Safety, pharmacokinetics and pharmacodynamics of VIS649, a humanized monoclonal antibody targeting APRIL, for the treatment of IgAN in a GLP toxicology study in cynomolgus monkeys

Susan E. Sloan*, Ph.D., James R. Myette, Ph.D., Zachary Shriver, Ph.D., David Oldach, M.D., and Brian J.G. Pereira, M.D.

Visterra Inc. (an Otsuka company)
275 2nd Avenue Waltham MA USA
*Presenting author
ssloan@visterrainc.com

ABSTRACT 0090

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Objective: IgA Nephropathy (IgAN) is the most common cause of glomerulonephritis. VIS649 is a humanized IgG2 monoclonal antibody targeting the cytokine A PRoliferation Inducing Ligand (APRIL) that has been implicated in the pathophysiology of IgAN. The preclinical effects of APRIL inhibition by VIS649 were evaluated in cynomolgus monkeys to better understand its safety and pharmacology.

Methods: VIS649 was administered by intravenous (IV) injection to cynomolgus monkeys at 25, 50, or 100 mg/kg on Days 1, 8, 15, and 22. Animals in the main and recovery studies were euthanized on Days 29 and at 20 weeks after the last administration, respectively.

Results and Discussion: There were no VIS649-related changes in body weight, food consumption, and additional clinical measurements. Systemic exposure to VIS649 increased with increasing levels of drug. VIS649 treated monkeys mounted humoral responses to KLH with kinetics comparable to vehicle group. All 3 dose levels demonstrated pharmacologic effect in reduction in mean serum IgA by 70-80%, IgG by 40-50%, and minimal reduction in IgM *vs.* vehicle. The VIS649 mediated reduction in IgA and IgG production was reversible. Serum levels of VIS649 and IgA during the recovery phase were used to refine a population PK/PD model. Model simulation results predict a favorable PK/PD relationship in humans.

Conclusions: Targeting APRIL with VIS649 achieved maximal serum IgA reductions in monkeys. Pharmacodynamic modeling and simulation indicate potential utility for its therapeutic use in humans.

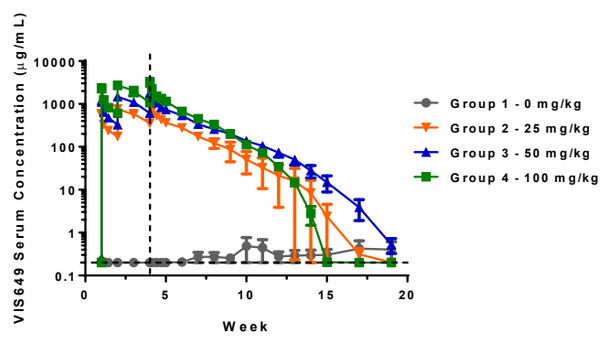
STUDY DESIGN

Group	Drug	Dose (mg/kg/wk)	Main Group (4 weeks)		Recovery Group (20 weeks)	
			Male (n)	Female (n)	Male	Female
1	Vehicle	0	3	3	2	2
2	VIS649	25	3	3	2	2
3	VIS649	50	3	3	2	2
4	VIS649	100	3	3	2	2

VIS649 IS WELL-TOLERATED

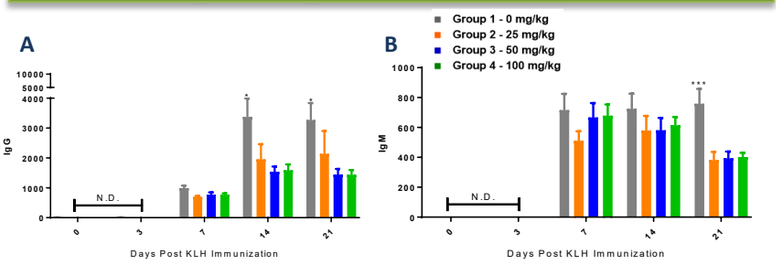
- No VIS649-related changes in mean body weight, food consumption, and additional clinical evaluations
- No VIS649-related change in tissue histopathology
- No VIS649-related changes in periphery lymphocyte subsets or monocytes by flow cytometry

