STUDY PROTOCOL

Version 1.4, 28-02-2014

Confidential

Title of the Study

Continuous wound infiltration after hallux valgus surgery

Abbreviated Designation

CWI-HVS

Study Design

Prospective, randomized, double-blind and placebo-controlled

Sponsor

Medical University of Innsbruck

as representative: Univ. Prof. Dr. Martin Krismer

Innrain 52, Christoph-Probst-Platz

6020 Innsbruck

Austria

Study protocol code of the sponsor CWI-HVS

EudraCT Number 2013-005106-64

SPONSOR OF THE STUDY

Confidentiality

The information provided in this protocol is strictly confidential and is made available to the principal investigators, potential principal investigators, health authorities, and ethics committees for inspection and/or review. It is prohibited to publish any information without prior written consent. Exempted herefrom shall be the act of obtaining a declaration of consent from a potential study participant. After execution, the regulations set out in this protocol shall be binding on all parties.

Declaration of the sponsor

The present study protocol has undergone critical review. The content is in accordance with the current risk/benefit assessment of the described methods as well as with the moral, ethical and scientific principles of Good Clinical Practice, the Declaration of Helsinki in its latest version and with local laws and ordinances.

PD Dr. Rainer Biedermann *Principal Investigator of the Study*	Place, Date, Signature
Univ. Prof. Dr. Krismer Martin *Head of Organizational Unit* *Representative of the Medical University of Innsbruck*	Place, Date, Signature

The signatories mentioned above confirm that they have read the present study protocol and confirm that the study protocol contains all information necessary for conducting the study. Moreover, they confirm to conduct the study according to the present study protocol. It is agreed that any information previously not published shall be subject to strict confidentiality.

SIGNATURES

Trial Product: Ropinaest® (ropivacaine hydrochloride) 2mg/ml amp. 10ml/-20ml injection solution

Study Title: Continuous wound infiltration after hallux valgus surgery

Abbreviated Title: CWI-HVS

EudraCT Number: 2013-005106-64

Declaration of the biometrician, the study coordinator and the responsible monitor:

I have read this study protocol and I agree with the content of this study protocol. I confirm that it contains all information necessary for conducting the study. I agree to conduct the study pursuant to the provisions set out in this protocol. In particular, I will comply with the moral, ethical and scientific principles of Good Clinical Practice (GCP), the Declaration of Helsinki in its latest version, the local laws and regulations as well as with the relevant regulatory requirements.

I will immediately indicate any changes to the responsibility of each of the signatories.

I confirm that I will treat with strictest confidentiality all information and documents which have not yet been published in advance. These documents include the study protocol, the Investigator's Brochure, case report forms and other scientific data.

Mag. Dennis Huber *Biometrician* Place, Date, Signature
PD Dr. Rainer Biedermann *Study Coordinator* Place, Date, Signature
Dr. Braito Inge *Responsible Monitor* Place, Date, Signature

SIGNATURES

Investigational Product: Ropinaest® (ropivacaine hydrochloride) 2mg/ml amp. 10ml/-20ml injection solution

Study Title: Continuous wound infiltration after hallux valgus surgery

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EudraCT Number: 2013-005106-64

Declaration of the center-specific principal investigator:

I have read this study protocol and I confirm that it contains all information necessary for conducting the study. I agree to conduct the study pursuant to the provisions set out in this protocol. In particular, I will comply with the moral, ethical and scientific principles of Good Clinical Practice (GCP), the Declaration of Helsinki in its latest version, the local laws and regulations as well as with the relevant regulatory requirements.

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Place, Date	Name in capital letters
	Signature

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List of abbreviations

AE	Adverse Event
AMG	Medicinal Products Act (Arzneimittelgesetz)
AR	Adverse Reaction
BASG	Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen)
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GCP	Good Clinical Practice
GZGG	Hallux Metatarsophalangeal Joint (Großzehengrundgelenk)
i. v.	intravenous
ICH	International Conference on Harmonization
ISF	Investigator Site File
KKS	Coordination Center for Clinical Studies (Koordinierungszentrum für Klinische Studien)
LPLV	Last patient last visit
NA	not applicable
ND	not done
p. o.	per os
ROM	Range of motion
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Statistical Analysis System
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UAR	Unexpected Adverse Reaction
VRS	Verbal Rating Scale
VPRS	Verbal Pain Rating Scale

Individuals/Institutions involved

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Synopsis

Sponsor	Medical University of Innsbruck
Title	Continuous wound infiltration after hallux valgus surgery
Abbreviated Designation	CWI-HVS
Target Population	Patients who undergo hallux valgus surgery.
Study Design	Prospective, Randomized, Double-blind, Placebo-controlled Trial
Study Aims	Primary Study Aim : Proof that there is a significant difference in pain between continuous wound infiltration and placebo during the first 48 postoperative hours. Secondary Study Aim: Proof that there is a significant difference in patient satisfaction and in the amount of rescue medication needed between continuous wound infiltration and placebo during the first 48 postoperative hours.
Study endpoints (dependent variables)	Primary endpoint Average and maximum VPRS (verbal pain rating score) for pain during the first 48 postoperative hours. Secondary endpoints (1) Endpoints related to safety during treatment period: *occurrence of AEs, ARs and UARs.* (2) Endpoints related to effectiveness: *patient satisfaction (VRS), clinical outcome (AOFAS forefoot score, ROM GZGG after 6 weeks), pain (VPRS) after 1, 2 and 6 weeks, need for rescue pain medication*
Number of Patients	50
Schedule	Study-related Recruitment time: 1 Year Planned Start (FPFV): 01-03-2014 Planned Study Completion (LPLV): 06/2017 Patient-related Duration of treatment: 6 weeks
Inclusion Criteria	• Male and female patients over the age of 18 years • Written consent of the patient after information • Patients undergoing a distal metatarsal osteotomy (only Chevron or Scarf) and lateral release of the adductor hallucis muscle with/without concomitant osteotomy of the proximal phalanx of the great toe (Akin) for idiopathic hallux valgus deformity.

