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CLINICAL OUTCOME OF AFABICIN IN BONE AND JOINT INFECTIONS: EFFICACY AND SAFETY FINDINGS FROM A PHASE 2 TRIAL OF A NOVEL ANTI-STAPHYLOCOCCAL AGENT

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ABSTRACT

Background: Staphylococci are the leading pathogens in bone and joint infections (BJI), which remain clinically challenging due to high recurrence rates (~40%). Afabicin, a FabI inhibitor with microbiome-sparing properties, is in clinical development as a targeted anti-staphylococcal agent. Results from the first cohort of a Phase 2 BJI trial (2–3 weeks treatment) showed that afabicin achieved clinical response rates comparable to standard of care (SoC) in patients with BJI. These findings are further supported by results from the second cohort (3–6 weeks treatment) presented in this abstract.

Methods: This multicenter, open-label Phase 2 study evaluated the safety, tolerability, and efficacy of afabicin (55 mg IV / 80 mg PO, BID) versus predefined SoC therapies in participants with osteomyelitis, septic arthritis, or prosthetic joint infections. Investigators selected from SoC options which included IV cefazolin, vancomycin, linezolid, or clindamycin, and oral linezolid or clindamycin. SoC treatments were administered per approved regional labelling. In Cohort 2, participants were randomized (5:1) to receive treatment for 21–42 days.

Results: Twenty-six participants (22 afabicin, 4 SoC), with confirmed staphylococcal infection, were included in the microbiological intent-to-treat (mITT) population in Cohort 2. Median treatment duration was 40 days (afabicin) and 38 days (SoC). Osteomyelitis was the most common diagnosis (65%), and *Staphylococcus aureus* was the predominant pathogen (n=21; 18 methicillin-sensitive *S. aureus*). All participants were responders at Day 8. At end of treatment (EOT), 25/26 participants were responders (21/22 afabicin, 4/4 SoC). At 4 and 12 weeks post-EOT, 18/22 afabicin and all SoC participants were responders. No drug-related SAE was reported.

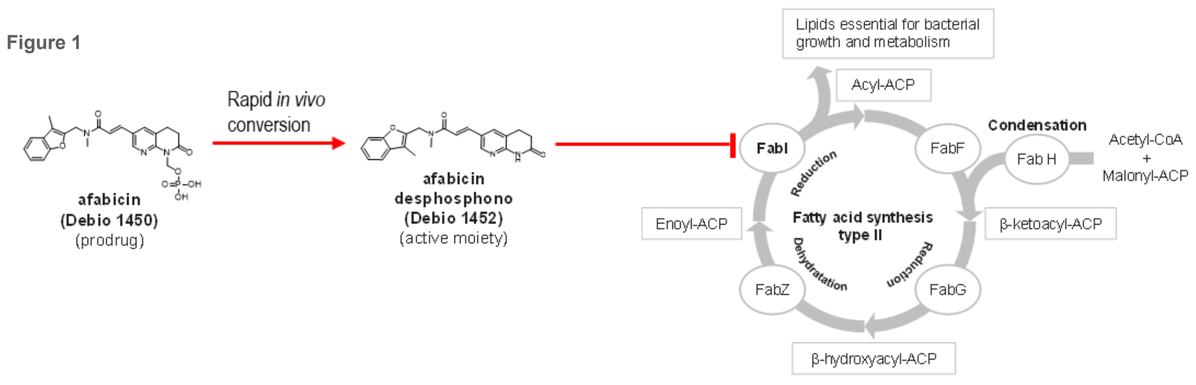
Conclusions: Afabicin offers IV to oral switch option and demonstrated a favorable efficacy and safety profile in participants with staphylococcal BJI treated for 3–6 weeks. These findings support continued clinical development of afabicin for BJI indications.

BACKGROUND

Staphylococcal infections pose a global challenge, with methicillin-resistant *Staphylococcus aureus* (MRSA) contributing significantly to antimicrobial resistance deaths. [1] The shortage of effective oral anti-staphylococcal treatments for long-term cases like BJI exacerbates the issue. Afabicin (Debio 1450) is a novel FabI inhibitor available for oral and parenteral use (Fig. 1). [2] Its active form, afabicin desphosphono, shows strong *in vitro* efficacy against both resistant coagulase-positive (MSSA, MRSA) and coagulase-negative staphylococci (CoNS), but limited action against non-staphylococcal species. [3]

Unlike several other antibiotics, oral treatment with afabicin is associated with preservation of gut microbiota, as shown in mice and in humans,[3] which may help reduce *Clostridioides difficile* infection risk and limit colonization by drug-resistant pathogens.
A completed Phase 2 trial assessed afabicin's safety and effectiveness in BJI patients; here we present the results from the second cohort of the study, in which participants were treated for up to 42 days with afabicin or SoC.