PHARMACOKINETICS OF VIS649



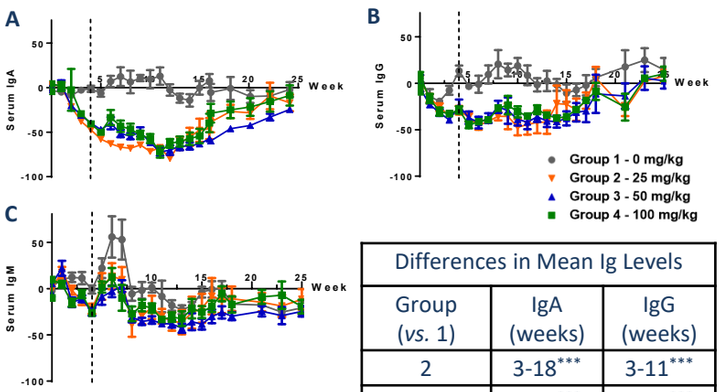
Monkeys (n=10/group) were administered VIS649 once weekly for 4 weeks by IV slow bolus injection. Discontinuation of dosing after 4 weeks is represented by the vertical hashed line followed by a 20-week recovery period (n=4/recovery group). VIS649 serum concentrations were measured and expressed as mean ± SEM.

KLH-SPECIFIC IgG AND IgM TITERS AFTER VIS649 TREATMENT



Monkeys (n=10/group) were IV administered vehicle or VIS649 on Days 1, 8, 15 and 22. All groups were immunized with 10 mg of KLH on Day 7. **A.** KLH-specific IgG titers (means + SEM, $^{*}p < 0.05$ *vs* Groups 3+4). **B.** KLH-specific IgM titers (means + SEM, $^{***}p < 0.001$ *vs* Groups 2, 3, 4). N.D. = Not Detected

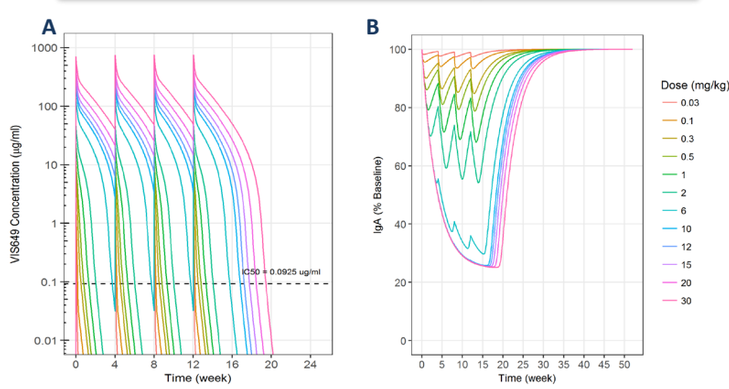
PHARMACODYNAMIC EFECT OF VIS649 ON SERUM Ig



Differences in Mean Ig Levels		
Group (*vs.* 1)	IgA (weeks)	IgG (weeks)
2	3-18***	3-11***
3	3-24***	3-11***
4	3-16***	3-11***

Circulating IgA (**A**), IgG (**B**), and IgM (**C**) levels were measured following VIS649 treatment in monkeys (n=10/main+recovery; n=4/recovery group). Data were expressed as the mean % Ig change from baseline ± SEM. Significant changes in VIS649-treated *vs.* vehicle were detected in multiple time points in IgA and IgG groups, using Holm-Sidak method and unpaired *t*-test ($^{***}p<0.001$).

VIS649 HUMAN SERUM PK and IgA SIMULATIONS



Simulated population predicted PK and % baseline IgA following 4 weekly IV VIS649 doses in humans. (A) Model-based simulations of VIS649 human serum concentrations. (B) Model-based simulations of IgA % change from baseline following weekly doses of VIS649 in humans.

SUMMARY

- VIS649 was safe and well-tolerated in cynomolgus monkeys
- Targeting APRIL with VIS649 led to significant reduction in serum IgA levels which was reversible following VIS649 dosing cessation
- VIS649 is a potential therapeutic monoclonal antibody candidate for the treatment of IgAN in humans