Exclusion Criteria	• A history of hypersensitivity / contraindication to one of the drugs administered, their ingredients or to drugs with a similar chemical structure. • Other methods of hallux valgus surgery / additional surgeries than those mentioned. • Neurological disorder that affects the sensorimotor function. • Surgery with general anaesthesia. • Surgery on the same leg within the last month. • Existing pregnancy.
Course of the Study	**See study protocol:** Visit 1 (day 0): admission and consent to study Visit 2 (day 1-3): surgery (day 1) and stay in hospital Visit 3 (day 7 ± 3): 1st outpatient follow-up Visit 4 (day 14 ± 3): 2nd outpatient follow-up Visit 5 (final visit, day 42 ± 7): 3rd outpatient follow-up
Study-related Procedures and Laboratory Examinations	AOFAS forefoot score (1x presurgical and 1x postsurgical), 1x presurgical pregnancy test
Trial Medication	Agent: ropivacaine 0.2 % Trade name: Ropinaest®2 mg/ml Manufacturer: Gebro Pharma GmbH, Fieberbrunn, Austria
Treatment Plan	*Treatment Group:* Trial Medication: ropivacaine 0.2 % Dose: 2 mg/ml Route of Administration: continuous wound infiltration Frequency: 2 ml/h Duration of Therapy: 24 hours *Control Group:* Trial Medication: NaCl 0.9 % Dose: 9 mg/ml Route of Administration: continuous wound infiltration Frequency: 2 ml/h Duration of Therapy: 24 hours

Visit Plan

	1 **Day 0** (Baseline Visit)	**2** **Day 1 - 3**	**3** **Day 7 ± 3**	**4** **Day 14 ± 3**	**XX** **Day 24 ± 7** (Final Visit)
Declaration of consent	√				
Inclusion / Exclusion criteria	√				
Demographic data	√				
AOFAS forefoot score	√				√
ROM GZGG	√				√
Randomization	√				
Laboratory examination of women of childbearing age (pregnancy test)	√				
Trial medication[1]		√ (24 hours)			
VRS pain	√	√ (every 4 hours)	√	√	√
Need for rescue medication		√			
AEs, SAEs and SUSARs		√	√	√	√

[1] Ropinaest® 2 mg/ml or or [sic] NaCl 0.9 % (physiological saline solution) to allow continuous wound infiltration at a rate of 2 ml/h for 24 hours

1 Introduction

1.1 Study background

Hallux valgus surgeries are orthopaedic surgeries which are performed on a frequent basis and which lead to significant pain, in particular within the first 24 postoperative hours. Continuous wound infiltration by means of local anaesthetic in the framework of multi-modal pain therapy has already been tested in many other surgeries (abdominal surgery, shoulder surgeries, hip and knee joint endoprosthetics).

1.2 Need for the study to be conducted

In particular within the first 24 postoperative hours, hallux valgus surgeries lead to significant pain even though NSAR and opiates are routinely administered. In order to further improve pain therapy, a multi-modal pain therapy is necessary. So far, the use of continuous wound infiltration following hallux valgus surgery has not been investigated. In order to prove the effectiveness of continuous wound infiltration by means of a local anaesthetic, the comparison with a placebo group is necessary. The routine use of continuous wound infiltration could further improve postsurgical pain therapy following hallux valgus, and could thus contribute to a higher patient satisfaction.

1.3 Risk/Benefit assessment

So far, other studies have reported no increased rate in local or systemic complications by insertion of a pain catheter and by usage of continuous wound infiltration, even when higher doses of the local anaesthetic were administered. The advantage of the method lies in particular in the local action mechanism with only small effects on the rest of the body.

Ropivacaine is, due to its favourable side effect profile, the local anaesthetic used most frequently for this indication. Possible side effects of ropivacaine include decrease/increase in blood pressure as well as in the heart rate, vertigo, headaches, nausea including vomiting, tingling and fever. Sudden life-threatening allergic reactions are rare and concern 1 to 10 treated persons out of 10000. Further serious side effects, which could be caused by an overdosage of Naropin, include problems when speaking, muscle twitching, trembling, convulsions and loss of consciousness.

Applying the study therapy could result in a reduced need for systemically effective analgesics and in less postsurgical pain. The head of the study deems the risk/benefit ratio favourable.

The study visits will be carried out in the course of the routine clinical follow-up examinations after 1, 2 and 6 weeks. This does not result in any additional risk or any additional stress for the patients.

2 Study aims

2.1 Primary study aim

The aim of this study is to document the effect of a postsurgical continuous wound infiltration in comparison with standard treatment. The average and maximum postsurgical pain during the first 48 postoperative hours was chosen as primary endpoint, which shall be recorded by means of VRS (verbal rating scale) for pain:

The null hypothesis is as follows: during the first 48 hours, there is no significant difference in postsurgical pain between continuous wound infiltration with Ropinaest® and placebo.

The alternative hypothesis is as follows: during the first 48 hours, there is a significant difference in postsurgical pain between continuous wound infiltration with Ropinaest® and placebo.

The significance level is chosen with $p < 0.05$.

2.2 Secondary study aims

The need for rescue pain medication, the patients' satisfaction with surgery and pain therapy (collected by means of VRS) and the clinical outcome (collected by means of AOFAS forefoot score) were defined as parameters of secondary objective. Furthermore, the occurrence of UAEs and AEs is collected. These shall be collected in a purely descriptive manner.

3 Description of the study

3.1 Study design

This is a monocentric, randomized, double-blind, placebo-controlled study.

3.2 Primary endpoint of the study

The average and maximum postsurgical pain during the first 48 postoperative hours was chosen as primary endpoint which shall be recorded by means of VPRS (verbal pain rating scale) for pain.

3.3 Secondary endpoint of the study

The need for rescue pain medication, the patients' satisfaction with surgery and pain therapy (collected by means of VRS) and the clinical outcome (collected by means of AOFAS forefoot score) were defined as parameters of secondary objective. Furthermore, the occurrence of UAEs and AEs as well as the need for rescue pain medication is collected.

3.4 Number of patients

The study includes a total of 50 patients, 25 of which are in the verum group and 25 of which are in the placebo group.

3.5 Schedule

The time needed for recruitment is estimated to be 1 year. Planned start (FPFV) is on 01-03-2014, planned study completion (LPLV) is on 31-06-2017. The duration of treatment including follow-up examination is 6 weeks.

4 Patient population

4.1 Inclusion criteria

- Male and female patients over the age of 18 years
- Written consent of the patient after information
- Patients undergoing a distal metatarsal osteotomy (only Chevron, Scarf) and lateral release of the adductor hallucis muscle with/without concomitant osteotomy of the proximal phalanx of the great toe (Akin) for idiopathic hallux valgus deformity.

4.2 Exclusion criteria

- A history of hypersensitivity / contraindication to one of the drugs administered or to their ingredients or to drugs with a similar chemical structure.
- Other methods of hallux valgus surgery and additional surgeries of the little toes other than those mentioned.
- Neurological disorder that affects the sensory-motor function.
- Refusing to participate in the study or refusal of consent to study.
- Existing pregnancy.
- Surgery on the same leg within the last month.
- Surgeries with general anaesthesia.

