Therapeutic Efficacy of a TLR7 Agonist for HBV Chronic Infection in Chimpanzees

Robert Lanford[1], Bernadette Guerra[1], Deborah Chavez[1], Vida L. Hodara[1], Xubin Zheng[2], Grushenka Wolfgang[3], Daniel B. Tumas[3]

Department of Virology and Immunology[1], Southwest Foundation for Biomedical Research and Southwest National Primate Research Center, San Antonio, TX 78227

Departments of Drug Metabolism[2] and Drug Safety Evaluation[3], Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404, USA

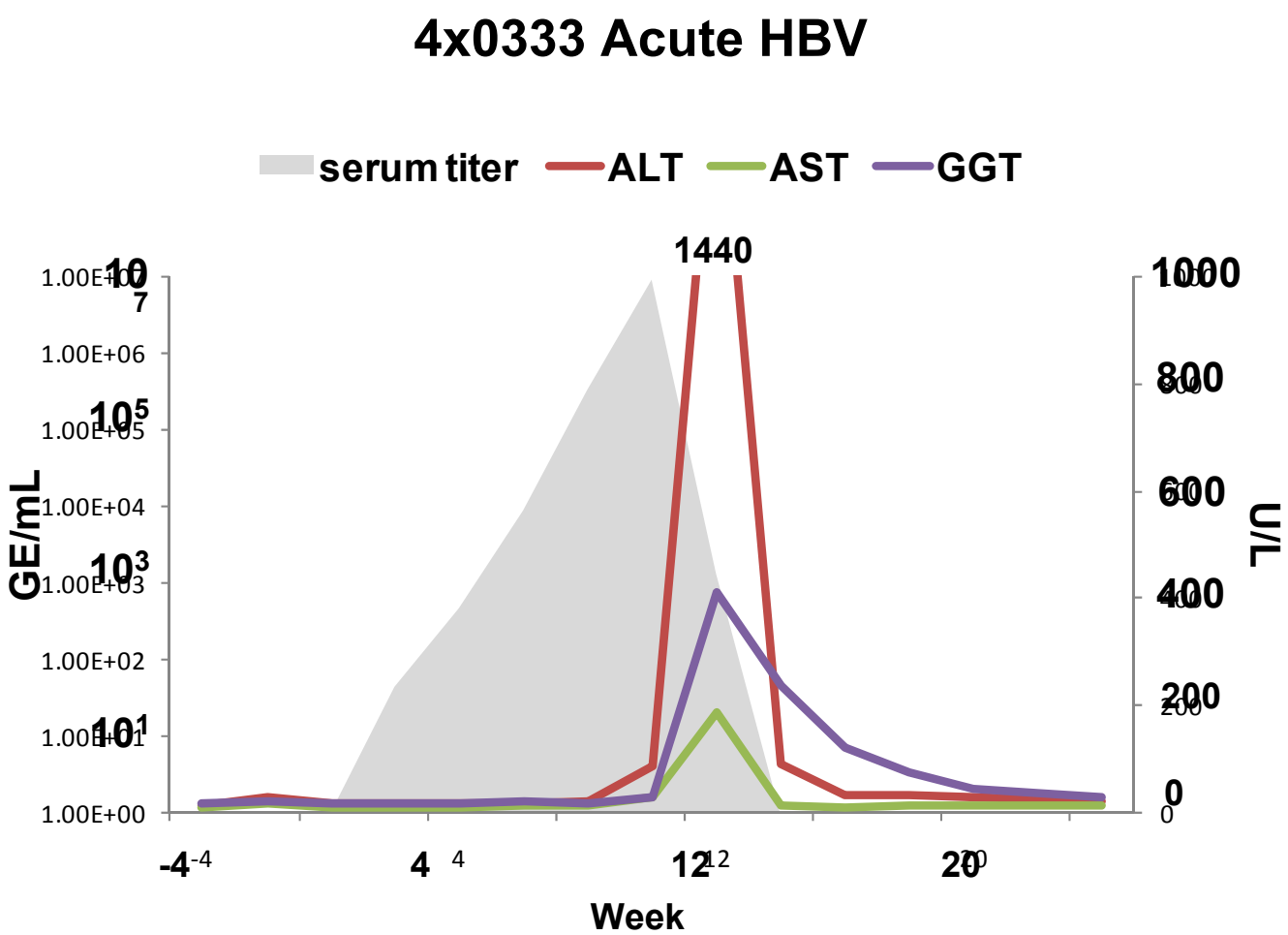
Gilead sponsored research program at SFBR. No other disclosure.

46th Annual Meeting of the European Association for the Study of the Liver
March 30-April 3, 2011 Berlin, Germany Oral Presentation #1771

Background

- TLR7 predominantly present in plasmacytoid dendritic cells.
- Stimulation induces IFN-α, immune stimulatory and select pro-inflammatory cytokines, and regulation of innate and adaptive immunity.
- GS-9620 is a orally available TLR7 agonist selective for induction of IFN-α and stimulatory cytokines.
- Induction of the innate immune response by GS-9620 has been characterized in monkeys, chimpanzees and humans.
- Approx. 6-fold less potent in chimpanzees in comparison to man.
- HBV infected chimpanzees were selected as the animal model for antiviral efficacy.