Figure 1



METHODS

Trial design:
Debio 1450-BJI-205 (NCT: 03723551) is an interventional, randomized, multicenter, open-label, active-controlled study of afabicin for the treatment of patients with BJI due to *S. aureus* (MSSA and MRSA) and/or CoNS. In the study, participants with osteomyelitis, septic arthritis, or prosthetic joint infections (PJI) were randomized (5:1) to receive afabicin or SoC for 2-3 weeks in Cohort 1,[4] and for 3-6 weeks in Cohort 2 (Figure 2).

Trial Objectives:
Primary: To assess the safety and tolerability of afabicin in the treatment of patients with BJI (septic arthritis, osteomyelitis, PJI) due to *S. aureus* and/or CoNS and to compare it to SoC.
Secondary: To evaluate the efficacy of afabicin in the treatment of patients with BJI due to *S. aureus* and/or CoNS.

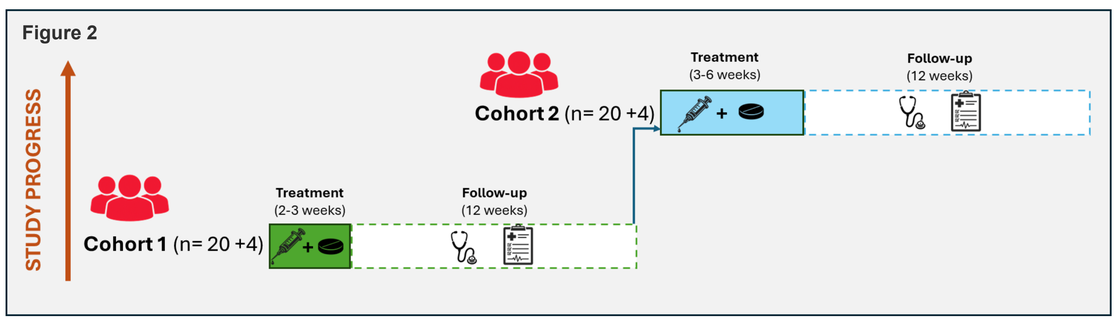
Trial Population:
Adult participants with a confirmed infection of BJI (septic arthritis, osteomyelitis, or PJI) due to *S. aureus* and/or CoNS.

Study Treatments:
Afabicin:
- IV: 55 mg BID for 1–14 days.
- Oral: 80 mg BID for the remaining duration.

Standard of Care (SoC):
Investigator's choice from pre-specified options (IV: cefazolin, vancomycin, linezolid, or clindamycin; Oral: linezolid or clindamycin) administered per regional labeling.
Criteria for switch from IV to oral: Resolution of acute toxicity of infection, tolerance of oral intake, and investigator discretion regarding the cessation of IV therapy.

Short term empiric treatment prior study treatment was allowed.

Figure 2



RESULTS

Primary diagnosis

Primary diagnosis: mITT population	Afabicin (N=22) n (%)	Standard of Care (N=4) n (%)
Osteomyelitis	13 (59.1)	4 (100)
Septic Arthritis	4 (18.2)	0 (0)
Prosthetic Joint Infection	5 (22.7)	0 (0)

N = Number of participants in population; mITT= microbiological intention to treat; n = Count; % = Percentage

Duration of treatment

mITT population	Afabicin (N=22) Median	Standard of Care (N=4) Median
Total Duration in days (IV & oral)	40.0	38.0
• IV Treatment Duration	8.0	9.0
• Oral Treatment Duration	27.5	30.5*

N = Number of participants in population; mITT= microbiological intention to treat
* One participant was given oral cephalexin instead of the pre-defined standard of care per protocol.