5 Trial medication

5.1 Description of trial medication (cf. also specialist information)

- Agent: ropivacaine 0.2 %
- Trade name: Ropinaest® 2 mg/ml

- Manufacturer: Gebro GmbH, 6391 Fieberbrunn, Austria

- Ingredients: The agent is: ropivacaine hydrochloride. Ropinaest® 2 mg/ml contains 2 mg of ropivacaine hydrochloride per ml solution (in the form of ropivacaine hydrochloride 1 H2O). Further components are: sodium chloride, hydrochloric acid and sodium hydroxide for pH regulation, water for the purpose of injection.

- Packaging: Naropin is a clear, colorless solution for injection. 10 ml and 20 ml ampoules of polypropylene in sterile blister packs with 5 pieces or 5x5 pieces (hospital pack).

- Storage: Keep the medicinal product out of the sight and reach of children. The medicinal product may not be used after the expiry date stated on the label and the carton. The expiry date refers to the last day of the indicated month. Do not store at temperatures above 25°C. Do not freeze. Normally, Ropinaest is stored at your doctor's practice or at the hospital. They are also responsible for the quality of the product if it is opened but not immediately used. The medicinal product must be visually inspected before use. The solution shall only be used if it is clear and practically free of particles and if the container is not damaged. They are also responsible for the right disposal of any Ropinaest that has not been used.

- Shelf life: From a microbiological point of view, the product shall be applied immediately after opening. If it is not applied immediately, the user – before using the medicinal product – is responsible for the duration and conditions of storage after opening which, in general, should not exceed 24 hours at 2 – 8°C.

- Precautions, incompatibilities: ropivacaine infusion solution is chemically and physically compatible with: Fentanyl citrate, sufentanil citrate, morphine sulfate, clonidine hydrochloride. From a microbiological point of view, mixtures should be used immediately. If they are not used immediately, the user – before using the medicinal product – is responsible for the duration and conditions of storage after opening which, in general, should not exceed 24 hours at 2 – 8°C.

5.2 List of side effects and interactions

The side-effect profile of ropivacaine is similar to the side-effect profile of other long-acting local anaesthetics of the amide type. Side effects are to be distinguished from physiological effects caused by the block anaesthesia itself (e.g. decrease of blood pressure and bradycardia during spinal/epidural anaesthesia).

Very frequently (> 1/10)

- Angiopathies: hypotension

- Disorders of the gastro-intestinal tract: nausea

Frequently (> 1/100)

- Diseases of the nervous system: headache, paraesthesia, daze Cardiac diseases: bradycardia, tachycardia

- Angiopathies: hypertonia

- Diseases of the gastro-intestinal tract: vomiting[b]

- Diseases of the kidney and urinary tract: urinary retention
- General disorders and administration site conditions: rise in temperature, rigor, back pain

Occasionally (> 1/1000)

- Psychiatric disorders: fearfulness
- Diseases of the nervous system: symptoms of a CNS toxicity (convulsions, grand mal type convulsions, epileptic seizures, daze, perioral paraesthesia, numbness of the tongue, hyperacousis, tinnitus, visual impairment, dysarthria, muscle twitching, tremor)**, hypoesthesia
- Angiopathies: syncope
- Diseases of the respiratory tract, chest and mediastinum: dyspnoea
- General disorders and administration site conditions: hypothermia

Rare (< 1/1000)

- Cardiac diseases: cardiac arrest, cardiac dysrhythmias
- General disorders and administration site conditions: allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

Acute systemic toxicity

Systemic toxic reactions mainly affect the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentrations of a local anaesthetic which may occur following (unintended) intravascular injection, overdosage or unusually quick absorption in highly vascularized areas. CNS reactions are similar in all amide-type local anaesthetics, whereas cardial reactions rather depend on the agent as far as quantity as well as quality are concerned.

CNS toxicity

CNS toxicity reactions occur gradually with signs and symptoms of increasing severity. Early symptoms such as visual and hearing impairments, perioral numbness, vertigo, light dizziness, tingling and paraesthesias are observed. Dysarthria, muscle rigidity and muscle twitching are more severe and may indicate the onset of generalized convulsions. These signs may not be falsely interpreted as neurotic behaviour. Unconsciousness and grand mal may follow which may last from a few seconds to several minutes. During the convulsions, hypoxia and hypercapnia, together with a breathing disturbance, quickly occur due to the increased muscular activity. In severe cases even apnoea may occur. Respiratory and metabolic acidosis increases and prolongs the toxic effects of the local anaesthetics. Improvement occurs after redistribution of the local anaesthetic from the central nervous system and the ensuing metabolism and elimination. Improvement can occur quickly if no great dosages of the medicinal product were injected.

Toxicity to the cardiovascular system

Cardiovascular toxicity proves to be a more serious condition. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of the local anaesthetic. I. v. infusion of ropivacaine in subjects caused a reduction in impulse conduction and

contractility. In general, toxic effects to the cardiovascular system are first manifested with CNS toxicity symptoms, except for when the patient receives general anaesthesia or if he/she is profoundly sedated with substances such as benzodiazepines or barbiturates.

5.3 Placebo, comparator product

- Agent: sodium chloride 0.9 %
- Trade name: physiological saline solution “Fresenius”
- Manufacturer: Fresenius Kabi Austria GmbH Hafnerstraße 36, 8055 Graz, Austria
- Ingredients: the agent is: sodium chloride. The other components are: hydrochloric acid, sodium hydroxide, water for injection purposes.
- Packaging: physiological saline solution “Fresenius” is a clear and colorless infusion solution, available in glass bottles, polyethylene bottles, polypropylene bottes, intravenous bags, vials, polyethylene ampoules and polypropylene ampoules.

5.4 Randomization

Randomization takes place in 2 groups as balanced randomization by means of a computer-generated random number sequence. This random number sequence is generated with the help of the website www.random.org (numbers, random sequence generator). The first 25 results are assigned to the verum group, the other 25 results are assigned to the placebo group. Upon admission to the study, the patients receive at random one of these numbers which are contained in sealed envelopes on which the numbers 1 to 50 are written. The randomization envelope is opened by an independent member of the nursing staff – who is not involved in the further treatment of the patient – several minutes prior to the start of surgery. Such member will fill a 50 ml perfusor syringe with either ropivacaine 0.2 % or physiological saline solution. The patients, surgeons as well as the care-taking nursing staff are blinded as regards the content. The deciphering list will only be opened after conclusion of the last follow-up examination.

