DEVELOPMENT AND CHARACTERIZATION OF CLYM116, A NOVEL FC-ENGINEERED ANTI-APRIL MAB WITH PH-DEPENDENT BINDING FOR IGA NEPHROPATHY

Stefan Beeck,[1] **Guangzhong Lin,**[2] **Jiangmei Li,**[2] **Feng Li,**[2] **Tim Mack,**[1] **Gary Hao**[1]

[1] Climb Bio, Wellesley, MA, USA; [2] Mabworks Biotech, Beijing, China.

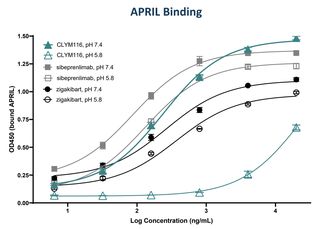
SA-PO0253

Introduction

- A Proliferation-Inducing Ligand (APRIL) plays a key role in the pathogenesis of IgA nephropathy. APRIL inhibition prevents the production of pathogenic IgA, the synthesis of anti-Gd-IgA1 autoantibodies, and the consequent immune complex formation that leads to kidney damage.[1]
- CLYM116 (MIL116) is a novel 'sweeper' anti-APRIL monoclonal antibody (mAb) designed to facilitate recycling of CLYM116 and elimination of APRIL through pH-dependent binding of APRIL. CLYM116 was engineered with Fc-mutations to increase serum half-life and diminish effector function.

CLYM116 demonstrated potent, pH-dependent binding to APRIL, blocked APRIL-BCMA/TACI interactions, and generally avoided HMW complex formation *in vitro*

CLYM116 potently bound APRIL at neutral pH, but not acidic pH, whereas first-generation anti-APRIL mAbs did not demonstrate this profile

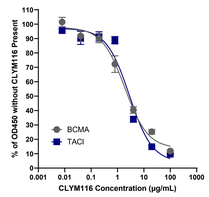


	K_D (M)	
	pH 7.4	pH 5.8
sibeprenlimab	1.71×10^{-10}	3.57×10^{-10}
zigakibart	2.03×10^{-9}	1.93×10^{-9}
CLYM116	2.35×10^{-9}	-

- -> Not calculable due to insufficient binding at concentrations up to 10 µg/mL

Binding affinity of CLYM116 and comparator mAbs to human APRIL was evaluated using surface plasmon resonance (SPR) by measuring the association rate constant ka (1/Ms), dissociation rate constant kd (1/s), and calculation of the affinity constant KD (Kd/Ka, M).

CLYM116 inhibited binding of APRIL to its receptors (BCMA, TACI) *in vitro*

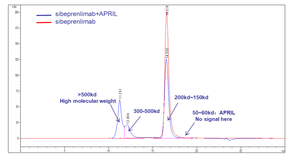


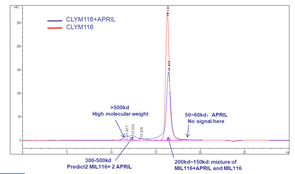
IC_{50} (µg/mL) for Inhibition of APRIL Binding

	TACI	BCMA
CLYM116	2.84	3.93
sibeprenlimab	3.21	0.75
zigakibart	3.08	2.49

Inhibition of APRIL binding to TACI/BCMA was measured by competition ELISA using recombinant human APRIL and the soluble extracellular domain of human APRIL receptors TACI or BCMA.

CLYM116 forms fewer high molecular weight (HMW) complexes vs sibeprenlimab, reflective of binding to distinct epitopes on APRIL





	HMW >500 kDa	300-500 kDa	150-200 kDa	50-60 kDa
APRIL	-	1%	-	98%
APRIL + CLYM116	3.2%	10%	82%	-
APRIL + sibeprenlimab	27%	13%	56%	-
APRIL + zigakibart	8%	12%	77%	-

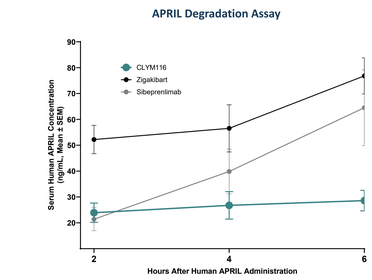
Anticipated MW of a 1:1 stoichiometry of mAb bound to trimeric APRIL is ~200 kDa (~150kDa + ~50kDa)

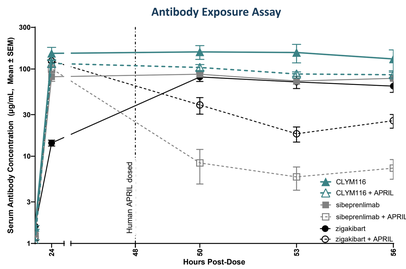
HMW complexes have been associated with potentially higher risk of immunogenicity[2]

Human APRIL and the antibodies were incubated at room temperature for 1 hour at ~1:3 molar ratio, and changes in aggregation were analyzed by SEC-HPLC.

CLYM116 showed enhanced APRIL elimination and antibody recycling in mouse models

In vivo APRIL degradation assay (top) and antibody exposure assay (bottom) support potential for enhanced APRIL elimination and antibody recycling through sweeper mechanism of action





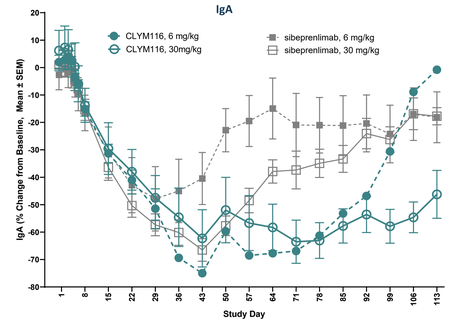
APRIL degradation assay (top): Wild type C57BL/6 mice were administered 10 mg/kg antibody subcutaneously (SC) at time 0 and 15 mg/kg human APRIL SC at 36 hours. Antibody exposure assay (bottom): Humanized FcRn transgenic mice were administered 10 mg/kg antibody SC at time 0 and human 15 mg/kg APRIL SC at 48 hours.