Key Safety

Number of participants with at least one:	Afabicin (N=22) n (%)	Standard of Care (N=4) n (%)
TEAE	17 (77.3)	3 (75.0)
Treatment-related TEAE	1* (4.5)	NA
SAE	4 (18.2)	0
Treatment Related Serious TEAE	0	NA
TEAE with Fatal Outcome	1** (4.5)	0
TEAE leading to Treatment Discontinuation	0	0

N = Number of participants in safety population; n = Count; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event; % = Percentage, NA= not applicable as only relatedness to afabicin was evaluated in the study
* Dizziness was reported as afabicin-related TEAE for 1 participant.
** Not considered related to afabicin treatment

- **TEAE incidence was similar in both treatment arms**
- **All TEAEs resolved spontaneously**
- **No treatment-related SAE**
- **No treatment-related death**
- **No TEAE led to study drug discontinuation**
- **No clinically relevant laboratory abnormalities** – ***data not shown***
- **No significant ECG abnormalities** – ***data not shown***

Key Efficacy

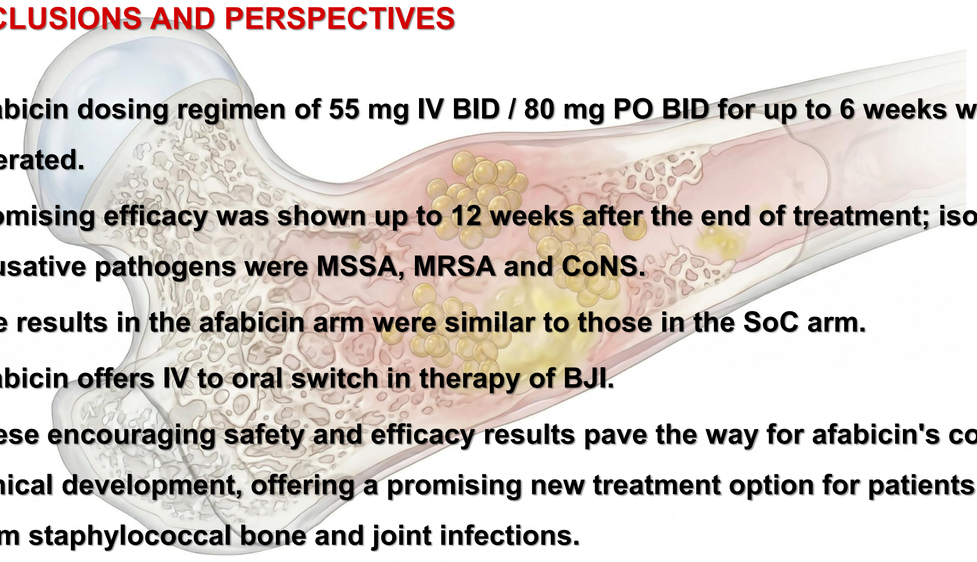
Clinical response at:	Afabicin (N=22) n (%)	Standard of Care (N=4) n (%)
EOT*	21/22 (95.5%)	4/4 (100%)
4 weeks post-EOT*	18/22 (81.8%)	4/4 (100%)
12 weeks post-EOT* (END OF STUDY)	18/22 (81.8%)	4/4 (100%)

Isolated causative pathogens:**
- *S. aureus:* n=21 (randomized to afabicin arm, 17; randomized to SoC arm, 4)
- CoNS: n=9 (randomized to afabicin arm)

N = Number of participants in mITT population; n = Count; CoNS= coagulase-negative staphylococci; EOT= end of treatment
* A strict response definition was applied as missed visits led to classification as non-responders. Response assessment was missing for 1 participant at each time point of 4 weeks post-EOT and 12-weeks post-EOT.
**Some participants may have had more than 1 pathogen at baseline.

- **The mITT population consisted of 26 participants (22 afabicin and 4 SoC)**
- **The clinical response rate of 3-6 weeks treatment of staphylococcal BJI with afabicin was similar to SoC**
  - **Treatment response was based on the improvement of disease-specific signs and symptoms and absence of complications attributable to the initial infection**

CONCLUSIONS AND PERSPECTIVES



- ✓ **Afabicin dosing regimen of 55 mg IV BID / 80 mg PO BID for up to 6 weeks was well tolerated.**
- ✓ **Promising efficacy was shown up to 12 weeks after the end of treatment; isolated causative pathogens were MSSA, MRSA and CoNS.**
- ✓ **The results in the afabicin arm were similar to those in the SoC arm.**
- ✓ **Afabicin offers IV to oral switch in therapy of BJI.**
- ✓ **These encouraging safety and efficacy results pave the way for afabicin's continued clinical development, offering a promising new treatment option for patients suffering from staphylococcal bone and joint infections.**

References and Acknowledgement

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