RESULTS FROM A PHASE 2 CLINICAL TRIAL FOR TREATMENT OF BONE AND JOINT INFECTIONS WITH AFABICIN, A FIRST-IN-CLASS SELECTIVE ANTI-STAPHYLOCOCCAL ANTIBIOTIC

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ABSTRACT

Background: Staphylococci are the most common causative pathogens in bone and joint infections (BJI). Treatment for BJI is a major clinical challenge, with recurrent and persistent infections occurring in 40% of patients. Afabicin is the most advanced FabI inhibitor in clinical development and has the potential to be the first microbiome-sparing anti-staphylococcal antibiotic. [1] Currently, a Phase 2 trial in BJI is enrolling patients to be treated for 3-6 weeks with afabicin or standard of care (SoC). Results of the first cohort of part B in this study (2-3 weeks treatment) are presented here.

Methods: In an ongoing multicenter, open-label, Phase 2 study, the safety, tolerability, and efficacy of afabicin was compared to those of SoC, in the treatment of patients with BJI. Patients with osteomyelitis, septic arthritis, or prosthetic joint infections were randomized (5 afabicin: 1 SoC) to receive IV and oral treatment for 14 to 21 days. Afabicin treatment (55 mg IV/ 80 mg PO BID) was compared to pre-defined SoC treatments.

Results: Twenty patients were included in microbiological intent-to-treat [mITT] population and were treated for up to 21 days with afabicin or SoC (17 afabicin and 3 SoC).
The mean treatment duration was 20.1 days for afabicin and 19.7 days for SoC. Overall, osteomyelitis was the most common diagnosis (85%). The most frequent baseline pathogen was *Staphylococcus aureus* (19 patients), and 18 patients had methicillin-susceptible *S. aureus*. All 20 patients were treatment responders at End of Treatment (EoT) visit. The clinical response at 4 weeks post EoT was 13 of 15 patients in the afabicin arm, consistent with patient exposure being above PK/PD targets derived from non-clinical modeling. All 3 patients in the SoC arm achieved clinical response at 4 weeks post EoT. At 12 weeks post EoT, the clinical response rate was 13 of 15 patients in the afabicin arm and 2 of 3 patients in the SoC arm. A similar safety profile was observed in the afabicin arm versus SoC arm.

Conclusions: The clinical response rate and safety profile of 2-3 weeks treatment of staphylococcal BJI with afabicin was comparable to SoC. These data support exploring longer durations of treatment in the study. Additionally, the impact of afabicin on BJI patient's gut microbiota will be explored.

INTRODUCTION

Staphylococcal infections are a significant global concern for multiple reasons, as methicillin-resistant *Staphylococcus aureus* (MRSA) contributes considerably to antimicrobial resistance (AMR)-related mortality, and the increasing frequency of coagulase negative staphylococci (CoNS) are associated with inserted foreign bodies infections. [2] In addition, the lack of well-established anti-staphylococcal oral treatment options for infections that require long-term antibiotic therapy, such as BJI, further contributes to this world-wide problem.

Afabicin (Debio 1450) is a first-in-class prodrug inhibitor of FabI, an essential enzyme in bacterial fatty acid biosynthesis (Fig. 1) for oral and parenteral use. [3] Whilst the prodrug, afabicin, has no antimicrobial activity, the active moiety afabicin desphosphono (Debio 1452, formerly AFN-1252) has potent activity against staphylococci including both coagulase- positive and coagulase-negative strains resistant to other antibiotic classes, but very limited activity against non- staphylococcal species. [1]

In contrast to oral treatment with clindamycin, linezolid or moxifloxacin, oral treatment with afabicin preserves the gut microbiota in mice and healthy subjects [1]. This may present relevant clinical advantages with important consequences for healthcare-associated infections and public health, e.g., potentially reducing susceptibility to *Clostridium difficile* infections and decreased risk of gut colonization with potential pathogens, including multi drug-resistant bacteria. [4]

The safety, efficacy and pharmacokinetics (PK) of afabicin are evaluated in an ongoing two-part Phase 2 trial in patients with BJI. Here we present results from the first cohort of Part B of the trial, where participants were treated for up to 21 days with afabicin or SoC.

