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Official Title of the Study

Optimization of the surgical and medical management of diabetic foot infections

NCT Number

NCT04081792

Date of this document

30 June 2022

Notification of the second interim analysis of a clinical trial or of a research project BASEC 2019–00778

"Optimization of the surgical and medical management of diabetic foot infections"

1. General study information

BASEC or PB_BASEC ID number	BASEC 2019–00778; ClinicalTrials.gov, NCT04081792
Title of the study	Optimization of the surgical and medical management of diabetic foot infections
Lead Ethics Committee (Swiss EC only)	Zurich
Sponsor	Prof. Dr. med. Ilker Uçkay
Principal Investigator	Dr. med. Felix WA Waibel

Was the study carried out in other countries than Switzerland?	Yes ☐ No X (Swiss study only)
International protocol publication	Waibel F, Berli M, Catanzaro S, Sairanen K, Schöni M, Böni T, Burkhard J, Holy D, Huber T, Bertram M, Läubli K, Frustaci D, Rosskopf A, Botter S, Uçkay I. Optimization of the antibiotic management of diabetic foot infections: protocol for two randomized controlled trials. Trials 2020 21(1):54. doi:10.1186/s13063-019-4006-z.
Context of this 2nd and last interim analysis	According to the study protocol, two interim analyses are foreseen: after the inclusion of the first 40 and 100 patients. The results of the first interim analysis after 20 testing episodes have been presented internally. In May 2022, with 237 episodes achieving the Test-of-Cure state, we perform the 2nd and last interim analysis. The reason for the delay lies in the four different strata of the trials. We waited to have completed a sufficient number of episodes for each stratum in the Per Protocol Populations: Hence this considerable delay of analysis. Nevertheless, the trials have a constant control since the investigators are also part of the treating clinicians' teams of the patients, thus controlling the outcome of the patients and the conduct of the trial

	continuously. Moreover, the second large monitoring event occurred in March 2022, just before this 2nd interim analysis.
Date of 2nd interim analysis	27 May 2022

2. Early termination

Has the study been terminated prematurely?	No X go to section 3. Study duration

3. Study duration

Date: Study start in Switzerland - Study involving persons: Date first patient/ first visit in Switzerland. - Study not involving people: data/sample collection started.	4 September 2019
Date: End of study in Switzerland - Study involving persons: Date last patient / last visit in Switzerland. - Study not involving persons: data/sample collection completed.	Ongoing; scheduled for mid-2023
Study completed?	Yes ☐ No ☒ N/A (Swiss study only)

4. Details on participating center(s)

Number of participating center(s) in Switzerland	
Active open center(s): 1	Balgrist University Hospital

5. Details on recruitment

Number of participants in Switzerland			
Target number: 436	Enrolled: 322	Prematurely terminated (drop-outs): 6	Completed (test-of-cure) 237

If possible, explain any gap between target number and enrolled number of participants	Study ongoing with the half of the patients not having finished the minimal follow-up period, very few dropouts. Recruitment rate: 81%.

6. Final study report (clinical trials only)

Is a summary of the final report on the clinical trial available and enclosed with this form?	Yes No ☒ If No, submit to the (Lead-) Ethics Committee within a year after completion or discontinuation of the clinical trial.

7. Interim results, absence of major biases and provisory non-inferiority assessments

Background: The minimal duration of (post-debridement) antibiotic treatment in diabetic foot infections (DFI) is unknown. Surgeons often exaggerate the antibiotic therapy. We investigate open questions in this field of research in real-life situations of adult, operated DFI patients.

Methods: Single-center, prospective-randomized non-inferiority trials, using a 1:1 randomization and allocating patients into a short or long postoperative antibiotic treatment group. The definition of short and long durations depends on the four stratifications: A) Conservative approach (debridement only) for soft tissue DFIs: 10 versus 20 days of systemic antibiotic therapy. B) Conservative Approach for bone infections (DFO): 3 vs 6 weeks of antibiotic therapy. C) Residual post-amputation soft tissue infection: 1 vs. 4 days of therapy; and D) Residual DFO after partial amputation: 1 vs. 3 weeks of antibiotic treatment. The primary outcome is "Clinical Failure" after a minimal follow-up period of six months, defined as the presence of any problem needing re-intervention. Secondary outcomes are microbiologically-identical recurrences and adverse events related to therapy. Non-inferiority margin is set at 20% for each stratum separately. We compare groups and use a multivariate logistic regression with the outcome "Clinical Failure".

Results: Among 394 DFIs hospitalized between September 2019 and December 2021, we included 318 episodes (inclusion rate 81%). The population of included and non-included DFI episodes was similar for most pathogens, sex and the number of surgical interventions, but non-included patients received less antibiotics because of a more radical surgery (amputation). Among the included cases,

237 episodes completed the Test-of-Cure visit (Per Protocol population), and constitute the base of this 2nd interim analysis (median age 65 years, 27% female patients).

Overall, 40 DFIs (40/237; 17%) failed clinically, and 5 revealed a microbiologically-identical recurrence (2%). A short antibiotic was not significantly associated with a higher failure risk (7/110 vs. 23/127 failures; *p*=0.59). The corresponding stratified results were (5/42 vs. 7/21 failures; *p*=0.04 for a conservative soft tissue treatment (group A); 9/26 vs. 10/42 failures; *p*=0.72 for the conservative DFO therapy (group B); 1/15 vs. 1/28 failures; *p*=0.10) for residual postamputation soft tissue infections (group C); and 2/27 vs. 4/35 failures; *p*=0.69 for residual DFO in the proximal bone stump after amputation (group D).
In multivariate logistic regression analysis, a short antibiotic duration did not influence overall failure rate (odds ratio 0.8, 95% confidence interval 0.4-1.7). Formally, at the stage of this 2nd interim analysis, our results were still underpowered to fulfil all formal requirements of non-inferiority regarding failure (overall 17 difference points [90% confidence interval: 13% to 21%]. In terms of adverse events (of which 3 were severe), cases with short antibiotic regimens yielded as many adverse events than those with a long course (4/110 vs. 4/127 adverse events; *p*=0.84).

Conclusion: In this 2nd interim analysis of our randomized-controlled trials, a shorter period of antibiotic treatment might be noninferior to longer treatment duration in terms of failure of operated DFI, with no obvious difference of adverse events. Other clinical variables are obviously much more determinant of failure than the prescribed antibiotic durations. We passed the halfway and continue all four trials until the completed inclusion of a total 436 DFI and DFO episodes.

8. Signatures of the investigators

I hereby confirm that / confirm that the information given on this declaration is correct and that the trials continue.

Date and place: Zurich, 31 May 2022

Print names: Prof. Dr. med. Ilker UCKAY; Dr. med. Felix WA Waibel

Signatures: