ERGEBNISBERICHT KLINISCHER PRÜFUNGEN NACH § 42b AMG

Sponsor/Company University Hospital Heidelberg represented in law by its Commercial Managing Director Katrin Erk, Im Neuenheimer Feld 672, 69120 Heidelberg on behalf of the Ruprecht-Karls-University Heidelberg, Medical Faculty Heidelberg		*(For National Authority use only)*
Name of finished product Unacid® or generic product		
Name of active ingredient Ampicillin/ Sulbactam 1/0.5g		

Title of study:

APOS study- Antibiotic Prophylaxis for preventing infectious complications in Orthognathic Surgery (APOS)

Principal investigator

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Following trial sites were positively voted by the leading and participating ethic committees, however sites were never initiated and had never enrolled patients:

Universitätsklinikum Frankfurt
Klinik für Mund-Kiefer-und Plastische
Gesichtschirurgie
Theodor-Stern-Kai 7
60596 Frankfurt/Main

Universitätsklinikum Würzburg
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Pleicherwall 2
97070 Würzburg

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Following trial sites were positively voted by the leading and participating ethic committees and were initiated, but had never enrolled patients:

Universitätsmedizin Göttingen
Klinik für Mund-, Kiefer- und Gesichtschirurgie
Robert-Koch-Straße 40
37075 Göttingen

Publication (reference):

Publication of the study protocol: The study protocol was published open access at BMC trials (https://pubmed.ncbi.nlm.nih.gov/34727951/): APOS-antibiotic prophylaxis for preventing infectious complications in orthognathic surgery: study protocol for a phase III, multicentre, randomised, controlled, double blinded, clinical trial with two parallel study arms. Ristow et al.; Trials. 2021 Nov 2;22(1):762. doi: 10.1186/s13063-021-05710-x.

Publication of the Results: The publication of the study results is currently in preparation.

Studied period (years): (date of first enrolment) 07.07.2021 - (date of last completed) 21.05.2024	**Phase of development:** III

Duration of study for each patient

max. 119 days

Study objectives

Primary objective: To demonstrate that no postoperative antibiotic prophylaxis is not inferior to antibiotic prophylaxis with respect to surgical site infections (SSI) in subjects having undergone Orthognathic surgery (OS). The primary hypothesis is that the SSI rate in subjects undergoing OS without antibiotic prophylaxis (no AP) is not clinically relevant higher than in subjects with antibiotic prophylaxis (AP).

Secondary objective: To evaluate further efficacy and subject-oriented parameters of no AP in comparison to AP.

Methodology

This trial was a multicentre, randomised, controlled, double blinded study with two parallel study arms. The trial was planned as non-inferiority trial.

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Number of patients planned and analysed

Planned: 1420

Analysed: 256 randomized (232 in mITT set, 221 in PP set, see below)

The subject recruitment was terminated prematurely. On January 29, 2024, the fourth Data and Safety Monitoring Board Meeting (DSMB) of the APOS study took place. Based on the data at interim, the DSMB Board recommended early termination of the study. With overall slow recruitment strength and clear trends in results, the DSMB Board saw no advantage in further recruitment to obtain more precise rate estimates in the benefit-risk-cost calculation. The Steering Committee of the APOS study decided in a subsequent meeting to follow the recommendation of the DSMB. Therefore, recruitment was stopped with immediate effect and randomization of further patients was no longer possible. Patients who have already been included up to this point were asked to continue treatment and follow-up in accordance with the protocol. The study was deregistered by the authorities and the ethics committees in due time. The database closure was performed on 17th of October, 2024.

Diagnosis and main criteria for inclusion:

Skeletal dysgnathia ICD 10: K07.1, K07.2

Key inclusion criteria:

- Subject scheduled for elective, primary OS (bimaxillary or mandibular only approach)
- Age at study enrolment ≥ 18 years < 65 years of age
- Ability of subject to understand character and individual consequences of the clinical trial
- Subject with basic literacy skills and ability to complete standardised health related questionnaires
- Written informed consent (must be available before enrolment in the study).
- For women with childbearing potential and men capable of reproduction: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods in accordance with CTFG recommendation during treatment period with IMP and for at least one day after the last dose of IMP.

Test product, dose and mode of administration, batch number:

Ampicillin/Sulbactam
Proprietary Name: Unacid® or generic product (ATC code: J01CR21)
Pharmaceutical formulation: Powder (dosage 1/0.5g) Ampicillin/Sulbactam for preparation of infusion solution
Mode of administration: iv infusion 1-1-1
Batch no.: Not uniform (depending on commercial product used)

In case Ampicillin/Sulbactam is not available in the dose of 1/0.5 g (e.g. due to supply shortage), Ampicillin/Sulbactam 2/1 g may be used alternatively for preparation of the infusion.