Acute Resolving HBV Infection in the Chimpanzee



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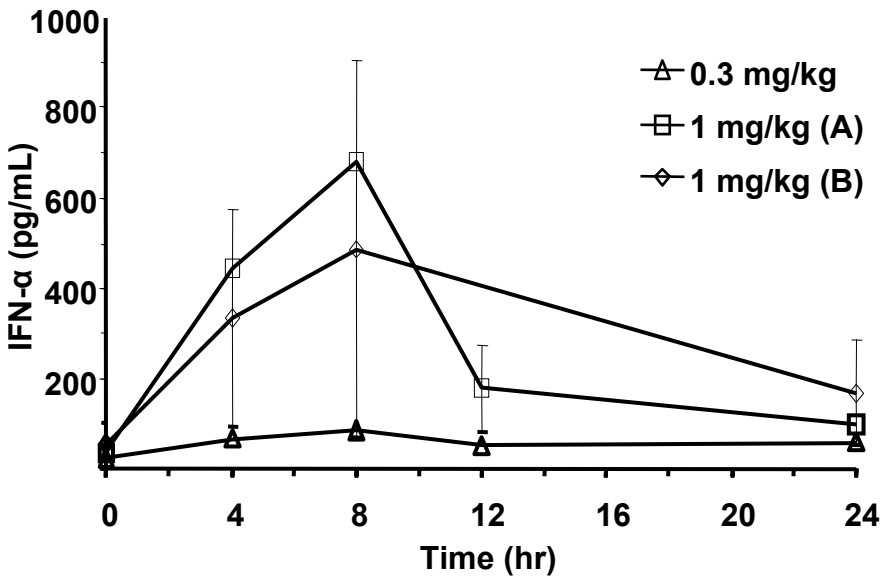
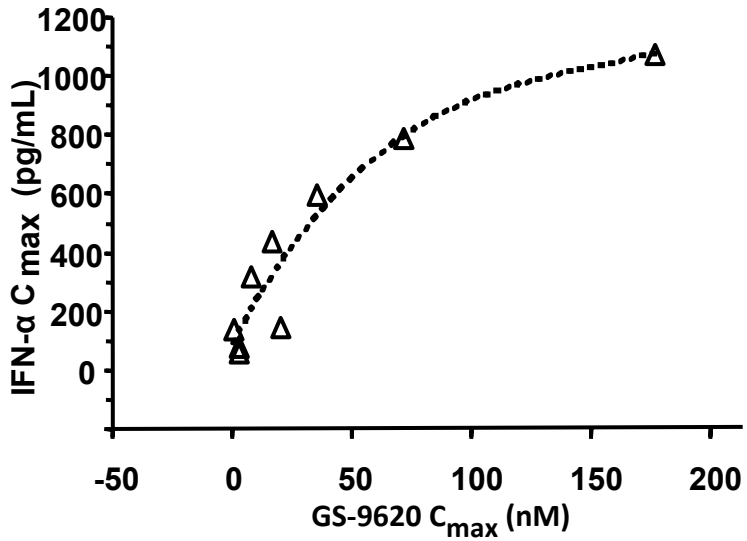
GS-9620 PK-PD Parameters in Uninfected Chimpanzees

To determine an appropriate starting dose for efficacy studies in infected animals, a single oral dose evaluation of PK, PD and tolerability was performed in uninfected chimpanzees.

