Plasma and Tissue
GSK1265744 Pharmacokinetics Following Long-Acting Parenteral Administration in Healthy Male and Female Subjects

Susan Ford, David Margolis, Shuguang Chen, Elizabeth Gould, William Spreen
GlaxoSmithKline
(Presentation O_02)

14th International Workshop on Clinical Pharmacology of HIV Therapy
April 22-24, 2013
Introduction

• GSK1265744 (GSK744) is a potent integrase inhibitor with robust short-term antiviral activity following oral monotherapy.

• Long-acting parenteral (LAP) IM/SC injections of GSK744 100 to 800 mg in healthy volunteers achieve similar plasma concentrations as oral drug in HIV-infected subjects.

• Infrequent LAP administration is a potential new paradigm for treatment and prevention of HIV.

Min et al. ICAAC 2009; San Francisco, CA. Abstract H-1228.
Mean Plasma GSK744 Concentration-Time Profiles Following Single 100-800 mg LAP Doses (200mg/mL nanosuspension)

Differences observed between split and unsplit dosing

Study Design: 2 Additional Single-Dose Cohorts

• Objectives
  • Evaluate PK split versus unsplit and batch effects
  • Evaluate tissue penetration

• Design
  • 400 mg IM single injection versus 400 mg IM split into two 200 mg gluteal IM injections—subtherapeutic dose but highest dose volume (2mL) allowed per protocol
  • 4 male and 4 female subjects per cohort
  • Serial plasma sampling
  • Tissue biopsies - Unsplit group at W2/8; split group at W4/12
    • Males
      • 2 rectal biopsies ~2-3 mm³ and ~10-30 cm from anal margin per flexible sigmoidoscopy procedure; enema 1 hour prior to procedure
    • Females
      • 1 cervical, 2 vaginal (distal and proximal) ~4 x 2 x 2 mm biopsies
Split Dosing Increases Absorption Rate for GSK744 400 mg IM

- Similar AUC(0-∞) between groups suggests extent of absorption not affected.
- Split dosing allows for loading dose strategy.
GSK744 Tissue Concentration Analysis

- Nonquantifiable tissue concentrations assumed = 25 ng/g (half LLOQ)
- All tissue samples had measurable but nonreportable concentrations
- Median split, unsplit (range) individual tissue:plasma ratios were
  - 0.16, 0.20 (NQ – 0.40) in cervical tissue
  - 0.19, 0.28 (NQ – 0.70) in vaginal tissue
  - NQ, 0.08 (NQ – 0.20,0.10) in rectal tissue
- Higher tissue concentrations correlated with higher plasma concentrations
GSK744 LAP Protective Against SHIV Infection in Macaque Rectal Challenge Study

- GSK744 plasma concentrations following LAP in macaques similar to humans
- GSK744 rectal tissue:plasma 0.1-0.3 in macaques at LAP dose of 10mg/kg
- Macaque vaginal challenge study ongoing

Andrews et al. CROI 2013; Atlanta, GA.
Summary

• Dose splitting increases rate but not extent of absorption
  • Allows for loading dose to achieve target concentrations

• Median tissue:plasma ratios ranged from 16%-28% in cervicovaginal tissue and were ≤8% in rectal tissues.
  • Limitations
    • Study conducted at subtherapeutic single doses (400mg IM)
    • Technical issues, possible enema dilution of rectal concentrations

• Despite similar low tissue:plasma ratios in human and macaques, 100% protection against SHIV rectal challenge at clinically relevant exposures.

• Data support evaluation of GSK1265744 LAP in PrEP at higher doses.
Acknowledgments

**GlaxoSmithKline**
Gary Bowers
Lee Moss
Glenn Talbot
Paul Savina
Steve Piscitelli
David Wilfret

**ViiV Healthcare**
Alex Rinehart
Jim Goodrich