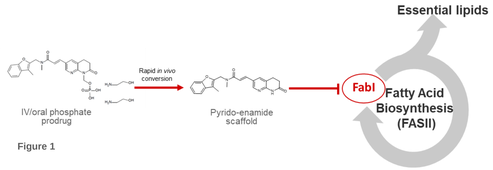


Figure 1

METHODS

Trial design:

Debio 1450-BJI-205 is an ongoing, interventional, randomized, multicenter, open-label, active-controlled study of afabicin for the treatment of patients with BJI due to *S. aureus* (both [MSSA] and [MRSA]) and/or CoNS. In part B of the study, patients with osteomyelitis, septic arthritis, or prosthetic joint infections (PJI) are randomized to receive afabicin or SoC (5:1) for 2-3 weeks in Cohort 1, and for 3-6 weeks in Cohort 2 (Figure 2).

Trial Objectives:

Primary objective

To assess the safety and tolerability of afabicin in the treatment of patients with BJI (septic arthritis, osteomyelitis, F) due to *S. aureus* (both MSSA and MRSA) and/or CoNS and to compare it to SoC.

Secondary objective

To assess the efficacy of afabicin in the treatment of patients with BJI due to *S. aureus* (both MSSA and MRSA) and/or CoNS.

Exploratory objective (selection)

To describe the PK profile in afabicin-treated patients

Trial Population:

Adult patients with a confirmed infection due to *S. aureus* and/or CoNS of the bone or joint, namely septic arthritis, osteomyelitis, or PJI.

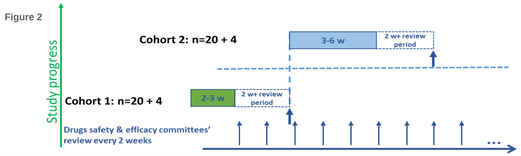
Study Treatments:

Afabicin: Patients are treated with afabicin IV at a dose of 55 mg BID for a minimum of 1 day and up to a maximum of 14 days, followed by a switch to oral afabicin at a dose of 80 mg BID for the remaining treatment duration. The switch from IV to oral therapy is made if the acute toxicity of the infection has resolved, the patient is tolerating fluids and a regular diet, and/or the Investigator determines that the patient no longer needs IV antibiotic therapy.

Standard of Care: Investigator's choice from pre-specified recommended options (IV: cefazolin, vancomycin, linezolid, or clindamycin, Oral: linezolid or clindamycin). The SoC is administered in accordance with the approved regional labelling.

Short term empiric treatment prior study treatment was allowed.

Figure 2



RESULTS

Primary diagnosis

Primary diagnosis: mITT population	Afabicin (N=17) n (%)	Standard of Care (N=3) n (%)
Osteomyelitis	14 (82.4)	3 (100)
Septic Arthritis	3 (17.6)	0 (0)

Duration of treatment

Duration of treatment (days): mITT population	Afabicin (N=17) Mean (SD)	Standard of Care (N=3) Mean (SD)
Total Duration (IV & oral)	20.1 (1.54)	19.7 (3.06)
• IV Treatment Duration	8.1 (3.02)	11.7 (4.04)
• Oral Treatment Duration	12.0 (3.08)	8.0 (1.00)

Key Safety

Number of Subjects with at least one: Safety population	Afabicin (N=18) n (%)	Standard of Care (N=4) n (%)
TEAE	10 (55.6)	2 (50.0)
Treatment Related TEAE	0	0
SAE	3 (16.7)	1 (25.0)
Treatment Related Serious TEAE	0	0
TEAE with Fatal Outcome	0	0
TEAE leading to:		
Drug Interrupted	0	0
Drug Withdrawn	0	0

N = Number of subjects in population; n = Count; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event; % = Percentage Source: Debiopharm data on file

- **55.6% of patients in afabicin arm had at least one TEAE**
- **No treatment-related TEAE**
- **All TEAEs resolved spontaneously**
- **No treatment-related SAE**
- **Four patients with unrelated SAEs (3/18 on afabicin, 1/4 on SoC)**
- **No clinically relevant laboratory abnormalities (hematology, clinical chemistry, liver enzymes, coagulation tests)**
- **No significant ECG abnormalities**

