Pharmacokinetics and Pharmacodynamics of Single Escalating Oral Doses of GS-9620 In Healthy Subjects

Gilead Sciences, Inc., Foster City, CA, USA; Covance Inc., Evansville, IN, USA

Poster Number 664

Introduction

- GS-9620 is an oral small-molecule TLR-7 agonist.
- GS-9620 exhibited moderate intersubject variability in plasma PK, resulting in ~30 to 50% lower drug exposures (data not presented).
- GS-9620 is a promising, oral immunomodulatory agent with potency in the low nM range.

Methods/Study Design

- In this double-blind, placebo-controlled study of 7 healthy human volunteers, single ascending doses of 0.1, 0.3, 1, 3, 6, 8, and 12 mg were administered. Data from 0.1, 0.3, 1, and 3 mg doses were previously presented.

Background

- GS-9620 is an orally available and extensively studied TLR-7 agonist.
- Preclinical studies have demonstrated that GS-9620 has potent pharmacologic activity in vitro and in vivo (Shianna KJ, BMJ. 2008 Aug 8;337:a2325). TLR-7 agonists may serve as a component of therapy for viral hepatitis (4, 5).

Safety Results

- No serious adverse events (SAEs) or individual subject discontinuations due to AEs or laboratory findings were reported.
- There were no serious adverse events (SAEs) or individual subject discontinuations due to AEs or laboratory findings.
- There were no serious adverse events (SAEs) or individual subject discontinuations due to AEs or laboratory findings.

Objective

- The primary objective was to evaluate the safety, tolerability, and pharmacokinetics (PK) of single oral doses of GS-9620 in healthy volunteers.

Results

- GS-9620 treatment dose is dose-dependent increase in select cytokines, chemokines, and IL-28B genotyping of the rs12979860 SNP was done using the ABI TaqMan allelic discrimination kit and the ABI7900HT platform in infected chimpanzees (Abstract 1771) and woodchucks (Abstract 1790).
- No systemic interferon was noted until 12 mg of GS-9620.
- Increases in % of T cells, B cells and NK cells expressing CD69 (an activation marker) were noted in subjects receiving GS-9620 at 8 and 12 mg doses.

Conclusions

- GS-9620 is a potent, oral small molecule agonist of TLR-7, which was safe and well tolerated in single ascending doses up to 12 mg PO. Preliminary data suggest GS-9620 achieved >70% of maximal plasma levels at 1 hour and 6 hours after dosing and demonstrated dose-dependent induction of multiple cytokines (including Interferon) pre-systemically, with the potential for decreased adverse events compared to systemic pegylated interferon.
- GS-9620 is promising, oral immunomodulatory agent with potent in vitro activity and in vivo select cytokines, chemokines, and IL-28B genotyping at Duke University Genotyping Facility.