

## INTRODUCTION & PURPOSE

Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of CAP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) at two sites. It interacts via four H-bonds and other interactions resulting in an "induced fit" whereby nucleotides in the PTC shift and further tighten the binding pocket around lefamulin.

Previous pharmacokinetic studies of lefamulin revealed that steady-state was reached after 2 days of oral administration every 12 hours, and the elimination half-life after oral administration was similar to that after intravenous (IV) administration (data on file, Nabriva Therapeutics). In addition, the exposure from 600 mg doses given as 3 x 200 mg capsules or as a 600 mg immediate-release (IR) tablet was equivalent to that of a 150 mg intravenous dose. In this study, we evaluated the safety and effect of food on the pharmacokinetics of a 600 mg IR tablet formulation of lefamulin compared with intravenous (150 mg) and lefamulin active pharmaceutical ingredient (API) in capsule (200 mg) formulations.

## OBJECTIVES

### Primary Objective:

Evaluate the absolute bioavailability and pharmacokinetics of lefamulin 600 mg IR tablet formulation in comparison with lefamulin 150 mg IV formulation

### Secondary Objectives:

Evaluate the relative bioavailability and pharmacokinetics of lefamulin 600 mg IR tablet formulation in comparison to lefamulin 600 mg active pharmaceutical ingredient in capsules (3 x 200 mg capsules)

Evaluate the pharmacokinetics of lefamulin 600 mg IR tablet formulation administered in the fasted state and 1 hour after high-fat, high-calorie breakfast

Evaluate the safety and tolerability of lefamulin administered as single oral and IV doses

## METHODS

This was a single-centre, single-cohort, open-label, randomised, 4-period crossover study conducted in 20 healthy subjects aged 18 to 55 years. All subjects received single doses of each of the following lefamulin treatments in random order at 4 study sessions and each treatment period was separated by at least 4 days.

**Treatment A:** 600 mg IR tablet administered orally in a fasted state

**Treatment B:** 600 mg active pharmaceutical ingredient (3 x 200 mg capsules) administered orally in a fasted state

**Treatment C:** 150 mg in 250 mL citrated-buffered saline administered as an IV infusion over 1 hour

**Treatment D:** 600 mg IR tablet administered orally in a fed state 1 hour after a high-fat, high-calorie breakfast

## RESULTS

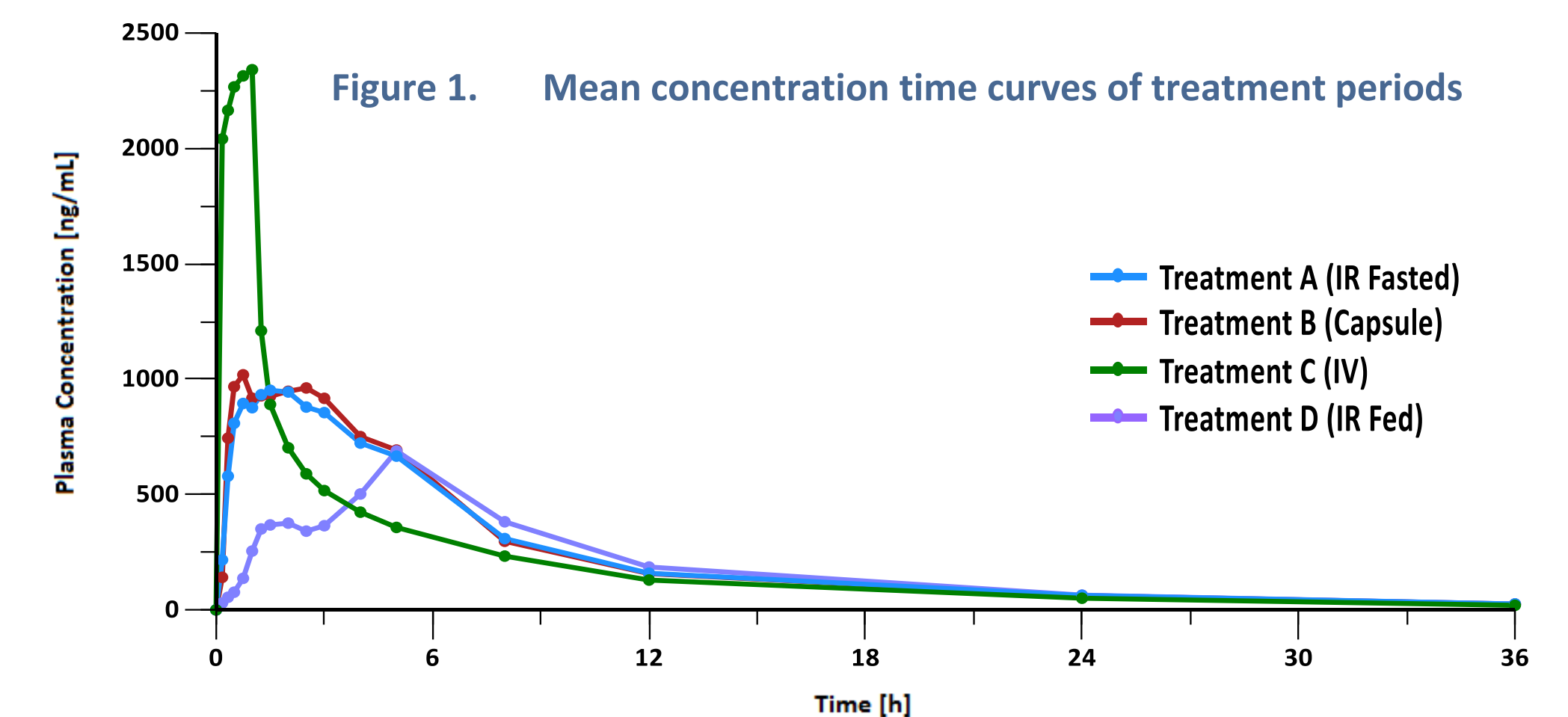
- The study demonstrated that the exposure to lefamulin after a single 150 mg IV infusion and after administration of 600 mg oral IR tablet in the fasted state met the criterion for bioequivalence with respect to AUC (Figure 1; Table 2).
- Absorption of lefamulin was rapid after oral administration, with a similar  $T_{max}$  compared to the 1h infusion (Table 1; Figure 1).
- Relative bioavailability of the tablet administered in the fed and fasted state ( $AUC_{0-inf}$  81.57% [ $CI_{90}$  75.34, 88.31%]) was slightly below the range for bioequivalence range of 80 to 125% (Table 2).
- The most common AEs reported were GI disorders, and the incidence was higher after dosing with Treatment A and B than Treatment C and D.
- Co-administration of lefamulin tablets with food resulted in a decrease in GI-related AEs (2 versus 12 events).
- All AEs reported were mild in severity, no subject required concomitant medication for treatment of an AE, no subjects were withdrawn due to an AE and all AEs resolved by study end. No clinically significant findings in any laboratory assessments, vital signs, ECGs or physical examinations were reported.