Reference therapy, dose and mode of administration, batch number:

Placebo: 0,9% sodium chloride (NaCl) solution, 1-1-1 iv.,

Batch no.: Not uniform (depending on commercial product used)

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Duration of treatment:

Treatment started on the day of surgery and ended on POD4. A total of 12 doses was administered to the subjects during treatment phase over a maximum time period of 96 hours. The first dose of study medication was administered postoperatively the latest in the evening of surgery day. On the following three days (POD1, POD2, POD3) subjects received three daily doses with clinical trial medication (dosing interval 6-8 hours or according to manufacturer's instructions). On POD4, subjects received the remaining infusions to have administered a total of 12 doses.

Criteria for evaluation (Efficacy/Safety)

Primary Endpoint:

Occurrence of postoperative SSI as defined by CDC/KISS within 30 days after surgery (POD30).

SSI is the most common and relevant complication after OS and may be associated with subject's discomfort, prolonged hospital stay, increased postoperative morbidity, and higher costs of medical care.

Secondary Endpoints:

1. Deep incisional SSI (A2), organ or space SSI (A3) as defined by CDC/KISS within 90 days after surgery (POD90)
2. Systemic infections, defined as a systemic inflammatory response syndrome associated with a postoperative SSI consecutive to OS
3. Length of hospital stay (LOS), defined as the number of days from the day of OS to the day of discharge
4. Participant's health related quality of life (HRQoL), measured by SF-36 and OHIP-G 14
5. Medication related adverse events, defined as gastrointestinal complications or allergic reactions due to antibiotic administrations

Safety:

Adverse and serious adverse events according to MedDRA coding.

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Statistical methods

The primary endpoint was assessed in a non-inferiority analysis with pre-defined non-inferiority margin to compare the proportion of SSI occurrence (no AP vs. AP) using a Mantel-Haenszel type test for non-inferiority adjusted for centre (grouped) at a one-sided level of $\alpha = 2.5\%$ using the pre-defined non-inferiority margin of $\delta = 4\%$. The primary efficacy analysis was based on the modified intention-to-treat (m-ITT) set including all randomized subjects who postoperatively received at least one dose of study medication (placebo or AP). Missing data for the primary outcome variable were replaced using multiple imputation from a fully conditional specification model with treatment group, location (bimaxillary or mandibular osteotomy), and centre as covariates. At this, the location according to surgery was used throughout the analyses, which may be different from the planned location given in the stratified randomization. The intention to treat principle is preserved as the patient is analyzed in the group as randomized. As such changes in the stratification factor may occur in both directions, effects on balancing and therefore power may be small. As the decision to change the operation plan is done blinded from randomized treatment no bias is introduced. Using the correct stratum/variable enables meaningful subgroup analysis. Centres with less than 50 patients in the mITT set were combined into one category. M = 100 imputations were done. Re-operation within 30 days prior to occurrence of SSI was handled with a hypothetical strategy, i.e., imputation was performed as for regular missing values.

All secondary outcomes were evaluated descriptively together with 95% confidence intervals for the corresponding effects.

The total number of adverse events (AE) and serious adverse events (SAE) during the observation period (starting with first administration of the investigational medicinal product and ending with last visit [i.e. 90 days after surgery/start of treatment]) were reported by group. The rates of patients experiencing at least one AE or SAE during the observation period were calculated per group.

Statistical analyses were performed using the software package SAS version 9.4.

Results: Study population and compliance with treatment

Nine patients in the AP and fifteen patients in the noAP group did not receive the allocated intervention at all. These patients are excluded from the primary analysis (modified intention to treat set, see Appendix 1). Therefore, the primary analysis set, the mITT set, consists of 119 patients in the AP group and 113 patients in the noAP group.

In the mITT set, 85.7% and 83.2% of patients received all twelve infusions in the AP and noAP group respectively. Less than 6 infusions were defined to be a major/relevant protocol deviation. This only applies to 2 and 3 patients, respectively.

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Results: Efficacy

In the mITT set, the primary endpoint occurred in 8.4% of patients in the AP group and in 24.2% in the noAP group. The risk difference is 0.160 (p-value 0.991, corresponding 95% CI: 0.060; 0.260). Sensitivity analyses show similar results proving robustness of the primary result.

Contrary to the assumptions at planning stage, the results are convincing in favor of AP with considerably less SSIs after OS in the AP group than in the no AP / placebo group. The lower limit of the 95% CI of the risk difference (2.5% one-sided) is above the non-inferiority margin of 0.04, proving inferiority of noAP vs. AP (in other words: superiority of AP over noAP).

Till POD 90, a SSI of grade A2 or A3 was observed in 6 and 10 patients in the AP and noAP group, respectively. Of these, only one SSI had grade A3, in the AP group. No systemic infection occurred.

