Glecaprevir/Pibrentasvir Combination Within Individual Particles Drives Optimal LAI Performance

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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], 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

- Long-acting injectable (LAI) strategies for hepatitis C Virus (HCV) offer a potential "**single-administration curative regimen**" overcoming adherence barriers associated with daily oral therapy.
- Our previous preclinical studies identified a **synergistic pharmacokinetic (PK) interaction** when glecaprevir (GLE) and pibrentasvir (PIB) were administered as a **fixed dose combination (FDC).** The FDC yielded a significant extension of the GLE terminal elimination half-life ($t_{1/2}$) and elevated PIB systemic exposure (AUC) compared to monotherapy controls.[1]
- To determine whether this PK enhancement is driven by a biological interaction at the depot site or a physicochemical modulation within the formulation itself, we investigated if the optimal PK profile requires **intra-particle co-formulation** (drugs combined within the same nanoparticle) or if it can be achieved *via* **inter-particle mixing** (a physical mixture of discrete GLE and PIB nanoparticles).

METHODS

- Solid Drug Nanoparticles (SDNs) were synthesised with a high drug loading (80 wt%) and 20 wt% excipient matrix, maintaining a **2:1 GLE:PIB ratio**. Male Sprague Dawley rats (n=4/group; 225-250g) were administered formulations *via* **intramuscular (IM)** or **subcutaneous (SC)** injection to compare three distinct particle architectures/regimens:
  1. **FDC (Co-formulation)**: GLE and PIB formulated together within the same individual nanoparticles.
  2. **MD (Mixed Dispersion)**: A physical mixture of discrete GLE-only and PIB-only nanoparticles combined in a single suspension.
  3. **SI (Separate Injections)**: Administration of GLE and PIB formulations into spatially distinct anatomical sites (contralateral thighs or flanks) to preclude depot interactions.
- Plasma concentrations were quantified over a 56-day period using a validated LC-MS/MS assay.
- PK parameters were derived *via* non-compartmental analysis.

Co-formulation within individual nanoparticles drives superior pharmacokinetics, maintaining therapeutic drug levels for **8 weeks** *in vivo*