5.5 Treatment scheme

5.5.1 Administration instructions

At the end of every patient's surgery, a pain catheter (InfiltraLong Katheter 19G x 420mm, Pajunk Medizintechnologie GmbH) is placed in the surgical wound through which ropivacaine 0.2 % (verum) or NaCl 0.9 % (placebo) is continuously administered at a rate of 2 ml/h during the first 24 postsurgical hours via a syringe pump. The catheter is removed on the following day in the course of the routine change of dressing.

As for standard pain treatment (Non Investigational Medicinal Product, NIMP), the patients receive naproxen 500 mg (Naprobene®, ratiopharm Arzneimittel Vertriebs-GmbH, Wien, Austria) p.o. in the morning and in the evening from day 1 to 8 as well as hydromorphine 2.6 mg (Hydal®, Mundipharma Ges.m.b.H., Austria) p.o. in case of VRS > 3 (every 4 hours at maximum) from day 1 to 3.

5.5.2 Emergency measures

In the unlikely case that an allergic reaction or signs of a systemic toxicity occur(s), the supply of the trial substance is interrupted immediately and emergency treatment in accordance with the responsible doctor is provided.

5.5.3 Concomitant medication

As for standard pain treatment (NIMP), the patients receive naproxen 500 mg (Naprobene®, ratiopharm Arzneimittel Vertriebs-GmbH, Wien, Austria) p.o. in the morning and in the evening as well as hydromorphine 2.6 mg (Hydal®, Mundipharma Ges.m.b.H., Austria) p.o. in case of VRS > 3 (every 4 hours at maximum) in the course of their stay in hospital. After discharge on the 2nd day following surgery, the patient is prescribed naproxen 500 mg 2x each day for 5 days.

5.6 Storing, issuing and taking back as well as documenting the trial medication (drug accountability)

The trial medication is provided by the nursing staff of the pain outpatient department of the University Hospital of Innsbruck. The investigator is responsible for issuing, taking back and documenting the trial medication in the trial center. The trial medication (including the pain catheters used) may only be used in the framework of this study and may not be used after its expiry date. Issuing and taking back the trial medication is documented in the Drug Accountability Log in the investigator site file (identification of patient, date and amount of medication issued). Upon receipt of the trial medication, the patients are to be carefully informed on how to use the trial medication.

5.7 Compliance

The continuous administration of the trial substance is ensured by the syringe pump catheter system and observed by the nursing staff.

5.8 Blinding and emergency envelopes

5.8.1 Blinding

The patients are assigned to one of the 2 treatment groups by means of random, computer-generated numbers which are contained in sealed envelopes on which the numbers 1-50 are written. The envelopes are provided by the investigator. The randomization envelope is opened by an independent member of the nursing staff – who is not involved in the further treatment of the patient – several minutes prior to the start of surgery. Such nursing staff of the pain outpatient department of the University Hospital of Innsbruck prepares the trial substance in a perfusor syringe and hands it over to the surgical nursing staff.

5.8.2 Emergency envelopes

Emergency envelopes for the identification of the trial substance are deposited at the ward's head of the respective care-taking station and are only opened in case of a probable vital threat caused by the trial substance.

5.8.3 Premature unblinding

Unblinding only takes place in case of a vital threat caused by the trial substance.

5.8.4 Regular unblinding

Regular unblinding only takes place after conclusion of the last follow-up examination including documentation.

6 Course of study

See also visit plan. On the day of hospitalization (visit 1, baseline, day 0) for hallux valgus surgery, the measures mentioned under point 6.1 are carried out as part of informing the patient on the surgery. On day 1, hallux valgus surgery is performed under local anaesthesia, at the end of the surgery the pain catheter (InfiltraLong-Katheter 19G x 420mm, Pajunk Medizintechnologie GmbH) is inserted to allow for continuous wound infiltration with ropivacaine 0.2 % or with physiological saline solution. After surgery, the care-taking nursing staff of the respective ward documents the pain level under continuous wound infiltration and standard pain treatment every 4 hours via VRS (visit 2, see point 6.2). On day 2 (first postsurgical day), the pain catheter is removed in the course of the first routine change of dressing during morning visit (approx. 07.30 a.m.). Under standard pain treatment, the care-taking nursing staff continues to document the pain level every 4 hours via VPRS. On day 3 (second postsurgical day), the patient is discharged from hospital. He/she receives a prescription for the intended pain medication as well as further follow-up appointments in 1 (visit 3), 2 (visit 4) and 6 weeks (visit 5). In the course of these outpatient postsurgical follow-ups, the examinations described under points 6.3 to 6.5 are carried out and AEs and SAEs are recorded. Visit 5 (outpatient 6 weeks follow-up) represents the end of the study's follow-up period. After conclusion of the study, the examining doctor decides on further outpatient follow-ups.

6.1 Visit 1 (baseline, day 0)

Prior to admission to the clinical trial, every patient must be informed in detail on the study. Information takes place in person by the treating doctor and in writing by means of the patient information. Only after all questions of the patient have been answered, he/she will be asked to sign two copies of the declaration of consent and to personally date it. Following this, the patient receives a copy of the patient information/declaration of consent; the second copy is kept in the investigator site file.

Upon visit 1, demographic data (age, sex, weight, size, BMI, side) is recorded. Furthermore, physical examination is carried out, including examination of the range of motion (ROM) of the hallux metatarsophalangeal joint (GZGG) as well as assessment of AOFAS forefoot score by means of the "AOFAS Hallux Metatarsophalangeal-Interphalangeal Scale" questionnaire and the average and maximum VPRS. Women of childbearing age undergo laboratory testing to exclude pregnancy. After final examination of the inclusion and exclusion criteria, the patient is admitted to the study, including his admission to one of the two treatment groups according to randomization as explained above.

6.2 Visit 2 (day 1 – 3)

On day 1, hallux valgus surgery is performed under local anaesthesia, at the end of the surgery the pain catheter (InfiltraLong-Katheter 19G x 420mm, Pajunk Medizintechnologie GmbH) is inserted to allow for continuous wound infiltration with ropivacaine 0.2 % or with physiological saline solution. After surgery, the care-taking nursing staff of the respective ward documents the pain level under continuous wound infiltration and standard pain treatment (see point 5.5) every 4 hours via VPRS. On day 2 (first postsurgical day), the pain catheter is removed in the course of the first routine change of dressing during morning visit (approx. 07.30 a.m.). Under standard pain treatment, the care-taking nursing staff continues to document the pain level every 4 hours via VPRS. On day 3 (second postsurgical day), the patient is discharged from hospital. He/she receives a prescription for the intended pain medication as well as further follow-up appointments in 1 (visit 3), 2 (visit 4) and 6 weeks (visit 5). Occurring AEs or SAEs are recorded in the course of the entire hospital stay.