Length of hospital stay was between 3 and 11 days with a mean value of 4.9 +/- 1.1 days in the AP group and 4.7 +/- 1.0 in the noAP group (mean difference -0.1, 95% CI: -0.4; 0.1).

The change in the SF-36 Mental component summary scale from baseline to POD 30 is in mean -0.18 +/- 9.69 in the AP group and 0.55 +/- 9.38 in the noAP group (mean difference 0.73, 95% CI -2.04; 3.50). The change in the SF-36 Physical component summary scale from baseline to POD 30 is in mean -8.18 +/- 8.73 in the AP group and -7.78 +/- 8.52 in the noAP group (mean difference 0.39, 95% CI: -2.11; 2.90).

The change in the OHIPG-14 from baseline to POD 30 is in mean -10.32 +/- 11.62 and -11.74 +/- 10.99 in the AP and noAP group, respectively, with mean difference of -1.42 (95% CI: -4.81; 1.97).

Medication related adverse events within 30 days after surgery were observed in 12 and 9 patients in the AP and noAP group, respectively. Thereof, 8 and 7 were gastrointestinal complications and 4 and 2 were allergic reactions in the AP and noAP group.

Results: Safety

All patients of the mITT set received at least one dose of study medication and are therefore in the safety set.

The number and proportion of patients in each group experiencing at least one AE of the respective type were reported. Only preferred terms (PT) that have occurred at least 5 times in total are shown in the table below. (S)AEs can be categorized into more than one PT. All SSIs were documented as AE and are included in the results described below.

A total of 96 patients experienced at least one AE in the observation period (42/35.3% in the AP group, 54/47.8% in the noAP group). While mild AEs happened were more common in the AP group (33/27.7% in the AP group, 46/40.7% in the noAP group), AEs with grade moderate or severe occurred slightly more often in the AP group (moderate: 18/15.1% patients in the AP group, 15/13.3% patients in the noAP group, severe: 3/2.5% patients in the AP group, no patient in the noAP group).

SAEs occurred rarely overall (2/1.7% patients in the AP group, 4/3.5% in the noAP group experienced one SAE) and were all resolved.

	AP (n=119)	**noAP (n=113)**	**Total**
Intensity			
- mild	33 (27.7%)	46 (40.7%)	79 (34.1%)
- moderate	18 (15.1%)	15 (13.3%)	33 (14.2%)
- severe	3 (2.5%)	0 (0.0%)	3 (1.3%)
Relationship to study drug			
- related	6 (5.0%)	9 (8.0%)	15 (6.5%)
- not related	39 (32.8%)	44 (38.9%)	83 (35.8%)
- missing	1 (0.8%)	3 (2.7%)	4 (1.7%)
System Organ Class			
- Cardiac disorders	0 (0.0%)	1 (0.9%)	1 (0.4%)
- Ear and labyrinth disorders	0 (0.0%)	2 (1.8%)	2 (0.9%)
- Gastrointestinal disorders	16 (13.4%)	14 (12.4%)	30 (12.9%)
- General disorders and administration site conditions	10 (8.4%)	7 (6.2%)	17 (7.3%)
- Hepatobiliary disorders	1 (0.8%)	0 (0.0%)	1 (0.4%)
- Immune system disorders	1 (0.8%)	0 (0.0%)	1 (0.4%)
- Infections and infestations	16 (13.4%)	32 (28.3%)	48 (20.7%)
- Injury, poisoning and procedural complications	5 (4.2%)	7 (6.2%)	12 (5.2%)
- Metabolism and nutrition disorders	2 (1.7%)	0 (0.0%)	2 (0.9%)
- Musculoskeletal and connective tissue disorders	3 (2.5%)	3 (2.7%)	6 (2.6%)
- Nervous system disorders	1 (0.8%)	0 (0.0%)	1 (0.4%)
- Product issues	2 (1.7%)	1 (0.9%)	3 (1.3%)
- Psychiatric disorders	1 (0.8%)	0 (0.0%)	1 (0.4%)
- Renal and urinary disorders	0 (0.0%)	1 (0.9%)	1 (0.4%)
- Respiratory, thoracic and mediastinal disorders	4 (3.4%)	2 (1.8%)	6 (2.6%)
- Skin and subcutaneous tissue disorders	6 (5.0%)	3 (2.7%)	9 (3.9%)
- Surgical and medical procedures	1 (0.8%)	0 (0.0%)	1 (0.4%)
- Vascular disorders	0 (0.0%)	2 (1.8%)	2 (0.9%)
Preferred Term			
- Constipation	2 (1.7%)	3 (2.7%)	5 (2.2%)
- Diarrhoea	6 (5.0%)	6 (5.3%)	12 (5.2%)
- Nausea	4 (3.4%)	6 (5.3%)	10 (4.3%)
- Postoperative wound infection	7 (5.9%)	26 (23.0%)	33 (14.2%)