Table 1. Summary Pharmacokinetic and Safety

	Treatment A	Treatment B	Treatment C	Treatment D
Dose	600 mg	600 mg	150 mg	600 mg
Route	IR Tablet	Capsules	IV	IR Tablet
Food status	Fasted	Fasted	NA	Fed
N	20	20	20	19
<b>Pharmacokinetics</b>				
$T_{max}$ (hours)	1.76 (0.50-5.00)	0.875 (0.50-4.00)	1.00 (0.17-1.02)	5.00 (1.05-8.00)
$C_{max}$ (ng/mL)	1170 (23.3%)	1210 (29.4%)	2370 (14.0%)	901 (29.4%)
$AUC_{0-inf}$ (ng·h/mL)	8180 (32.5%)	8400 (30.5%)	7920 (16.5%)	6630 (33.0%)
$t_{1/2}$ (hours)	9.15 (11.0%)	9.01 (10.5%)	8.91 (9.5%)	8.72 (12.2%)
<b>Safety (n = 20)</b>				
GI-related AEs (mild) (# of subjects)	12 (9)	12 (9)	0	2 (1)
Moderate/severe AEs	0	0	0	0
<i>Abdominal pain</i>	6	4	0	1
<i>Nausea</i>	2	5	0	0
<i>Dyspepsia</i>	1	2	0	0
<i>Diarrhea</i>	2	1	0	1
<i>Abdominal discomfort</i>	1	0	0	0

Table 2. Ratio of  $AUC_{0-inf}$  of Oral and IV of Lefamulin in the Fasted and Fed State

Test	Absolute F%		$AUC_{0-inf}$ Ratio of Oral 600 mg and IV 150 mg (%)			
	Geometric Mean Ratio	$CI_{90}$ Lower	$CI_{90}$ Upper	Geometric Mean Ratio	$CI_{90}$ Lower	$CI_{90}$ Upper
IR Tablet Fasted	25.84	23.72	28.14	103	94.9	113
IR Tablet Fed	21.08	19.24	23.09	84.3	76.9	92.4



## CONCLUSIONS

- Lefamulin was generally well tolerated, regardless of route of administration
- Single doses of 600 mg IR tablets in the fasted state were bioequivalent to a 150 mg intravenous infusion with respect to AUC
- The bioavailability of the IR tablet after a high fat/high calorie meal was slightly lower than that in the fasted state and did not reach the threshold for bioequivalence

## REFERENCES

(1) Prince WT, Ivezic-Schoenfeld Z, Lell C, Tack KJ, Novak R, Obermayr F, Talbot GH. Phase II clinical study of BC-3781, a pleuromutilin antibiotic, in treatment of patients with acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother* 2013;57:2087-94.

## ACKNOWLEDGMENTS

We thank the volunteers, investigator, and study personnel who made this study possible. Medical writing support was provided by Scott Newcomer, MS of Davenport Scientific Services, LLC. Funding for medical writing support was provided by Nabriva Therapeutics.