6.3 Visit 3 (day 7 ± 3)

Routine outpatient wound check. Occurring AEs or SAEs, and the maximum and average pain level (VPRS) are documented.

6.4 Visit 4 (day 14 ± 3)

Routine outpatient suture removal. Occurring AEs or SAEs, and the maximum and average pain level (VPRS) are documented.

6.5 Visit 5 (final visit; day 42 ± 7)

Routine outpatient 6 weeks follow-up including x-ray foot in 2 planes. Occurring AEs or SAEs, and the maximum and average pain level (VPRS) are documented. Furthermore, physical examination is carried out, including examination of the range of motion (ROM) of the hallux metatarsophalangeal joint (GZGG) as well as assessment of AOFAS forefoot score by means of the “AOFAS Hallux Metatarsophalangeal-Interphalangeal Scale” questionnaire. Patient satisfaction is collected by means of VRS.

6.6 Follow-up examinations

After conclusion of the study, the examining doctor decides on further outpatient follow-ups.

6.6.1 Assessment of effectiveness

Effectiveness is assessed by the care-taking nursing staff – which is blinded as regards the therapy group – collecting data concerning the VPRS for pain during the patient’s stay in hospital which is repeated every 4 hours. For this, the patient indicates the current pain level on a scale ranging from 0 - 10 (0 meaning no pain, 10 meaning the maximum pain imaginable).

Before surgery and in the course of the postsurgical outpatient follow-ups, the respective care-taking doctor assesses not only the pain level by means of VPRS for pain but also the ROM of the hallux metatarsophalangeal joint. Furthermore, upon visit 1 and 5, AOFAS forefoot score is assessed by means of the „AOFAS Hallux Metatarsophalangeal-Interphalangeal Scale“ question-

naire (see annex) and patient satisfaction is assessed by means of VRS.

6.6.2 Safety assessment

AEs, ARs, UARs and SAEs are recorded during the patient's stay in hospital and during outpatient follow-up examinations. AEs to be expected include in particular wound healing disorders and wound infections.

6.6.3 Radiographic examinations

6 weeks after surgery there is a routine x-ray of the foot in 2 planes in the course of the final follow-up. This is the standard treatment in our department and is thus no examination specific to the study.

6.7 Further treatment of the patients after conclusion of the trial

After conclusion of the study, the examining doctor decides on further outpatient follow-ups.

6.8 Drop-out of patients (drop-out)

Patients may – at any time at their own wish – withdraw from the clinical study prematurely and without giving reasons and without facing any consequences for their future treatment. Furthermore, the investigator may exclude patients from the study for reasons of health risks.

The reason for the patient's drop-out of the study is recorded in the CRF. All patients who drop out of the study have to undergo a final examination (corresponding to visit 5) after 6 weeks, the results of which are documented in the CRF.

6.9 Premature termination of the clinical trial

The sponsor is entitled to prematurely terminate the study due to relevant medical/administrative causes. The reasons for discontinuing the study are documented in detail. Patients who are still under treatment when the trial is cancelled, have to undergo a final examination which is documented in the CRF. If the investigator has ethical concerns regarding the continuation of the study, this has to be reported to the sponsor immediately.

The sponsor is entitled to terminate the clinical trial prematurely, if

- the patient recruitment rate is insufficient,
- serious problems with the quality of the collected data, which cannot be solved, occur,
- unforeseeable circumstances have occurred in the respective trial center which do not allow for the clinical study to be continued,
- early proof is provided that one treatment group is superior or, respectively, inferior to the other treatment group (determined by interim evaluation),
- unjustifiable risks and toxicities have occurred (decision following renewed risk/benefit assessment),
- new scientific findings, which appear when the study is being carried out, do not allow for the study to be continued.

The head of the study may decide on cancelling the study with the sponsor or the protocol committee.

7 Adverse events, adverse reactions

7.1 Definitions

An **Adverse Event (AE)** is any noxious occurrence in a person concerned (study participant) who has been administered an investigational product, and which is not necessarily causally related to this treatment. This may be disorders, clinical signs or symptoms which occur or worsen after the patient has been included in the study.

An **Adverse Reaction (AR)** is any adverse and noxious reaction to an investigational product, regardless of its dose.

An **Unexpected Adverse Reaction (UAR)** is an adverse reaction, the nature or severity of which is not consistent with the available information on the investigational product.

A **Serious Adverse Event (SAE)** or, respectively, **Serious Adverse Reaction (SAR)** is any untoward event or any adverse reaction which

- results in death or
- is life threatening or
- results in persistent or significant disability or incapacity or
- requires inpatient hospitalization or causes prolongation of existing hospitalization or
- results in congenital anomalies or birth defects.

A **suspected unexpected serious adverse reaction** is called **Suspected Unexpected Serious Adverse Reaction (SUSAR)** according to the Clinical Trials Directive (Directive 2001/20/EC).

7.2 Documentation of AEs

All Adverse Events, including intercurrent disorders, are to be documented in the patient's file and subsequently in the CRF.

In case an Adverse Event occurs, the patient is to be observed in any case until the symptoms have disappeared or until the pathological laboratory results have returned to their original values, regardless of the causal relationship between the event and the trial medication. Should a persistent secondary disease result from the Adverse Event, this is to be appropriately documented upon conclusion of the study. All findings and results have to be documented on the respective page for Adverse Events in the patient's file as well as in the CRF. The following information is necessary:

- nature of Adverse Event (sign, symptom or disease)
- differentiation (serious/not serious)
- beginning and end of occurrence
- intensity
- causality to investigational product

- measures as regards the investigational product or actions to restore or ameliorate the patient's well-being.
- outcome of event.

7.3 Documentation of SAEs

For documenting the SAEs, the following points are to be strictly complied with:

- The SAE has to be documented on the respective AE page in the CRF and on the SAE form.
- Every SAE has to be reported, in a way as complete as possible, by the investigator to the sponsor within 24 hours .
- The monitor has to check the investigator's data for completeness and has to ensure that the information included in the SAE report matches the information in the database and in additional data sources.

