Preclinical Pharmacokinetic Assessment of a Long-acting Solid Injectable for Hepatitis C Virus

640

Usman Arshad[1,3], Henry Pertinez[1,3], Joanne Sharp[1,3], Helen Cox[1,3], Joanne Herriott[1,3], Edyta Kijak[1,3], Eduardo Gallardo-Toledo[1,3], Jonathan Massam[2,3], Andrew B. Dwyer[2,3], Alison Savage[2,3], James J. Hobson[2,3], Catherine Unsworth[2,3], David L. Thomas[4], Paul Curley[1,3], Steve P. Rannard[2,3], Andrew Owen[1,3]

Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, UK, [2]Department of Chemistry, University of Liverpool, UK, [3]Centre of Excellence for Long-acting Therapeutics (CELT), University of Liverpool, UK, [4]Department of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

BACKGROUND

- Glecaprevir (GLE) and pibrentasvir (PIB) are direct-acting antiviral agents administered in combination for the treatment of Hepatitis C virus (HCV).[1] Oral administration of this combination, typically as three tablets, once daily for 8-12 weeks, has demonstrated high efficacy.
- However, the daily dosing regimen poses challenges, including adherence concerns, access limitations in resource-constrained environments, and the potential for inconsistent plasma drug concentrations.[2]
- To address these limitations, the development of a long-acting (LA) injectable formulation of GLE/PIB is being investigated. We have previously reported on a LA liquid injectable[3], this work evaluates the preclinical pharmacology of a novel LA solid injectable designed to achieve prolonged pharmacokinetic exposure and sustained antiretroviral activity, offering an alternative to daily oral administration.

METHODS

- GLE/PIB solid drug nanoparticles (SDNs) were synthesised via an emulsion spray-drying process. These SDNs were then processed into solid injectable pellets utilising vacuum compression moulding.
- The resulting solid injectable pellets, with a cylindrical geometry of 11 mm in length and 2 mm in diameter, comprised 30 wt% GLE, 30 wt% PIB, and 40 wt% excipient (30 wt% Plasdone C15 and 10 wt% AOT). The total doses of each drug contained within a pellet were 13.5 mg GLE and 13.5 mg PIB.
- For *in vivo* evaluation, the solid injectable pellets were administered by subcutaneous injection using a 12-gauge needle in male Sprague Dawley rats (n=4, weighing between 250 and 300 g) each rat receiving x2 pellets: x1 in each flank of the scapular region, for a total dose of 27 mg GLE + 27 mg PIB.
- Plasma concentrations of GLE and PIB were quantified over a 13-week period using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.
- Subsequent pharmacokinetic analysis was performed using the PK Solver software program.[4]

A novel long-acting solid injectable of **glecaprevir / pibrentasvir** displayed **sustained** therapeutic concentrations for more than 8 weeks *in vivo*

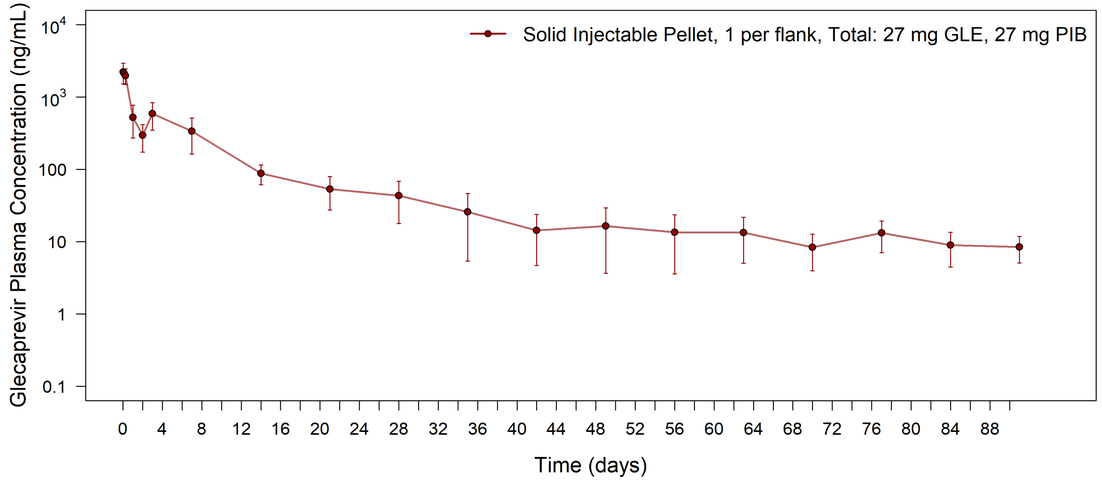


Figure 1. Plasma concentration-time curve in Sprague Dawley rats following administration of a glecaprevir/pibrentasvir solid injectable. Data are expressed as the mean ± SD (n = 4).

RESULTS

- Detectable plasma concentrations of both GLE and PIB were maintained over the entire 91-day duration of the study (Figure 1). The maximum plasma concentration (C_{max}) for GLE was observed approximately 2 hours post-administration, while PIB C_{max} was observed at approximately 11 hours post-administration (Table 1).
- After adjusting for dose, the solid injectable and previously reported liquid suspension[3] exhibited comparable drug release kinetics, as evidenced by similar C_{max} and terminal flip-flop release half-lives.
- No behavioural abnormalities or visible injection-site reactions were observed.

Table 1 Pharmacokinetic Parameters of LA GLE/PIB

Parameters	GLE	PIB
$AUC_{0\text{-}8\ weeks}$ (µg.h/mL)	169 ± 69	47.3 ± 6.6
C_{max} (ng/mL)	2490 ± 500	248 ± 46
T_{max} (Hours)	2	11
$T_{1/2}$ (Days)	43	38

CONCLUSIONS

- The rapid attainment of high drug concentrations following administration suggests that this approach may mitigate the need for an oral lead-in phase, which could be suboptimal for the treatment of chronic infections
- Future investigations will focus on evaluating dose linearity and proportionality; assessing pharmacokinetic variability relative to liquid formulations; estimating achievable human doses and treatment durations; and evaluating patient acceptability of the solid injectable administration method.

Author Contact Information

Usman Arshad, u.arshad2@liverpool.ac.uk

References

[1]Zeuzem, 2018. [2]Brown, 2020. [3]Arshad, CROI 2024. [4]Zhang, 2010.

Acknowledgements

This research was funded by Unitaid as part of project LONGEVITY (2020-38-LONGEVITY).