IFN-α Induction @ 0.3 and 1 mg/kg



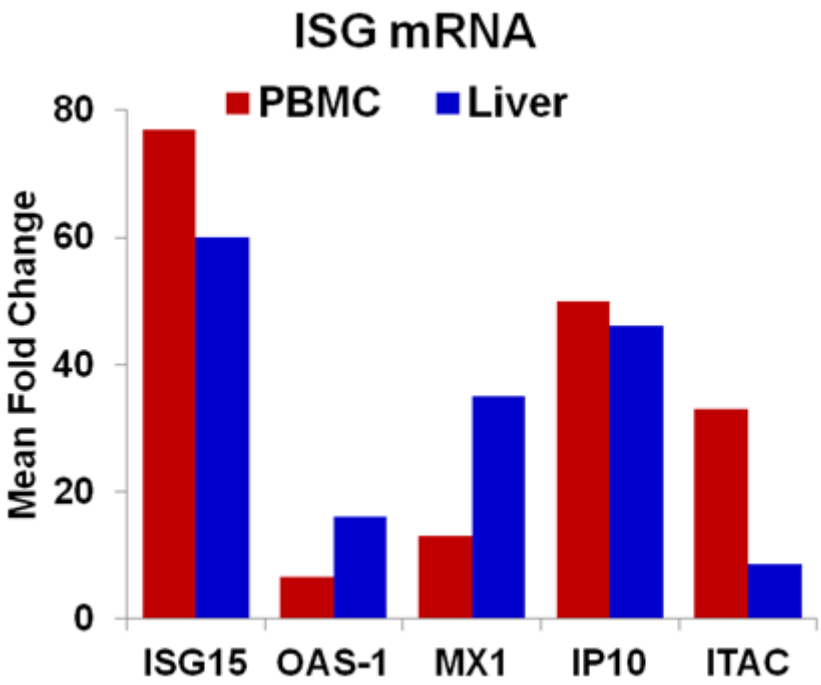
C_{max} GS-9620 vs IFNα

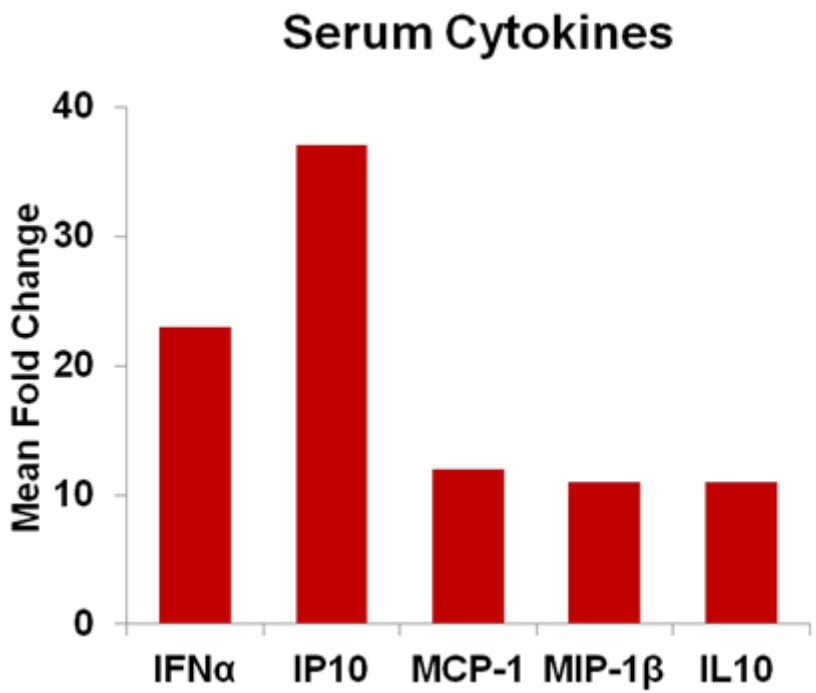


N = 3 animals at 0.3 mg/kg, n =3 at 1 mg/kg (A), and n =4 at 1mg/kg (B).

ISG and Serum Cytokine Induction in Uninfected Chimpanzees

Pharmacodynamic responses in uninfected animals after a single oral GS-9620 dose of 1 mg/kg.

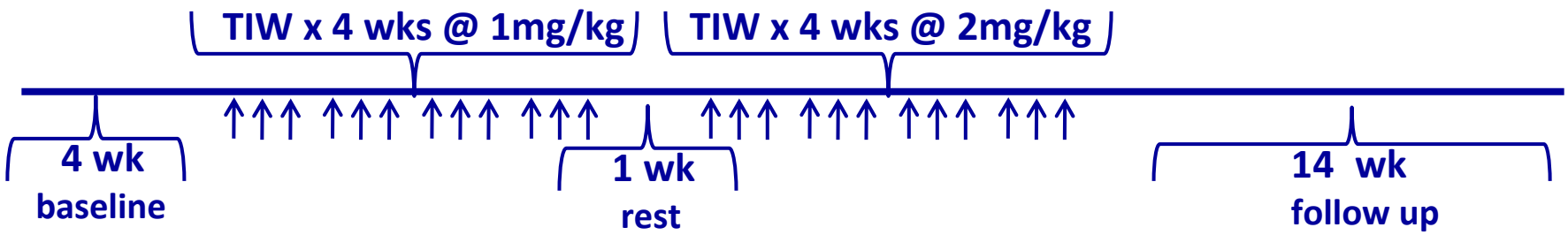




Mean of the peak fold increases are shown at 8 hrs post dosing at 1 mg/kg for n=7 animals.

