Notification of the second interim analysis of a clinical trial or of a research project BASEC 2019-00646 (24 May 2022)

1. General study information

BASEC or PB_BASEC ID number	2019-00646 ; ClinicalTrials.gov NCT04048304.
Title of the study	Short postsurgical antibiotic therapy for spinal infections: protocol of prospective, randomized, unblinded, noninferiority trials (SASI trials).
Lead Ethics Committee (Swiss EC only)	Zurich
Sponsor	Prof. Dr. med. Ilker Uçkay
Principal Investigator	PD Dr. med. Michael Betz

Was the study carried out in other countries than Switzerland?	Yes ☐ No X (Swiss study only)
International protocol publication	Betz M, Uçkay I, Schüpbach R, Gröber T, Botter SM, Burkhard J, Holy D, Achermann Y, Farshad M. Short postsurgical antibiotic therapy for spinal infections: protocol of prospective, randomized, unblinded, noninferiority trials (SASI trials). Trials. 2020 Feb 6;21(1):144. doi: 10.1186/s13063-020-4047-3.
Context of this 2nd interim analysis	According to the study protocol, three interim analyses are foreseen: after the inclusion of the first 20, 60, and 120 patients. The results of the first interim analysis after 20 testing episodes have been presented internally. Now, with 50 episodes complete and 48 further episodes on way, we anticipate the second interim analysis from the first 60 to the 50 completed cases. Additionally, the writing of this analysis coincidences with the 2nd anniversary of the study start. We write this second interim analysis in the form of a report..
Date of 2nd interim analysis	31 July 2021

Approval by the independent study data committee	24 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.	7 August 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
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): 2	Balgrist University Hospital; Zollikerberg Hospital

5. Details on recruitment

Number of participants in Switzerland			
Target number: 236	Enrolled: 100	Prematurely terminated (drop-outs): 4	Completed (end-of treatment) 50

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, few dropouts

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

Briefly, the trials involves two strata of operates spine infections: with and without remaining infected osteosynthesis material. The 1:1 randomisation allocates half of the eligible patients into a short and a long postoperative antibiotic arm; which are 3 vs. 6 weeks in absence of a residual infected implant; or 6 vs. 12 weeks in case of a remaining infected implant. The study target are 236 infection episodes and non-inferiority is set at a margin of 10%. The minimal follow-up for implant-related infections is 1 year.

7.1. No major inclusion bias

Of 170 potentially eligible patients, 96 (56%) have been included in the study. The population of included and excluded patients are similar regarding key elements of spine infections. The sex, the median number of surgical debridement, the presence of an infected implant, as well as the proportion of key pathogen such as *S. aureus* or Gram-negative germs did not differ between the included and the excluded infections. The only important difference is that excluded patients are treated longer with systemic antibiotics, which is the *raison d'être* of this trial. In other words, participation in these SASI trials reduced the overall duration of antibiotic prescription among the spine infection patients.

7.2. Clinical failures and microbiologically-identical recurrences

The number of clinical failures after the end of treatment are 4 (4/96; 4%), of which two are true microbiological recurrence due to *S. aureus*; occurring in the same patient, who is a formed IV drug addict patient. The other two failures are a secondary endocarditis during treatment and clinical failure without the proof of recurrent pathogens. The number of failures are small and better than most literature reporting the outcome of spine infections.

Intention-To-Treat population	*Short antibiotic arm*	*Long antibiotic arm*
Failures implant-related infections	2/31	0/31
Failures non-implant infections	1/15	1/19
- *of which microbiological recurrences*	*1/15*	*1/19*

7.3. Adverse events

The number of mild, moderate and severe adverse events were equally distributed between the short and long antibiotic arms. For implant-free spine infections, these proportions were 47% vs. 41%. They

were 65% vs. 71% for implant-related infections, when including the mild events. Among all 59 single adverse events, 36 (61%) yielded a link to the antibiotic treatment of various extent.
Most adverse events occurred within three weeks of therapy start. The corresponding differences between the short and long antibiotic arms were all insignificant.

Fatal cases: 1	Serious Adverse Events (SAEs): 6	Serious Adverse Drug Reactions SADRs 2	Suspected Unexpected Serious Adverse Reactions, 0
Have all safety cases been reported to the (Lead-) Ethics Committee within the regulatory timelines?		Yes ☒ No N/A ☐	

7.4. Non-inferiority assessments
In the ultimate Per-Protocol population analysis, and solely for implant-related infections, so far only the outcome "microbiologically-confirmed infectious recurrence" fulfils the statistical non-inferiority requirements (5.6% percentage points [90%CI 9.2% to 9.8%]). Regarding the overall clinical failures or the stratum of implant-free spine infections, the calculations with the available study populations are underpowered. They cannot be definitively assessed by now due to (yet) insufficient follow-up times.

8. Signature of the applicant

I hereby confirm that / confirm that (

- The above information given on this declaration is correct; and

Date and place: Zurich, 24 May 2022

Print names: Prof. Dr. med. Ilker UCKAY; PD Dr. med. Michael Betz

Signatures: