Metabolism and Excretion of Ledipasvir (GS-5885) in Humans

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Ledipasvir (LDV, Formerly GS-5885)

- Novel HCV NS5A inhibitor
- Picomolar potency against GT1a and 1b
  - Potency maintained against cross-class resistant mutants
    - NS3: A156T, R155K, D168E
    - NS5B: S282T, Y448H
- Safe and well tolerated in clinical studies
- Once daily dosing
- Limited clinically significant drug interactions
- No safety signals in preclinical/clinical studies
LDV Clinical Pharmacology Summary

- Solubility limited absorption
- LDV is a weak inhibitor of P-gp and BCRP
- LDV may be coadministered with:
  - P450 or UGT substrates
  - P-gp inhibitors
  - Moderate or hepatic P-gp and P450 inducers
  - Acid reducing agents (H2RAs)
  - Mild or moderate hepatic impairment
- Ongoing Phase 1 studies:
  - TQT
  - Renal impairment
  - Severe hepatic impairment
Objectives

♦ Primary Objective
  – To determine the mass balance of LDV.

♦ Secondary Objectives:
  – To evaluate the pharmacokinetics of LDV and its metabolites
  – To determine the metabolite profile of LDV in humans
  – To assess the safety of single dose of LDV
Methods: Study Design

- Phase 1, open-label, single dose, mass-balance study in 8 healthy male subjects conducted at a single center in the USA

- Single dose of an ethanolic solution of 90 mg LDV containing 100 μCi [\textsuperscript{14}C]-labeled LDV in a capsule administered after a standardized meal
Methods: Release Criteria and Sample Analysis

♦ Real-time total radioactivity analysis using LSC was conducted on whole blood, plasma, urine and feces to inform sample collection and release criteria:
  – Whole blood and plasma collected until:
    • 2 consecutive samples < 2X background, or both urine and fecal collections were discontinued
  – Urine and feces were collected and subjects were confined to the study center until:
    • 2 consecutive 24-hr collections of urine and feces ≤ 1% of the administered dose and the cumulative $[^{14}\text{C}]$-total radioactivity recovered in urine plus feces was > 90% of the administered dose

♦ Samples were analyzed for:
  – $[^{14}\text{C}]$-total radioactivity by LSC
  – HPLC radio-profiling (pooled samples)
  – HPLC/MS/MS analysis
Results: Subject Demographics and Safety

Demographics

♦ 8 male subjects enrolled, 7 subjects completed the study
  – 1 discontinuation due to AEs unrelated to study drug (constipation)
    • Discontinued at day 9 (~85% radioactivity recovered), included in analysis set
♦ Mean age: 29 yrs (range: 19 - 41)
♦ Mean weight: 74.9 kg (range: 67.6 - 87.5)
♦ Race: 5 White, 2 African American, 1 Other

Safety

♦ LDV was well tolerated
♦ No Grade 2 or higher laboratory abnormalities or drug-related adverse events (AE)
♦ 3 Grade 1 AEs were considered study drug related (change of bowel habit in 1 subject, and headache and photophobia in 1 subject)
Results: Excretion of Total Radioactivity

- Overall, high recovery of $[^{14}\text{C}]$ radioactive dose in excreta: 87%
  - Predominantly in the feces: 86%
  - Minimally in the urine: 1.2%
Results: Whole Blood and Plasma Exposure

♦ Whole blood and plasma $[^{14}\text{C}]$-total radioactivity exposure:
  - Whole blood and plasma undetectable at 36 and 48 hours post dose respectively
  - Whole blood to plasma ratio 0.51-0.66
    - Exclusion of radioactivity from erythrocytes
♦ Plasma LDV by LC/MS/MS and $[^{14}\text{C}]$-total radioactivity profiles comparable
♦ Consistent with non-clinical data
Radio-Profiling Results

Radio-profiling:
- Plasma radio-profiling using AUC pooled samples:
  - LDV accounted for >98% of total plasma exposure
  - No unidentified metabolite accounted for >1.0% of total plasma exposure
- Fecal radio-profiling:
  - LDV was the major component, 70% of dose
  - M19 accounted for 2.2% of dose
  - No unidentified metabolite accounted for >1.7% of the dose
- Urine radio-profiling:
  - LDV not detected in urine
  - No unidentified metabolite accounted for >0.6% of the dose
- All metabolites accounting for >1% of dose were previously detected in non-clinical studies
LDV is the predominant (>98%) species circulating in plasma.
The human data are consistent with the established non-clinical profile of LDV.

Values reported are % of dose administered
Total [14C]-radioactivity recovery ~87%: ~86% in Feces, ~1% in Urine
* Signifies position of radiolabel
Conclusions

♦ LDV is minimally metabolized and primarily eliminated in the feces, with renal excretion as a minor elimination pathway
  – Supports use in patients with renal dysfunction

♦ A single dose of $[^{14}\text{C}]-$LDV was safe and well tolerated

♦ Ledipasvir is being evaluated in Phase 3 studies in combination with sofosbuvir (an NS5B nucleotide prodrug inhibitor) as a fixed dose combination (FDC; SOF/LDV) for the treatment of chronic genotype 1 HCV infection
  ♦ with and without ribavirin
  ♦ in treatment naïve and treatment experienced patients.