PK and Efficacy Study Design

3 HBV chronically infected chimpanzees: Oral dosing three time per week

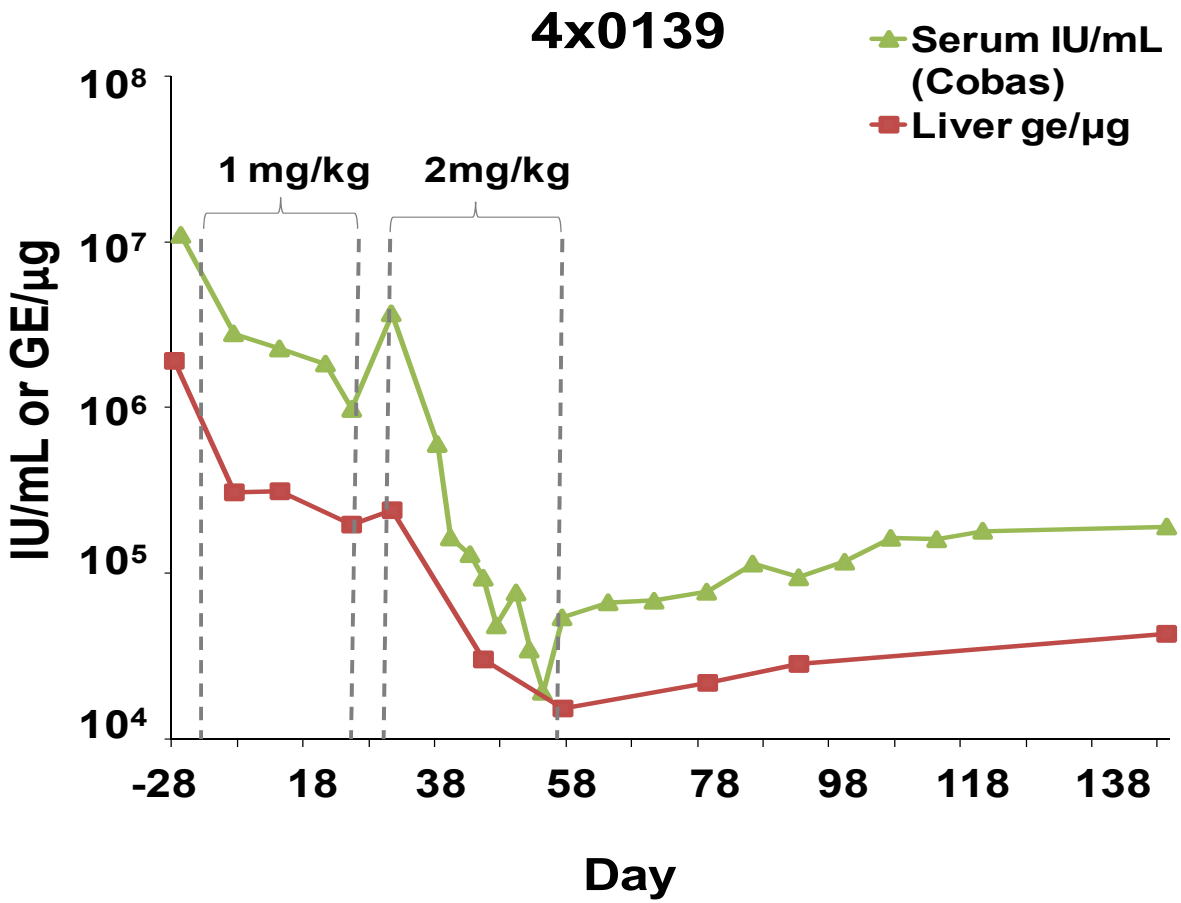


- **HBV DNA, HBeAg and HBsAg**
- **ISGs in PBMC and Liver, Cytokine/Chemokine**
- **Lymphocyte activation markers**
- **Liver histology**
- **Safety parameters: CBC, blood chemistries, observations**

Baseline Characteristics of HBV Chronically Infected Chimpanzees

Animal ID	Baseline HBV DNA	HBeAg	Anti-HBeAg	Anti-HBcAg	Sex	Duration of HBV Infection
4x0139	$6.5x10^7$	+	-	+	F	30 Years
4x0328	$2.5x10^5$	+	-	+	M	> 24 Years
4x0506	$1.6x10^4$	-	+	+	F	> 27 Years