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- Purulent discharge	1 (0.8%)	4 (3.5%)	5 (2.2%)
- Rash	3 (2.5%)	2 (1.8%)	5 (2.2%)
- Swelling face	4 (3.4%)	3 (2.7%)	7 (3.0%)

Summary and Conclusions

As definitive treatment guidelines are still lacking, many surgeons continue to use postoperative broad-spectrum antibiotics, causing not only increased costs but also contributing to the potential for antibiotic resistance. Especially in orthognathic surgery (OS) there is no current consensus regarding antibiotic prophylaxis (AP). While perioperative antibiotic prophylaxis is the evidence-based standard for preventing postsurgical infections, no evidence supports the use of prolonged postoperative prophylactic antibiotics. Hence, there was an urgent need for an appropriately designed prospective clinical trial, comparing treatment without postoperative AP to treatment with postoperative AP after OS. As a highly standardised procedure on an exceeding homogenous study population and identical processes all over the world, elective OS provides comparable intervention groups with balanced baseline characteristics, comparable surgical duration, even when performed within multiple centres. Therefore, evaluating AP after OS was expected to be of high scientific value representable for other surgical clean-contaminated procedures.

The APOS study (Antibiotic Prophylaxis for preventing infectious complications in Orthognathic Surgery) was designed as multicentre, randomised, controlled, double-blinded clinical trial with two parallel study arms to demonstrate that no postoperative AP (intervention/noAP group) is not inferior to AP (control/AP group) with respect to surgical site infections (SSI) in patients having undergone OS. The primary efficacy endpoint was defined as the occurrence of postoperative SSI within 30 days of surgery. Secondary endpoints were further efficacy and subject-oriented outcomes within 90 days after surgery. The entire trial was initially planned for 54 months, with an enrolment of 1420 patients within 39 months.

Of the originally planned 14 centers, only 8 met the necessary criteria for ethical approval, of which 7 centers then participated in the active recruitment of patients. After 36 months with overall slow recruitment (FPI June 2021), the data safety and monitoring board (DSMB) recommended in their 4th meeting January 2024 to stop the APOS study. The decision was based on an interim analysis on data available at this time point (performed by an independent biometrician). The DSMB concluded from the data that the study question had been answered, and further recruitment of additional patients would not result in any improved precision. Furthermore, the DSMB believed that the clear study results should be published earlier therefore being advantageous for both experts and the patient group. Following this recommendation, recruitment was prematurely stopped (LPO May 2024).

After assessment for eligibility of n=300 patients over all participating centres, n=256 patients met the inclusion criteria and were randomized (AP group n=128; noAP group n=128). After intervention and follow up, n=119 patients for the AP group and n=113 patients for the noAP group were included in the primary analysis (mITT set). Baseline characteristic were equally distributed for both groups throughout all centres. The results of the primary endpoint (SSI within 30 days after surgery) showed a clinically relevant difference between the two groups in favour of the AP group (8.4% vs. 24.4% in the AP vs. no AP group; difference in proportions 0.160 [95% CI: 0.060; 0.260], based on multiple imputed data). This shows no significant p-value (p=0.991) and hence non-inferiority is (statistically) not shown.

In contrast to the initial study hypothesis, the results of this study show that the sole perioperative administration of AB in OS is not sufficient to prevent postoperative SSI. The results are convincing in favor of AP with considerably less SSIs after OS in the AP group than in the no AP /placebo group. As clean-contaminated procedure with direct communication of surgically mobilised osseous segments into the oral and/or nasal cavity as well as the maxillary sinuses combined with the insertion of osteosynthesis material might provide the basic rationale for these results.

The risk of a postoperative SSI not only jeopardizes the success of the surgical procedure as it can lead to increased bacterial infection of the osteosynthesis material, but also might have an indirect influence on patient-oriented outcome measures such as patient's discomfort, prolonged hospital-stay and increases postoperative morbidity, thus, the cost of medical care. This study is the first prospective phase III, multicentre, randomised, controlled, double blinded, clinical trial with two parallel study arms with a high level of evidence. The results can support clear recommendations regarding prolonged AB therapy after OS in the future.

DATE OF REPORT:

List of Amendments

Initial/amended document(s)	Date of approval of competent authority (BfArM) and date of vote of IEC	Comment/short description of reason of amendment/change of trial conduct/measures taken
Initial protocol version 02 (10.02.2021) and corresponding ICF (V02, 18.02.2021)	BfArM: 25.02.2021 IEC: 03.03.2021	-
Protocol version 03 (25.02.2021) and corresponding ICF (V03, 08.03.2021)	BfArM: 17.03.2021 IEC: 30.03.2021	Conditions of the authority were fulfilled: Observation and documentation of adverse events until patients' last visit (POD90).

Stop of Recruitment: 19.02.2024

Appendix 1: CONSORT Flow Diagram