VIS649 Reduces Serum IgA Levels in NHPs Dose-Dependently: PK/PD Exposure-Response Modeling for Translation to Treatment of IgA Nephropathy

SE Sloan PhD[1], F Engler PhD[2], KJ Szretter PhD[1], JR Myette PhD[1], K Narayan PhD[1], BL Sundaresh[1], BJG Pereira MD[1]

[1]Visterra, Inc.
275 2nd Avenue Waltham MA 02451
[2]Certara Inc. 6 Campus Drive Parsippany NJ 07054
Email: ssloan@visterrainc.com
Phone: (617) 401-2011

ABSTRACT

Background. VIS649 is a humanized IgG2 monoclonal antibody that targets A PRoliferation-Inducing Ligand (APRIL), a cytokine that is implicated in IgA nephropathy (IgAN) pathogenesis. Targeting APRIL activity to reduce levels of aberrantly glycosylated circulating IgA1 may alter IgAN disease progression.

Methods. Cynomolgus monkeys (n=4/group) were IV administered either vehicle or VIS649 (0.5, 2.5 and 10 mg/kg) once weekly for 4 weeks, and followed by 8 weeks without treatment. Study endpoints included serum VIS649 and immunoglobulin (Ig) levels. Temporal changes in IgA concentration after VIS649 administration were described with a population pharmacokinetic/pharmacodynamic (popPK/PD) model, using an indirect response model to describe the dynamic relationship between VIS649 serum concentration (PK) and circulating IgA concentration (PD).

Results. At the 0.5 and 2.5 mg/kg dose levels, there was a ~50% reduction in serum IgA levels. VIS649 administration at 10 mg/kg levels resulted in a ~70% serum IgA reduction. The effect of VIS649 on reducing IgA levels was reversible after discontinuation of VIS649 treatment. There was a lesser effect on serum IgG while IgM level was not affected. In a parallel study, a reduction in IgA+ mononuclear cells in GALT and tonsil tissues was observed, consistent with the effect of APRIL on Ig class switching and plasma cell survival in the mucosal compartment. These data were used to develop a popPK/PD linear model. Model simulation of single dose VIS649 in humans, in the range of 1-3 mg/kg, predicts a maximal (~70%) reduction in IgA levels followed by a dose-dependent return to baseline. Model simulation of repeated monthly doses suggest dose levels in the 0.3 to 3 mg/kg range will maintain a reduction in IgA levels below 50% of baseline.

Conclusions. VIS649 treatment reduces serum IgA levels in NHPs in a dose proportional manner. These data point to a clear potential therapeutic use of VIS649 in humans with IgAN.

CYNOMOLOGUS MONKEY *IN VIVO* DOSE RANGE STUDY

4 Weekly IV Doses → **8 Week Recovery**

- Monkeys were administered 0.5, 2.5, and 10 mg/kg of VIS649; or saline control (n = 4 males per group) once weekly.
- There were no VIS649-related clinical signs or changes to body weights, food consumption, or clinical pathology parameters at any dose level.