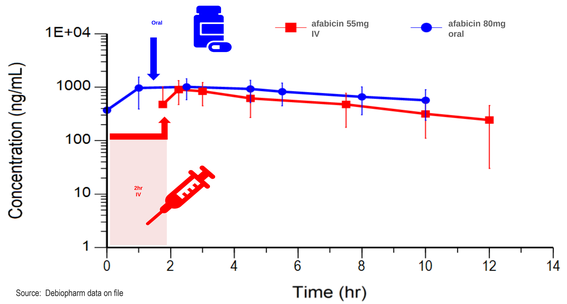
Key Efficacy

Treatment response at:	Afabicin (N=17) n (%)	Standard of Care (N=3) n (%)
EOT	17/17 (100%)	3/3 (100%)
4 weeks post-EOT	13/15 (86.7%)	3/3 (100%)
12 weeks post-EOT (END OF STUDY)	13/15 (86.7%)	2/3 (66.7%)
Isolated causative pathogens • *S. aureus:* (n=19 MSSA) • CoNS (n=1, *S. haemolyticus, randomized to afabicin)*		

CoNS, coagulase-negative staphylococci; EOT, end of treatment; mITT, microbiological intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus* Source: Debiopharm data on file

- **The mITT population consisted of 20 (17 afabicin and 3 SoC) of the 22 enrolled patients, as two patients were not eligible for the efficacy analysis, one in each treatment arm**
- **The clinical response rate of 2-3 weeks treatment of staphylococcal BJI with afabicin was comparable to SoC**
  - **Treatment response was based on the improvement of disease-specific signs and symptoms and absence of complications attributable to the initial infection**

PK profile of afabicin desphosphono following administration of afabicin 55 mg IV BID (Day 1) and 80 mg PO BID (EOT)



Source: Debiopharm data on file

Afabicin desphosphono PK, PK/PD parameters	Day 1 (IV)			EOT (PO)		
	AUC_{0-12} (ng.h/mL)	fAUC/MIC	C_{max} (ng/mL)	AUC_{τ} (ng.h/mL)	fAUC/MIC	$C_{max,ss}$ (ng/mL)
Geomean (CV%)	6390 (48%)	40.8 (73%)	930 (14%)	9490 (55%)	65.7 (109%)	1180 (44%)
n	15	14	15	13	13	13

AUC_{0-12}= area under the curve from time 0 to 12 h; AUC_{τ} = area under the curve during a dosing interval at steady-state; *f*AUC/MIC = area under the curve from time 0 to 24 h, for free drug concentrations over minimal inhibitory concentration ratio; BID = twice daily; C_{max} = maximal observed plasma concentration; $C_{max,ss}$ = C_{max} at steady-state; CV% = geometric coefficient of variation; EOT = end of treatment (i.e., Day 15 to Day 21); Geomean = geometric mean; IV = intravenously; PD = pharmacodynamic; PK = pharmacokinetic; PO = orally; *n*: number of participants. Source: Debiopharm data on file

- **After both IV and oral administrations, afabicin was rapidly converted into its active moiety afabicin desphosphono**
- **Plasma exposure after the first 55 mg IV dose and multiple 80 mg BID oral doses were comparable, indicating good oral bioavailability and rapid steady-state**
- **In all patients, the PK/PD index (*f*AUC/MIC) was above the PK/PD target (2-log kill) established in a non-clinical model (See Poster P-1229 for full details)**

CONCLUSIONS AND PERSPECTIVES

- **Afabicin dosing regimen of 55 mg IV BID / 80 mg PO BID for up to 3 weeks was well tolerated. The safety results in the afabicin arm were similar to those in the SoC arm.**
- **All patients treated with afabicin were responders at EOT.**
- **These results suggest that afabicin could be used effectively in clinical practice for treatment of BJIs caused by staphylococci.**
- **Afabicin offers IV to oral switch option with adequate target attainment against staphylococci.**
- **The presented results supported initiation of Cohort 2, which is currently ongoing with the treatment duration of 3-6 weeks.**
- **The impact of afabicin on BJI patient's gut microbiota is also being explored in Cohort 2.**

References and Acknowledgment

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