Tolerability, Safety and Pharmacokinetics in Healthy Subjects of Single Intravenous Doses of Debio 1450 (Previously AFN-1720), a Prodrug of the Staphylococcocal-specific Antibiotic Debio 1452 (Previously AFN-1252)

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Introduction and Purpose

Debio 1450 (previously known as AFN-1720) is a recently developed prodrug of the FabI inhibitor Debio 1452 (previously known as AFN-1252) that targets staphylococcal fatty acid biosynthesis. Debio 1452 has highly potent specific-spectrum activity against staphylococci, including all known drug-resistant mechanisms e.g. MRSA and VISA strains, with an MIC_{90} of 0.016 µg/ml against >5000 strains. Debio 1452 has excellent efficacy in mouse models of infection including thigh abscess, skin abscess, granuloma pouch, pneumonia and septicemia models.

Debio 1452 has demonstrated its good safety and tolerability in a full range of oral Phase 1 studies, and recently completed an oral Phase 2a study in Acute Bacterial Skin and Skin Structure Infections (ABSSSI) due to *Staphylococcus* with overall cure rates of 93% and an excellent safety profile.

Debio 1452 is a BCS Class II drug with limited aqueous solubility, whereas its prodrug Debio 1450 has much improved oral bioavailability in preclinical models (see poster P1717) and an excellent solubility profile. This study reports the safety, tolerability and pharmacokinetics (PK) of Debio 1450 in healthy subjects after IV administration of single-ascending doses.

Methods

A placebo controlled, double blind, single-ascending dose IV Phase 1 study was conducted in healthy subjects under an IND in the USA.

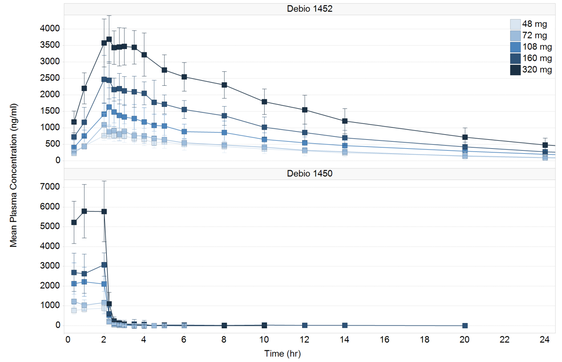
Debio 1450 was formulated in sterile 5% dextrose in water and administration was by a 2 hour intravenous infusion at dose levels of 48 - 320 mg Debio 1450.

Each cohort consisted of 8 healthy volunteers, 6 of which were randomized to study drug and 2 of which were randomized to placebo. All subjects were assessed for vital sign measurements, ECGs, physical examinations, and clinical laboratory tests including hematology, coagulation, urinalysis, serum chemistry and ATCH and cortisol levels.

Plasma samples collected at designated time points were analyzed simultaneously for both Debio 1450 and Debio 1452 using a GLP-validated HPLC/MS/MS method. PK parameters were estimated using a non-compartmental approach.

Results

Time-concentration Profiles of Debio 1452 and Debio 1450 after IV Administration of Debio 1450 to Healthy Human Subjects



- Administration was by 2 hour IV infusion
- Debio 1450 was rapidly converted to Debio 1452
- Tmax of Debio 1450, the prodrug, occurred at 1 -2 hours into the infusion while Debio 1452 Tmax was seen approximately 15 min after the end of infusion

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Results

Mean PK Parameters of Debio 1450 and Debio 1452 following Administration of Debio 1450

	Debio 1450 (prodrug)						Debio 1452 (active metabolite)			
Debio 1450 Dose (mg)	T_{max} (hr)	C_{max} (ng/ml)	Half life (hr)	AUC_{inf} (hr*ng/ml)	Vz (L)	Cl (L/hr)	T_{max} (hr)	C_{max} (ng/ml)	Half life (hr)	AUC_{inf} (hr*ng/ml)
48	2.00	897	0.83	1,603	45	37	2.25	837	7.0	8,704
72	2.00	1,334	0.64	2,142	39	42	2.38	1,101	7.3	9,990
108	1.00	2,211	0.74	3,974	36	34	2.25	1,596	7.9	17,010
160	1.00	3,641	1.18	5,853	58	34	2.25	2,960	7.6	29,066
320	2.00	5,822	0.90	10,735	48	37	2.25	3,740	7.8	45,414

Geometric mean (n=6); except median for T_{max} (calculated from the infusion start)

- Debio 1450 was rapidly converted to Debio 1452 and showed short half lives (~ 1 hr) and high clearance values
- Exposures (AUC and Cmax) for both the prodrug and the active metabolite were linear with dose
- Debio 1452 demonstrated half lives of 7 – 8 hours at all dose levels
- Debio 1452 therapeutic levels are expected to be achieved at Debio 1450 doses of ~240 mg (equivalent to Debio 1452 doses of ~180 mg)

Safety and Tolerability of Debio 1450 in Healthy Human Volunteers

- There were no clinically significant trends in clinical laboratory results, vital sign measurements, or ECG measurements
- No SAEs or serious TEAEs were reported
- The most frequently reported TEAE overall was headache
- The incidence of headache increased with the dose level
- This safety and tolerability profile is highly consistent with that of the historical Debio 1452 data (>200 patients)

Conclusions

- Debio 1450 was rapidly converted in humans to the active metabolite Debio 1452
- Debio 1452 showed linear PK and appropriate half-lives
- Debio 1450 was well tolerated with a safety profile consistent with Debio 1452
- These data highly support the continued development of Debio 1450 as a safe and effective therapeutic for serious staphylococcal infections