep and Durable IgA Suppression with Long Serum Half-Life[2]



Data from a head-to-head study in NHPs, 4-6 animals/cohort, single SC administration.



Toxicity study in NHPs, 10-14 animals/cohort, SC 116 on days 1, 15, 29. A subset were observed through an 8-wk recovery; 4 in the control and 100 mg/kg cohort were observed through an extended 6-mo recovery, during which the 100 mg/kg cohort showed sustained IgA suppression (>70% from baseline) through Day 183.

- CLYM116 showed a ~2-3x longer serum half-life vs sibeprenlimab*
- CLYM116 deeply suppressed IgA production with a longer duration of effect than sibeprenlimab,* consistent with CLYM116's longer half-life

Sibeprenlimab analog was generated using published sequences (GSRS GHX28QZ7DD); **Note: Confirmed ADA+ animals were excluded from the analyses*

RESULTS: MODELING, PHASE 1 DESIGN, AND INITIAL PHASE 1 SAFETY IN HV

CLYM116-Specific PK/PD Modeling Workflow

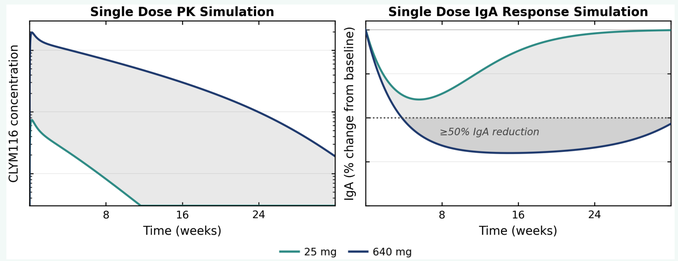
Cyno PK/PD modeling (2-compartment + TMDD; Indirect-response IgA, IgG, IgM)

Allometric extrapolation to human using exponents tuned for half-life-extended mAbs

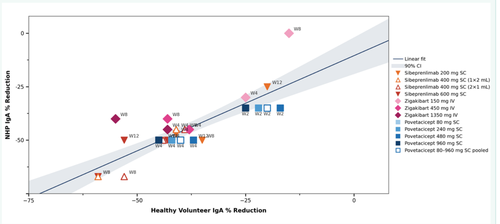
Healthy-volunteer SAD/MAD simulations (PK, IgA, Gd-IgA1, IgG, IgM)

Validation against emerging Phase 1 observations (NCT07248865, NCT07375958)

Translational PK/PD Modeling Predicts Dose-Dependent and Sustained IgA Suppression Across the Phase 1 Dose Range



NHP IgA Reduction Predicts Human Responses Across APRIL-Targeting Agents[3-8]

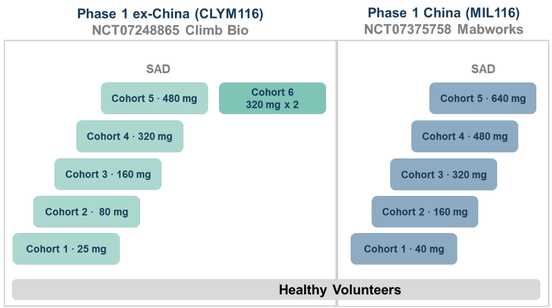


Global Phase 1 Strategy Provides Integrated HV Population PK Foundation

Parallel ex-China + China SAD datasets (N≈80, doses 25-640 mg) will yield a robust population PK foundation with built-in ethnic sensitivity assessment to de-risk next phase dose selection.

Scan QR code for more information on NCT07248865

Scan QR code for more information on NCT07375758



Enrollment into each subsequent dose cohort after Safety Review Committee decision

Results: Phase 1 Safety in Healthy Volunteers

Preliminary safety data from ongoing studies in ex-China and China* evaluating single doses up to 320 mg (n=49):

- No DLTs, SAEs, Grade ≥3 AEs, or AE-related discontinuations
- All AEs mild to moderate (Grade 1-2), transient, and self-resolving
- Injection site reactions observed in 2 participants, both Grade 1, resolved without intervention

**The China study is placebo-controlled and remains blinded. The reported population (n=49) includes participants who received CLYM116 or placebo.*

CONCLUSIONS

- ✓ A translational PK/PD model derived from NHP data projected healthy human exposure and **dose-dependent IgA suppression** for CLYM116, supports the potential for **less-frequent dosing**.
- ✓ Literature analysis shows **strong correlation in IgA reduction between NHP and HV** studies.
- ✓ CLYM116 has been generally **well tolerated in HV to date,** with no unexpected safety findings.
- ✓ These data support **continued clinical development of CLYM116**.

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AE adverse event; **APRIL** A Proliferation-Inducing Ligand; **DLT** dose limiting toxicity; **GSRS** Global Substance Registration System; **HV** healthy volunteers; **Ig** immunoglobulin; **IgAN** IgA nephropathy; **mAb** monoclonal antibody; **MAD** multiple ascending dose; **NHP** non-human primates; **PD** pharmacodynamic, **PK** pharmacokinetic; **SAD** single ascending dose; **SAE** serious adverse event; **TMDD** target-mediated drug disposition