Antiviral Response in High Titer Chimpanzee



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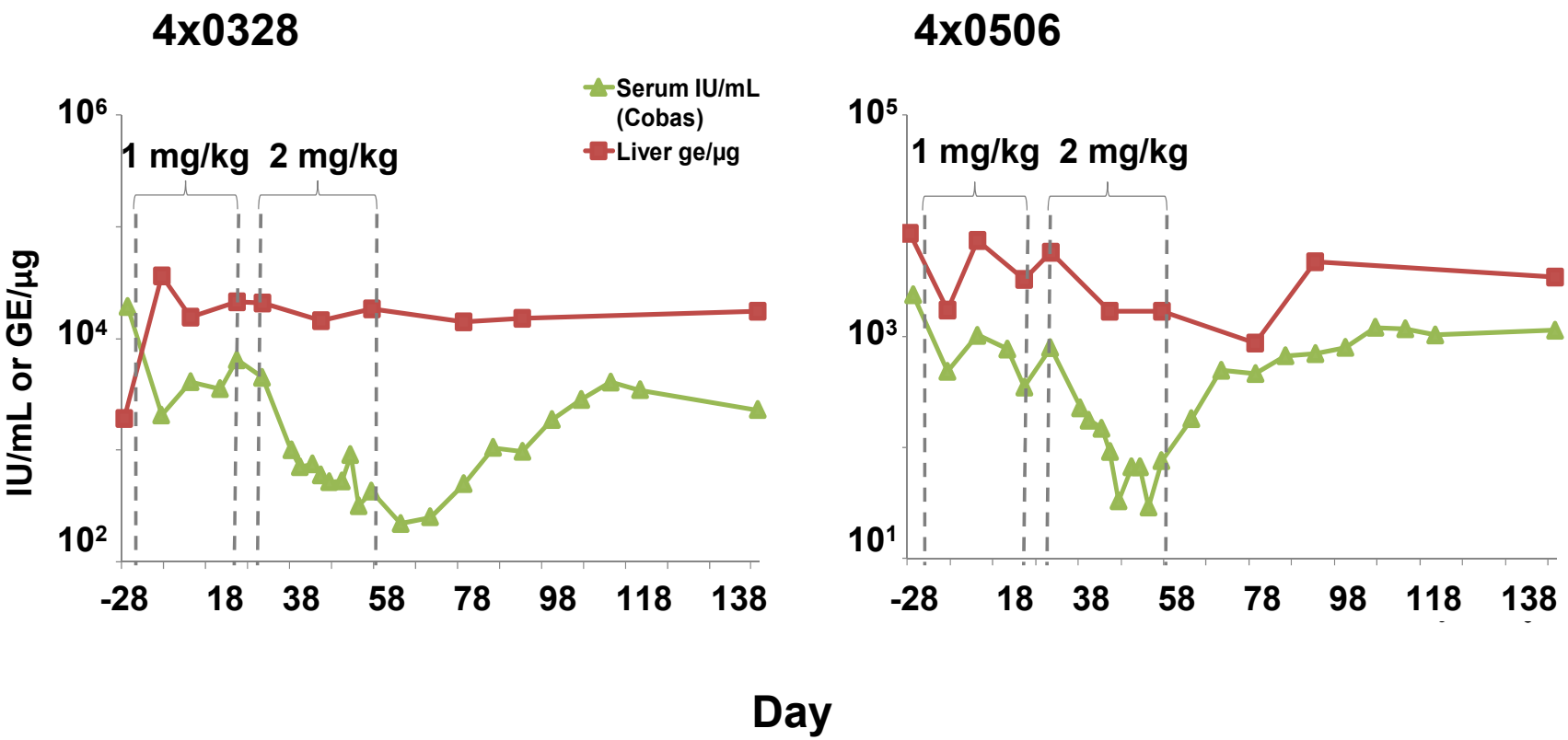
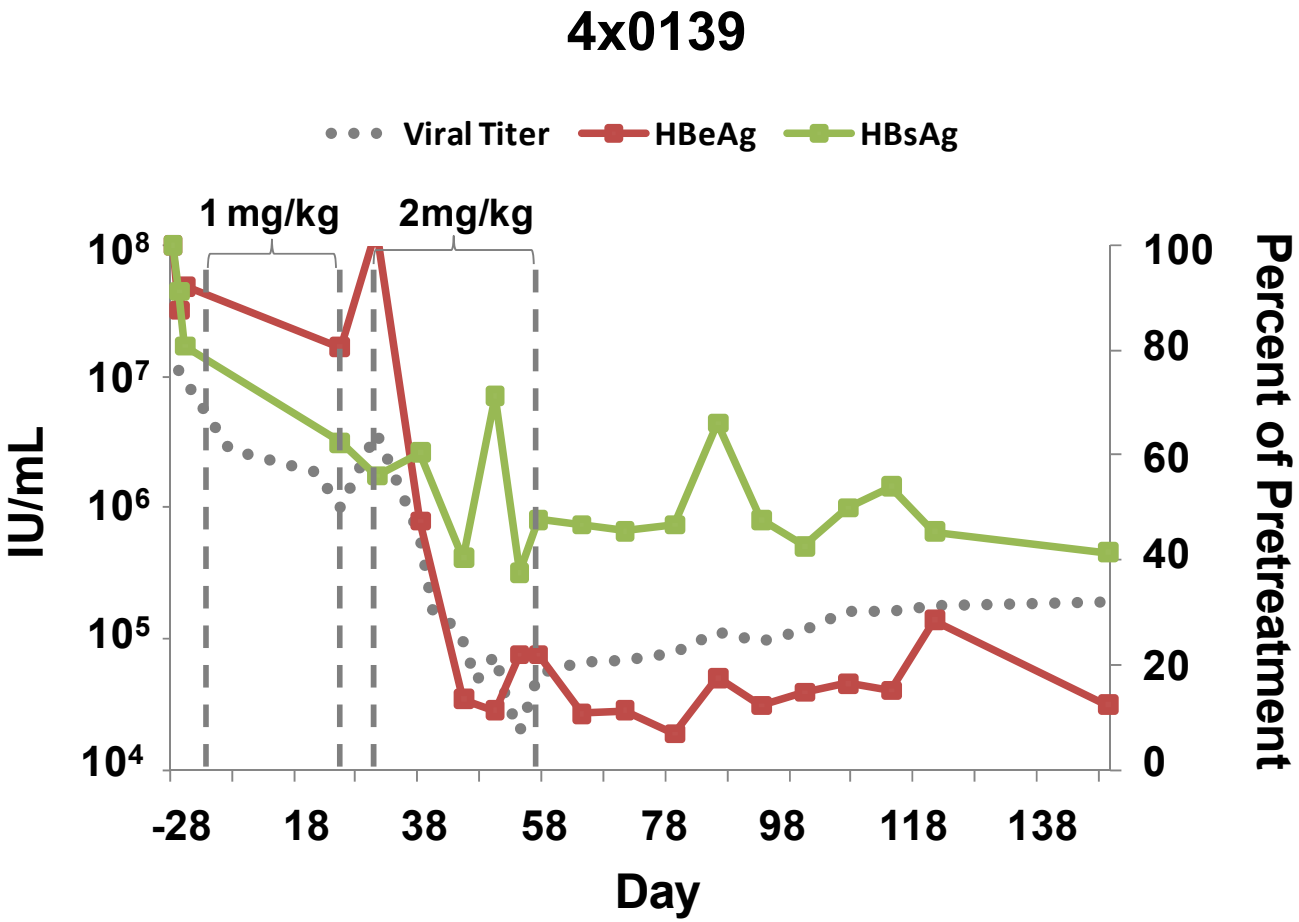
Antiviral Response in Low Titer Chimpanzees