PHARMACODYNAMIC EFFECTS OF VIS649 ON SERUM IG

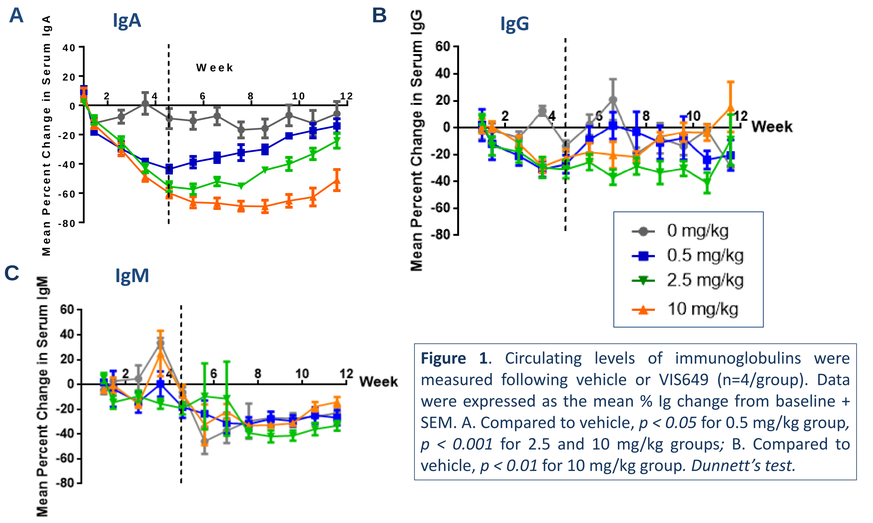

Figure 1. Circulating levels of immunoglobulins were measured following vehicle or VIS649 (n=4/group). Data were expressed as the mean % Ig change from baseline + SEM. A. Compared to vehicle, $p < 0.05$ for 0.5 mg/kg group, $p < 0.001$ for 2.5 and 10 mg/kg groups; B. Compared to vehicle, $p < 0.01$ for 10 mg/kg group. *Dunnett's test.*

- At the 0.5 and 2.5 mg/kg dose levels, there was a ~50% reduction in serum IgA levels *vs.* vehicle group. At 10 mg/kg, VIS649 treatment caused a ~70% serum IgA reduction *vs.* vehicle
- There was a lesser effect of VIS649 on serum IgG level, and no significant reduction in serum IgM *vs.* vehicle
- VIS649-mediated effects were dose proportional and reversible

REDUCED IgA+ CELLS BY IMMUNOHISTOCHEMISTRY

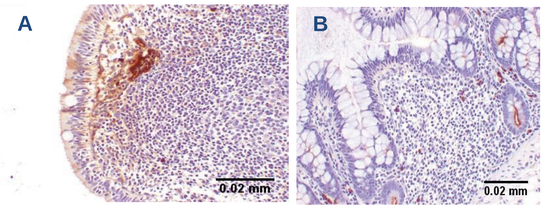

Figure 2. Histological studies of IgA+ cells in the gut-associated lymphoid tissue *GALT* (A+B) revealed reduced IgA+ mononuclear cells (shown in *brown*) in 25mg/kg VIS649-treated (B) *vs.* vehicle (A) groups, respectively. Representative images are shown (20X).

- A reduction in IgA+ mononuclear cells in GALT and tonsil (latter data now shown) was observed, consistent with APRILs effect on Ig class switching and plasma cell survival in the mucosal compartment.

VIS649 HUMAN SERUM PK and IgA SIMULATIONS

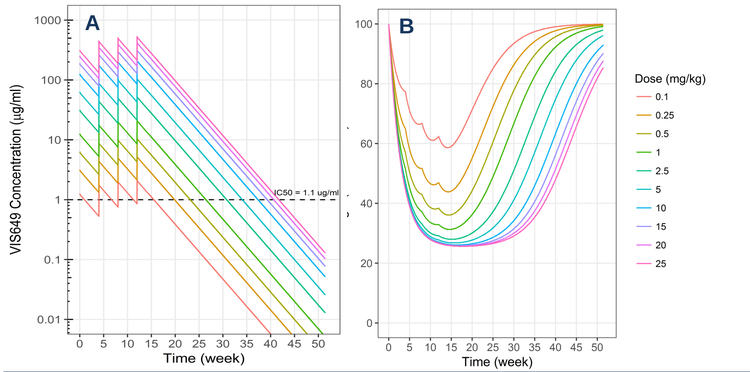

Figure 3. Simulated population predicted PK and % baseline IgA in humans. (A) Model-based simulations of VIS649 human serum concentrations. (B) Model-based simulations of IgA % change from baseline following monthly doses of VIS649 in humans. The linear model was scaled to predict human VIS410 PK and resulting impact on % baseline IgA by the following assumptions: allometric exponent on CL assumed to be 0.85[1] all other PK parameters assumed to scale linearly with weight, IgA turnover and VIS649-APRIL binding assumed to be equivalent between species. *1. Deng, Rong, et al. "Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned?." MAbs. Vol. 3. No. 1. Taylor & Francis, 2011.*

- Population PK/PD modeling predicted an estimated maximal ~75% reduction in serum IgA, consistent with observed maximal inhibition
- Simulation results predict a favorable PK/PD relationship in humans

SUMMARY

- Targeting APRIL with VIS649 led to significant dose-proportional reductions in serum IgA level which were reversible following VIS649 dosing cessation
- Reductions in serum Ig levels were associated with reduced IgA+ mononuclear cells in in the mucosal compartment
- Population PK/PD modeling simulation results predict a favorable PK/PD relationship in humans
- VIS649 is a potential therapeutic monoclonal antibody candidate for the treatment of IgAN in humans

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