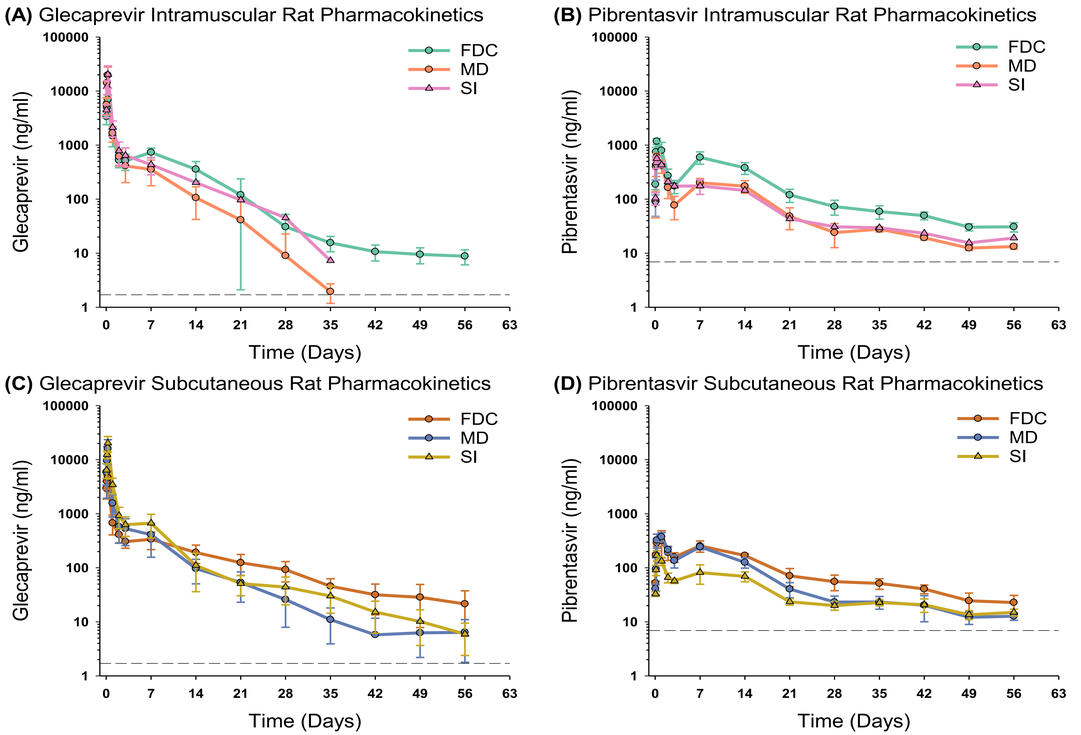


Figure 1. Comparative plasma concentration-time profiles of glecaprevir and pibrentasvir following IM and SC administration of FDC, MD, and SI. Data are expressed as the mean ± SD (n = 4). Dashed lines represent the clinical target concentration (10^{th} percentile of human oral C_{trough}: GLE 1.7ng/ml and PIB 6.9ng/ml).

Table 1 Pharmacokinetic parameters of glecaprevir and pibrentasvir following different long-acting injectable formulations and routes of administration in rats

Glecaprevir						
Formulation	Intramuscular			Subcutaneous		
	C_{max} µg/mL	AUC_{last} µg.h/mL	$t_{1/2}$ days	C_{max} µg/mL	AUC_{last} µg.h/mL	$t_{1/2}$ days
FDC	**7.0**	**353**	**16.2**	**4.6**	**237**	**12.1**
MD	19.7	398	3.8	15.9	366	8.1
SI	20.2	467	5.0	20.3	519	8.3
Pibrentasvir						
Formulation	Intramuscular			Subcutaneous		
	C_{max} µg/mL	AUC_{last} µg.h/mL	$t_{1/2}$ days	C_{max} µg/mL	AUC_{last} µg.h/mL	$t_{1/2}$ days
FDC	**1.2**	**249**	**11.3**	**0.3**	**129**	**14.4**
MD	0.6	104	11.7	0.4	99	11.8
SI	0.6	105	14.2	0.2	50	20.1

RESULTS

- The FDC formulation demonstrated **superior PK performance** irrespective of administration route (IM or SC). The MD **failed to provide** the half-life extension of GLE or the exposure enhancement of PIB seen in the FDC group (Table 1).
- **Therapeutic plasma concentrations** (benchmarked against approved human oral dosing exposures) were consistently maintained for the **full 8-week duration** only in the FDC group.
- **No overt toxicity**, behavioural changes, or injection site reactions were observed, confirming preliminary safety of the high-loading SDN approach.

CONCLUSIONS

- The lack of PK benefit in the MD group suggests **biological mechanisms** (localised enzyme/transporter inhibition) are not the primary driver of the interaction.
- The data support a hypothesis of **mutual dissolution modulation**: the presence of poorly soluble PIB within the particle matrix restricts the release of GLE, extending its half-life. The presence of the more soluble GLE enhances the wetting and dissolution rate of PIB, increasing overall bioavailability.
- While **SC administration** generally resulted in **higher systemic exposures** compared to IM dosing, ultimate selection of route for human dosing also needs to consider that higher doses are available for IM.
- **Co-formulation within individual particles** is a critical design parameter for this HCV LAI and represents a **platform strategy** for combining molecules with divergent solubility profiles.

Author Contact Information

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

References

[1]Arshad U, Pertinez H, Sharp J, *et al.* Preclinical Pharmacokinetic Assessment of a Hepatitis C Virus Long-Acting Injectable Formulation [CROI Abstract 161]. Top Antivir Med. 2024;32(1):583

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