Reduction in Serum HBsAg and HBeAg in High Titer Chimpanzee



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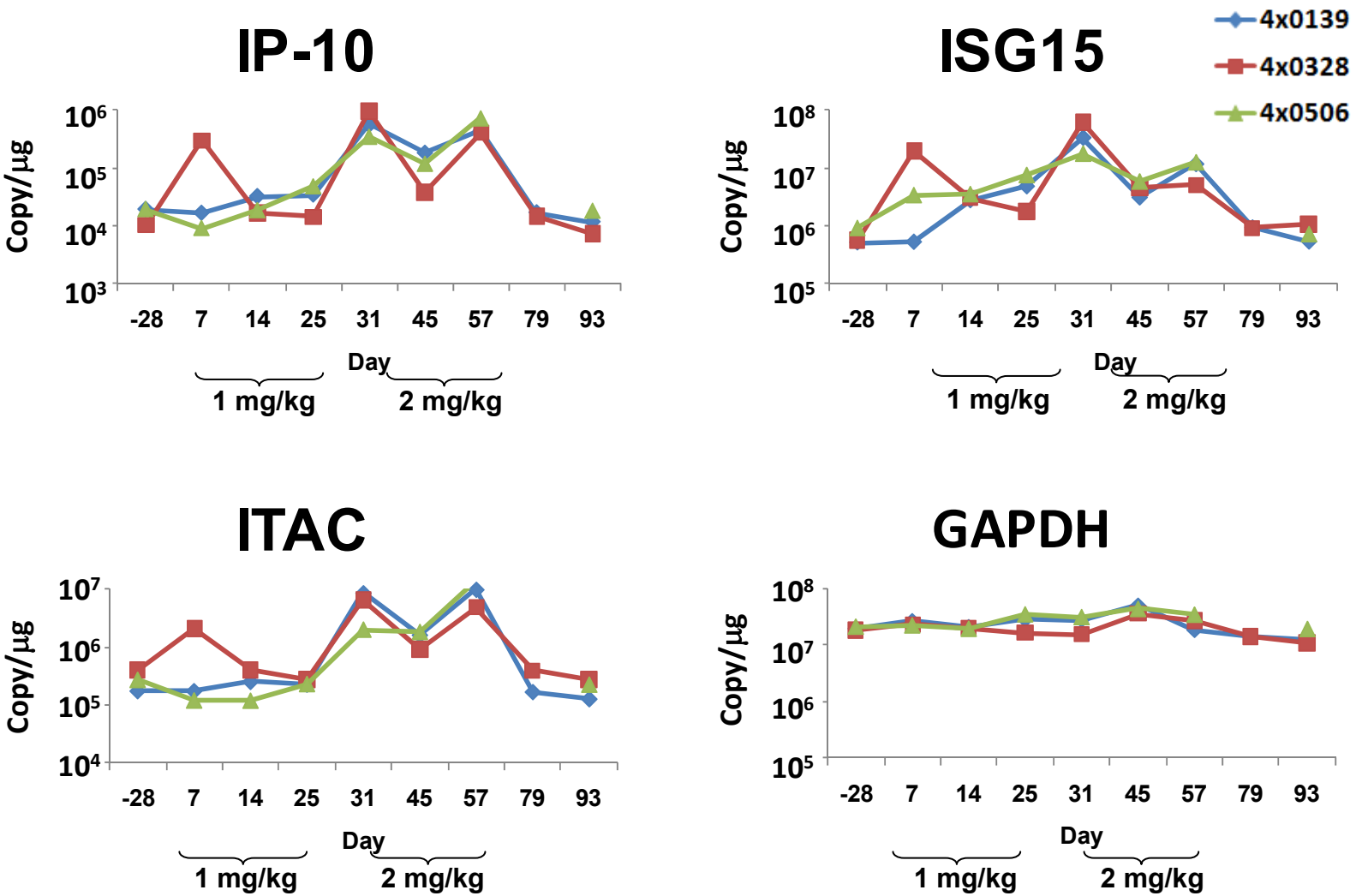
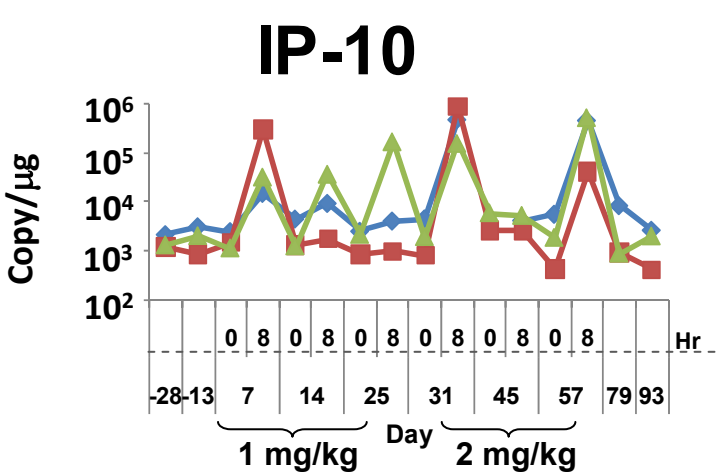
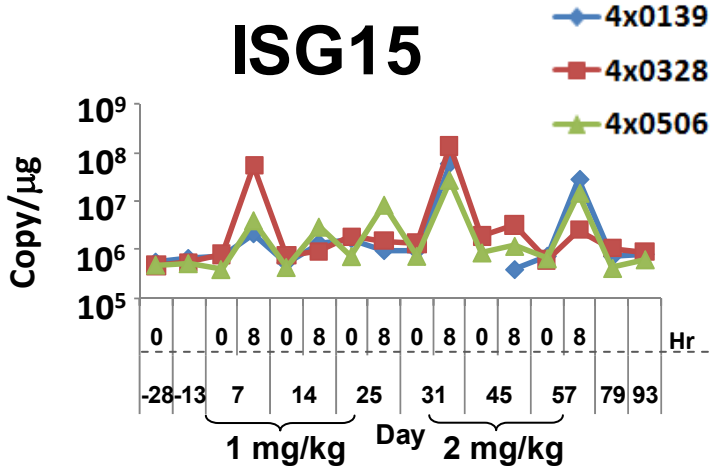
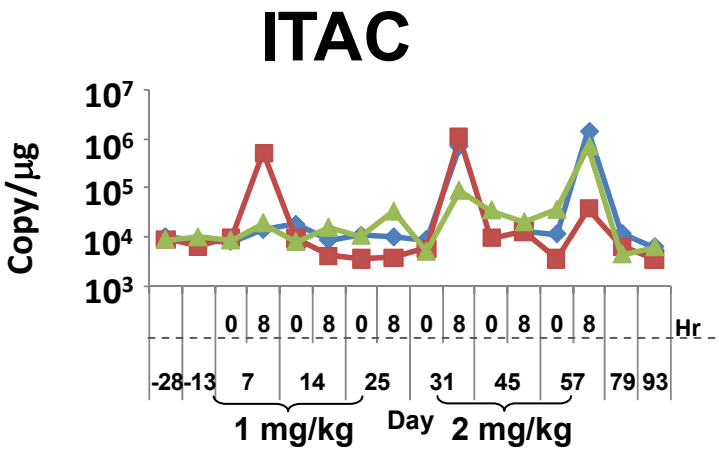
Induction of ISG Transcripts in Liver