CLYM116 demonstrated a ~2-3 fold longer half-life vs. sibeprenlimab and deep and durable suppression of APRIL and IgA after a single, subcutaneous administration to nonhuman primates (NHPs)

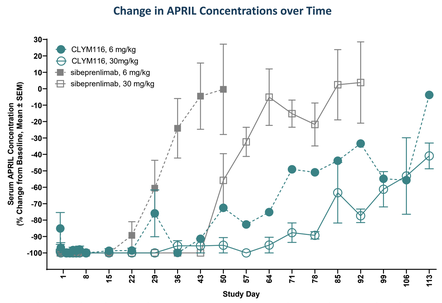
CLYM116 showed high bioavailability (~85%) and a ~2-3x longer half-life vs. sibeprenlimab across doses

	CLYM116		sibeprenlimab	
	6 mg/kg	30 mg/kg	6 mg/kg	30 mg/kg
T_{max} (h)	48	36	24	24
C_{max} (µg/mL)	95.8	558	68.4	383
AUC_{INF} (µg*h/mL)	44,400	321,000	18,200	126,000
$t_{½}$ (days)	19.5	24.2	7.5	8.4

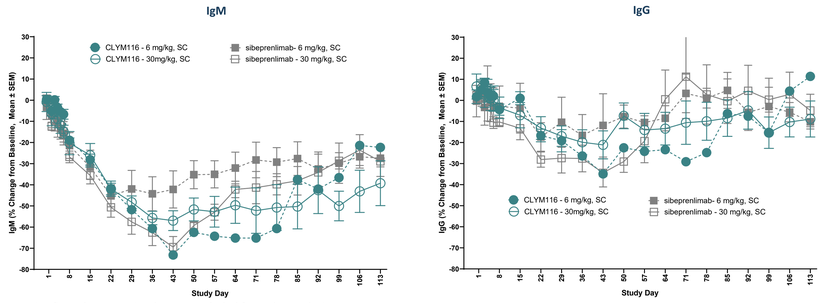
CLYM116 deeply suppressed IgA production with a longer duration of effect than sibeprenlimab, consistent with CLYM116's longer half-life



CLYM116 demonstrated robust and durable free APRIL suppression



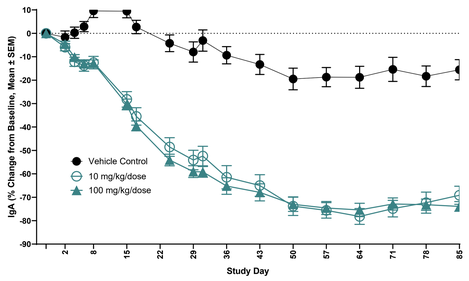
CLYM116 showed suppression of IgM and modest suppression of IgG



Data from a head-to-head study in nonhuman primates, 4-6 animals per cohort, single subcutaneous administration. Confirmed ADA+ animals were excluded from the analysis.

Similar magnitude of IgA suppression and favorable tolerability in NHP toxicology study

CLYM116 showed deep and durable IgA suppression through the recovery period



- CLYM116 100 mg/kg cohort observed through the extended recovery period demonstrated sustained IgA suppression (>70% from baseline) through Day 183

Favorable tolerability observed in multiple NHP studies

- No local tolerance issues identified on histopathology
- No CLYM116-related toxicity findings

Toxicity study in nonhuman primates, 10-14 animals per cohort, subcutaneous dosing on days 1, 15, 29. A subset of animals were observed through an 8-week recovery period; 4 animals in the control and 100 mg/kg cohort were observed through an extended 6-month recovery period. Confirmed ADA+ animals were excluded from the analysis.

CONCLUSIONS

- CLYM116 showed enhanced APRIL elimination and efficient antibody recycling in mouse models compared to first-generation anti-APRIL mAbs, consistent with its sweeper mechanism
- CLYM116 demonstrated a differentiated pharmacokinetic and pharmacodynamic profile compared to a first-generation anti-APRIL mAb, with extended half-life and deep, durable IgA reductions, without drug-related toxicity findings, in NHPs
- CLYM116, with its unique anti-APRIL sweeper mechanism, has the potential to demonstrate a differentiated, disease-modifying activity profile in IgAN

CLIMBBIO

REFERENCES

1. Mathur M et al., Journal of Clinical Medicine 2023. 2. Ratanji KD et al, J Immunotoxicol 2014. Zigakibart and sibeprenlimab analogs were generated by Mabworks using published sequences (https://drugs.ncats.io/substance/WM18Z62RTI, https://drugs.ncats.io/substance/GHX28QZ7DD)

ACKNOWLEDGEMENTS

This work was sponsored by Climb Bio, Inc. and Beijing Mabworks Biotech Co., Ltd. Additional data interpretation and analysis provided by Edgar Charles, MD, Perrin Wilson, PhD, and Paul Tarantino, PhD of Climb Bio. Medical writing and editing assistance were provided by Kate Lewis, MA. funded by Climb Bio.

CONTACT

info@climbbio.com
www.climbbio.com

Mabworks