7.4 Reporting of Adverse Events and Adverse Reactions

All adverse events which occur during the present study which are reported spontaneously or reported after consultation with the doctor or which are observed by the same are to be documented and commented in the case report form. Unexpected adverse events are to be documented in relation to their effect on the risk/benefit situation of the subjects, and are to be reported to the sponsor, to the Clinical Trials Coordination Center (KKS) of the Medical University of Innsbruck as well as to the responsible ethics commission.

Should, from the investigator’s point of view, the adverse event observed, regardless of whether it is serious or not, challenge the continuation of the study, the study is to be suspended immediately. Thereafter, the decisions of the responsible parties (Data Safety Monitoring Board, ethics commission, investigator, sponsor) on how to proceed are to be awaited. If the investigator deems the adverse event not relevant in this regard, the other committees mentioned (ethics commission) are free to order the study to be stopped (subsequently decision on continuation or termination of the study). So, in principle, each of the parties mentioned (investigator, ethics commission, sponsor) may issue a study stop. Within a committee, the regulations on taking decisions internally agreed upon, shall apply.

7.4.1 Definitions

See point 7.1

<u>SUSAR criteria:</u>

- The adverse reaction has to be serious.
- A causal relationship between investigational product and adverse reaction must be suspected.
- The adverse reaction has to be unexpected. The definition of unexpectedness of an event is oriented towards the reference safety information.

7.4.2 Duty to report suspected unexpected serious adverse reactions (SUSARS)

The sponsor must notify the ethics commission as well as the Austrian Federal Office for Safety in Health Care (Bundesamt für Gesundheit und Sicherheit, BASG) on SUSARs (additionally noting them in the respective case report form) by means of the official form (including additional narrative brief description, if available anonymized enclosures such as copy of results of an autopsy, etc., and, in the case of an unexpected serious adverse event, comment on the new up-to-date risk/benefit situation for the subject). Adverse reactions which have occurred as part of the same clinical trial at home or abroad are subject to notification (sec. 41 e of the AMG).

Deadlines for notification:

- In case of death or life-threatening reactions: within seven calendar days at the latest; information on further measures is to be transmitted within an additional time limit of eight days.
- All other SUSARs: immediately after they become known, however, within 15 calendar days at the latest.

The obligation to notify BASG of SUSARs begins once all requirements for conducting the study are met (favourable opinion given by the ethics commission and non-prohibition by BASG). The obligation to notify ends upon completion of the respective study in Austria, provided that the national end of study has been reported to the authority (in an informal letter).

Once a year, the sponsor has to transmit an annual safety report (Development Safety Update Report, DSUR pursuant to ICHE2F) with all suspected serious adverse reactions (SSARs) to BASG and to the ethics commission.

8 Documentation

The investigator is responsible to ensure that the trial is conducted in accordance with the GCP guidelines, AMG as well as the study protocol, and that the data is correctly entered into the CRF. All data collected in this study has to be entered into the CRF by persons authorized to do so. This also applies to data belonging to patients who were excluded from trial.

The investigator notes the participation on a special patient identification list. This list enables a later identification of the patients and contains the patient number, the patient's full name, his/her date of birth, and the date of admission to the clinical trial. The patient identification list remains in the trial center after conclusion of the trial. In addition, the participation of the patient in this clinical trial has to be noted in the patient's file (trial medication, patient number/randomization number, start and end of trial).

Furthermore, it has to be ensured that the person who is responsible for documentation in the CRF can be identified. A list with signature and initials of the persons who may make entries in the CRF will be recorded in the investigator site file (ISF) and in the Trial Master File.

8.1 Case report form (CRF)

Any and all patient data and examination results shall be entered into the CRFs (Case Report Forms) specifically created for this study.

The case report forms may only be completed with a **black ballpoint pen**. Corrections are to be made in such a way that old entries remain legible (it is not allowed to use correction products). Corrections are to be signed and dated by the authorized person who makes the corrections. Data which is not available or which has not been collected, has to be clearly marked as such (NA or ND). The reasons to do so should be documented, if necessary.

The investigator ensures that any and all patients' data is entered into the CRFs immediately, legibly, completely, correctly and in accordance with the patients' files.

The monitor serves the completed original pages after they have been checked for plausibility and completeness on the sponsor; a copy remains with the investigator and is stored for 15 years.

8.2 Investigator site file

An investigator site file is made available to the trial center. The investigator stores all those documents which are required for the clinical trial in this file. As part of the monitoring, the investigator site file is checked for up-to-datedness and completeness according to the regulations. After the study has been concluded or cancelled, the investigator site file is to be stored for 15 years.

8.3 Data storage

8.3.1 Obligation of the sponsor to store data

All essential data relating to the clinical trial has to be stored by the sponsor for a duration of 15 years after completion or cancellation of the clinical trial. The sponsor shall archive the data and documents relevant to the trial pursuant to legal provisions.

8.3.2 Obligation of the investigator to store data

Records and documents relating to testing or issuing trial medication (e.g. case report forms, declarations of consent, lists on the medication distribution and other relevant documents) are to be stored by the investigators for at least 15 years.

The medical charts and other original data shall be stored for the longest possible period that the hospital, the institution or the private practice enables.

9 Monitoring and audit

Monitoring and audits are carried out in the context of the clinical trial for the purpose of quality assurance.

9.1 Monitoring

The investigator agrees that the monitor checks data in order to ensure satisfying data collection and compliance with the study protocol.

Furthermore, the investigator agrees to collaborate with the monitor and provide him, whenever necessary, all necessary information. This includes access to all documents relating to the study, including the originals of the patients' files relevant to the study. The task of the investigator covers ensuring that the patients' files are as complete as possible, i.e. recording information on anamnesis, concomitant diseases, admission to the trial, visitor data, examination results, drug issuing as well as Adverse Events. It shall also be made possible for the monitor to check data as well as to compare it with the relevant patients' files pursuant to the SOPs and the ICH GCP guidelines in the predetermined time intervals in order to ensure compliance with the study protocol and continuous recording of data. For that, all original medical findings which are necessary as a source for the data in the database are checked. By signing the declaration of consent, the patient has agreed to such checking.

Further tasks of the monitor include:

- checking whether the trial center complies with the requirements of the clinical trial (patient population, equipment, storage of study materials, etc.)
- instructing the investigator and the study staff on the clinical trial
- checking the investigator site file for completeness and up-to-datedness
- documenting patient status
- source data verification
- checking the prescribed notification of SAEs
- checking proper and safe storage as well as storage life of the trial medication
- counting the trial medication returned (drug accountability), checking compliance.