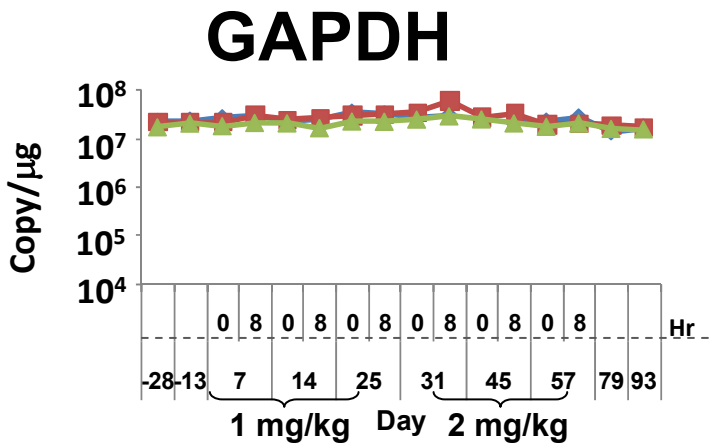


Induction of ISG Transcripts in PBMC









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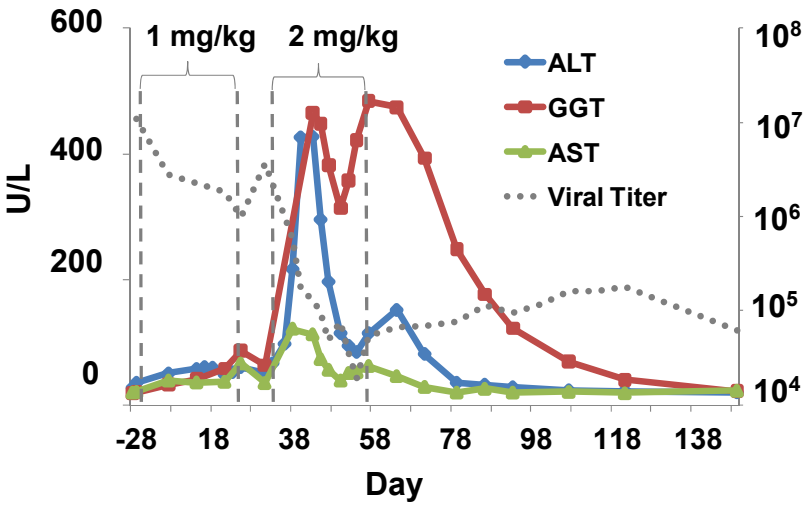
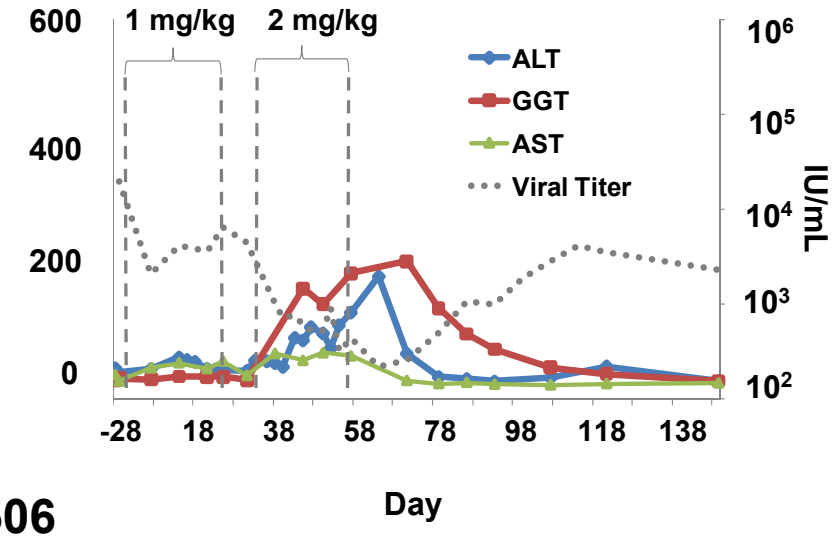
Serum Levels of Liver Enzymes: ALT, GGT & AST

4x0139

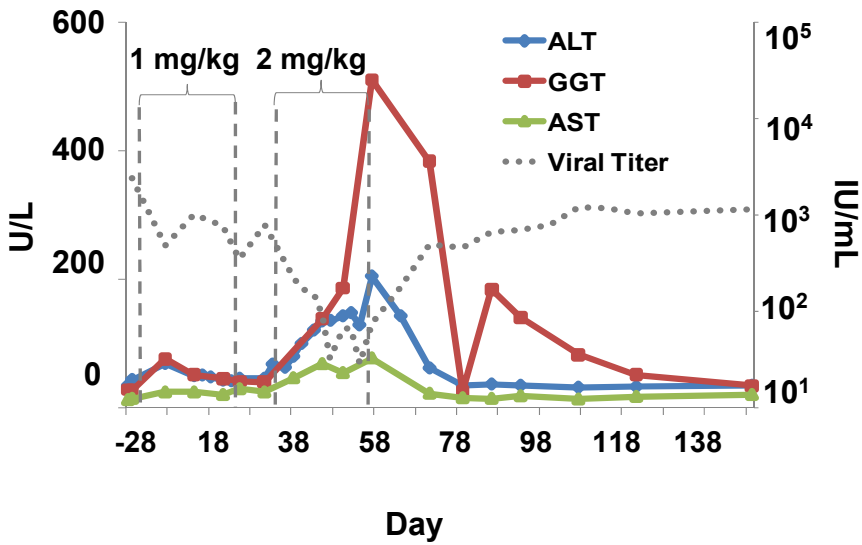


4x0139 had a dosing holiday on Days 43, 45 and 47.

4x0328



4x0506



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Activation of Peripheral Blood Cells

Cell Population	Marker	Fold Increase in Percent Positive Cells (Range)
B Lymphocytes	CD69	3-5 fold
CD8 T lymphocytes	CD69 CD25	2-5 fold 2-5 fold
CD4 T lymphocytes	CD25	2-4 fold
NK and NKT Cells	CD69	2-6 fold

Evaluated on Day -28 and 8 hours post dose on Days 7, 14, 25, 31, 45 and 57.

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Conclusions

- **Oral GS-9620 for 8 weeks reduced serum and liver viral DNA in all three HBV infected chimpanzees.**
- **The mean maximal reduction in serum viral load was 2.2 logs, with a duration of at least one log reduction from 64 days to >121 days.**
- **Reductions in viral load correlated with reductions in serum HBsAg in all three animals and with reduction of HBeAg in one animal.**
- **GS-9620 induced dose dependent increases in serum IFN-α, ISGs in PBMCs and liver, and activation of lymphocyte subsets: CD8+ T and NK cells.**
- **Increased liver enzymes were observed and returned to baseline by the end of the study.**