The monitor shall treat all information as confidential and shall maintain the patients' fundamental right to integrity and protection of their privacy.

9.2 Audit

In order to guarantee that the trial is conducted pursuant to GCP guidelines, internal (e.g. by the sponsor) and external (e.g. by the authorities) audits may be conducted. The auditor is independent vis-à-vis the employees who are involved in the trial.

During the audit, the following points are checked, amongst others:

- conduction of the trial according to the study protocol
- validity of data
- quality of trial pursuant to GCP guidelines.

Following every external audit, the investigator receives an audit confirmation by the auditor. This confirmation must be kept in the investigator site file in order to have it at disposal in case of an inspection by the authorities. The audit report is transmitted to the study sponsor. At the end of the trial, an audit certificate is enclosed to the final report. In addition, authorities may conduct audits and inspections pursuant to the Austrian Medicinal Product Act.

10 Data entry and data management

Study with paper-based documentation

Data is managed and processed by the data manager by means of the software SPSS Statistics (company IBM, Armonk, New York, USA) and Excel (company Microsoft, Redmond, WA, USA).

Data is validated by the programmed range, validity and consistency checks. Additionally, there is a manual/visual check for medical plausibility pursuant to the requirements of GCP. If necessary, queries may occur which are to be transmitted to the respective trial center on special forms. On the basis of the forms, the investigator has to review and answer those discrepancies. These forms are then returned to data management where those discrepancies are corrected in the database accordingly. The forms are stored together with the case report form at the trial center and by data management.

Upon study completion, the database is closed after all entries have been entered and all queries have been resolved. This process is documented.

11 Statistics

11.1 Sample size planning

Statistical planning and analysis takes places under the direction of Mag. Dennis Huber of the Institute for experimental orthopaedics.

By using the software G*Power (Franz Faul, University of Kiel, Germany), an a priori sample size analysis is carried out. The following parameters shall be assumed for the calculation of the optimal sample size:

- Primary target variable: average VRS (verbal rating scale; 0-10) for pain
- Clinically-relevant difference: 1
- Number of groups: 2 (same group size)
- Statistical methods:
  - Test family: t-test
  - Statistical test: means; difference between two independent means (groups)
  - Type of power analysis: a priori
- Formulation of hypothesis: two pages
- Effect size: Cohen's d = 1 (large effect size)
  - assumed mean difference: 1
  - assumed standard deviation: 1
- Type 1 error: 5 %
- Type 2 error: 20%
- Test power: 80%

- Group size: N1=N2
- Drop-out rate: approx. 10 %

An a priori sample size analysis using the parameters mentioned above, results in a targeted minimal power of 0.80 and with a Cohen's d of 1 (reveals large effects) results in a number of 34 people necessary (17 per group). Considering that the drop-out rate is expected to be at 10 %, the optimal sampling size is 40 feet (20 per group). By means of the sampling size used by us, it should be possible to reveal effects of large size with sufficient power.

11.2 Randomization

Randomization takes place in 2 groups as balanced randomization by means of a computer-generated random number sequence. This random number sequence is generated with the help of the website www.random.org (numbers, random sequence generator). The first 20 results of this list are assigned to the verum group, the other 20 results are assigned to the placebo group. Upon admission to the study, the patients receive at random one of these numbers which are contained in sealed envelopes on which the numbers 1 to 40 [sic] are written. The randomization envelope is opened by an independent member of the nursing staff – who is not involved in the further treatment of the patient – several minutes prior to the start of surgery. Such member will fill a 50 ml perfusor syringe with either ropivacaine 0.2 % or physiological saline solution. The patients, surgeons as well as the care-taking nursing staff are blinded as regards the content. The deciphering list will only be opened after conclusion of the last follow-up examination.

11.3 Statistical methods

11.3.1 Dependent variables

Primary dependent variable (primary study endpoint)

- Average VPRS (verbal pain rating scale; 0-10) for pain during the first 48 postoperative hours.

- Maximum VPRS (verbal pain rating scale; 0-10) for pain during the first 48 postoperative hours.

Secondary dependent variables (secondary study endpoints)

- Endpoints related to safety during the treatment period: *Occurrence of AEs, ARs and UARs.*
- Endpoints related to the effectiveness: *Patient satisfaction (VRS), clinical outcome (AOFAS forefoot score, ROM GZGG after 6 weeks), maximum and average pain (VPRS) after 1, 2 and 6 weeks, need for rescue pain medication*

11.3.2 Definition of analysis sets

The intent-to-treat population to be analysed includes all randomized patients to whom the trial medication has been given. The statistical analysis of this set decides on the statement statistically significant or not statistically significant. The per protocol population is also analysed, i.e. those patients for whom no major protocol deviations have occurred.

11.3.3 Data analysis

Confirmatory data analysis

The primary dependent variables (average and maximum VRS for pain during the first 48 postoperative hours) shall be analysed in a confirmatory way for two independent samples using a t-test. This shall be done by means of the current version of the software SPSS Statistics (company IBM, Armonk, New York, USA).

Exploratory data analysis

All secondary dependent variables – patient satisfaction (VRS), clinical outcome (AOFAS forefoot score, ROM GZGG after 6 weeks), maximum and average pain (VPRS) after 1, 2 and 6 weeks – shall be analysed in a purely descriptive way by means of using the currrent version of the software SPSS Statistics (company IBM, Armonk, New York, USA).

12 Reporting

Minutes of the meetings of the different committees are drawn up in order to document the process and development of the study.

12.1 Trial report

Any and all information concerning this clinical trial are to be treated as confidential. The investigator carries out the statistical analysis and draws up an integrated final report; these are then evaluated and signed by the sponsor as well as by all other responsible persons. All information contained in this report are strictly confidential.

12.2 Publications

The final results of this clinical trial shall be published in a renowned specialist journal. Dr. Braito Matthias will be lead author, PD Dr. Rainer Biedermann will be corresponding author. The publication or presentation of the results is to be commented and approved a priori by the investigator and the sponsor. Data protection concerning all patient data has to be safeguarded for all publications. It is not planned to publish interim or partial results. Prior to its start, the study is registered on www.clinicaltrials.gov.

13 Ethical, legal and administrative aspects

13.1 Responsibilities of sponsor and investigator

Pursuant to the AMG, the sponsor of the clinical trial assumes responsibility for launching, organising and financing the clinical trial to be conducted. In this context, sponsor and investigator ensure that the clinical trial is conducted in compliance with existing laws and regulations, pursuant to the ICH GCP guidelines (1996), the declaration of Helsinki (1996) as well as the dispositions set out in the AMG and GCP ordinance (2004). The investigator accepts the requirements of the undersigned study protocol.

Responsibilities of the investigator include amongst others:

- understanding of the properties of the trial medication described in the Investigator's Brochure or in the specialist information
- understanding and implementation of the treatment plan
- ensuring that enough time and capacities for conducting the trial are available
- correct collection and documentation of data, reporting
- supplying any and all data to the sponsor, monitor or to the respective authorities for audits and/or inspections
- ensuring that information on patients as well as all information obtained from the sponsor are treated as confidential by all persons involved in the trial.

Pursuant to the AMG, each investigator assumes responsibility for conducting the clinical trial in the trial center.

13.2 Decision of the ethics commission and notification to authorities

PD Dr. Rainer Biedermann (representative of the sponsor) applies to the ethics commission of the Medical University of Innsbruck and to the Austrian Federal Office for Safety on behalf of the sponsor.

13.3 Patient information and declaration of consent

Prior to the start of the trial, each patient must declare his/her consent to the investigator in writing, after first having been informed – orally and in writing – on the nature, meaning and consequences of the clinical trial in a way that is complete and understandable for him. The content of this information is documented on the declaration of consent. The patient is informed if significant new findings on the trial medication emerge during the study.

The patient’s declaration of consent for the participation in the clinical trial is dated and signed by the patient as well as by the doctor. The patient receives a copy of the signed patient information/declaration of consent. The second copy is filed in the investigator site file by the doctor.

It is expressly noted that no examinations related to the study may be performed until a legally valid declaration of consent of the patient is submitted.

13.4 Patient insurance

On behalf of the sponsor, the patient insurance prescribed pursuant to the AMG has been taken out for all patients with the following insurance company:

Company name: Zürich Versicherungs-Aktiengesellschaft, SBU-Firmenkunden

Insurance number: 07208763-1

Address: Schwarzenbergplatz 15; 1010 Vienna

Phone: +43 (01) 501 25 1240

Fax: +43 (01) 501 25 1507

With this, damages to health are insured against with a maximum coverage sum of 370,000.00 euros for each participant. This insurance covers all possible damages that the patient suffers directly or indirectly because of the trial medication or because of operations in connection with the clinical trial.

In order not to lose their insurance coverage, the patients have to strictly follow the instructions given by the trial staff. Furthermore, the patients may not undergo any other medical treatment during the clinical trial without consent of the investigator (an exception to this are emergencies). Patients must inform the investigator immediately on any emergency treatment. The patients have to immediately report to the investigator and to the insurance company any damage to health which may have resulted from the clinical trial. Furthermore, the patients must take all appropriate measures which serve the purpose of elucidating the cause and extent of the damage that has occurred.

The patient may inspect the insurance conditions at the investigator's place and, if requested, he/she may obtain a copy.

13.5 Data protection and obligation to secrecy

Collection, transfer, storage and analysis of personal data within this clinical trial is made pursuant to legal dispositions (Federal Data Protection Act). The prerequisite for this is the voluntary consent of the patients within the framework of the declaration of consent prior to the participation in the clinical trial. During their information on this clinical trial, the patients are informed in this regard on the following:

1. Data that is collected as part of this clinical trial is recorded on paper forms or electronic data carriers, is treated as confidential and may only be passed on, without the patients being mentioned by name (pseudonymized), to

   - the commissioner of the study in order to conduct a scientific analysis and assessment of adverse events,
   - the competent federal authority, the ethics commission of the Medical University of Innsbruck and the European Database in order to review the orderly conduction of the study as well as to evaluate study results and adverse events.

2. Insofar as it is necessary for reviewing the clinical trial, representatives of the commissioner (monitors, auditors) and/or of the competent monitoring authority who are authorized and sworn to secrecy may inspect the personal data available at the investigator. For this measure, the investigator is released from his professional obligation to secrecy.

3. The consent to the collection and processing of personal data in the framework of this clinical trial is irrevocable. A patient will be instructed that he may end his/her participation in the clinical trial at any time – without giving reasons and without facing any subsequent detriments. In case the declaration of consent is revoked, the data stored up to this point will still be used without the patient being mentioned by name, if necessary, in order to assess the effects of the medicinal product at trial and to ensure that interests of the person concerned which are worth protecting are not harmed.

14 Changes to the study protocol (amendments)

In order to ensure that broadly comparable results are obtained in all trial centers, as well as in the interest of proper data evaluation, a change to the trial conditions agreed upon and set out in this study protocol is not intended.

However, in exceptional cases changes to the trial conditions are possible. These are only made after mutual agreement has been reached between the investigator and the sponsor. Any change to the study procedure as set out in the study protocol has to be made in writing, giving the respective reasons, and has to be signed by all persons responsible for the study. The changes shall then be deemed as part of the study protocol. If necessary (e.g. when changing the medication dose and/or in case of other significant changes which indicate a direct influence on the safety of the study participants), approval of the changes to the study protocol has to be obtained from the relevant ethics commission and/or authorities as well as from the patients, and the amendment is to be submitted to the federal authority.

15 Annex

Hallux Metatarsophalangeal-Interphalangeal Scale

Pain (40 points)	
None	40
Mild, occasional	30
Moderate, daily	20
Severe, almost always present	0
Function (45 points)	
Activity limitations	
No limitations	10
No limitation of daily activities, such as employment	7
Limited daily and recreational activities	4
Severe limitation of daily and recreational activities	0
Footwear requirements	
Fashionable, conventional shoes, no insert required	5
Comfort footwear, shoe insert	3
Modified shoes or brace	0
MTP joint motion (dorsiflexion plus plantarflexion)	
Normal or mild restriction (75° or more)	10
Moderate restriction (30°-74°)	5
Severe restriction (less than 30°)	0
IP joint motion (plantarflexion)	
No restriction	5
Severe restriction (less than 10°)	0
MTP-IP stability (all directions)	
Stable	5
Definitely unstable or able to dislocate	0
Callus related to hallux MTP-IP	
No callus or asymptomatic callus	5
Callus, symptomatic	0
Alignment (15 points)	
Good, hallux well aligned	15
Fair, some degree of hallux malalignment observed, no symptoms	8
Poor, obvious symptomatic malalignment	0
Total=	100

American Orthopaedic Foot and Ankle Society
From: http://www.aofas.org/i4a/pages/index.cfm?pageid=3494

VRS for Pain

no pain	□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10	worst possible pain

VRS for overall satisfaction with operation / pain management

not satisfied	□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10	very satisfied

16 Literature

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