Study Protocol

Multi-centre, Double-blind, Randomised, Active- and Placebo-Controlled, Confirmatory Trial to Demonstrate Efficacy and Safety of Traumed® Gel in Patients having Acute Ankle Sprain

Development Phase: Phase III

EudraCT-Number: 2016-004792-50

Protocol Code: C1502

Investigational Product: Traumed® Gel

Indications: Acute ankle sprain

Coordinating Investigator: Prof Dr med Thomas Becker
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Sponsor: Biologische Heilmittel Heel GmbH
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Protocol Approval Signature Page

I have carefully read this protocol and agree to conduct the study according to the protocol specifications and in compliance with the ICH GCP Guidelines and the Declaration of Helsinki and after having obtained approval from the Ethics Committee and consent in writing from the patients. Signing this form constitutes a written agreement between the Investigator, Biologische Heilmittel Heel GmbH, and their representative.

National Coordinating Investigator

[redacted]

19.2.2020

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[redacted]

13.2.20

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Sponsor's Representatives

I have carefully read this protocol and agree to conduct the study according to the protocol specifications and in compliance with the ICH GCP Guidelines and the Declaration of Helsinki and after having obtained approval from the Ethics Committee and consent in writing from the patients. Signing this form constitutes a written agreement between the Investigator, Biologische Heilmittel Heel GmbH, and their representative.

[redacted] 04 Feb. 2020

Dr Bernd Seilheimer — Date
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[redacted] 5. 2. 2020

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Dr Christine Frank — Date
Senior Clinical Project Manager
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Biostatisticians

I have carefully read this protocol and agree to conduct the study according to the protocol specifications and in compliance with the ICH GCP Guidelines and the Declaration of Helsinki and after having obtained approval from the Ethics Committee and consent in writing from the patients. Signing this form constitutes a written agreement between the Investigator, Biologische Heilmittel Heel GmbH, and their representative.

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February 5, 2020

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Protocol Signature Page

I have carefully read this protocol and agree to conduct the study according to the protocol specifications and in compliance with the ICH GCP Guidelines and the Declaration of Helsinki and after having obtained approval from the Ethics Committee and consent in writing from the patients. Signing this form constitutes a written agreement between the Investigator, Biologische Heilmittel Heel GmbH, and their representative.

Investigator:

_____ _____

Name, Function: Date
Institution:

Site Number: _____

Protocol Synopsis

<table>
<tr><td>Sponsor:
Biologische Heilmittel Heel GmbH</td><td>Name of Medical Product:
Traumed® Gel</td><td>Active Ingredient(s):
Homeopathic preparation, containing herbal and mineral ingredients as described in the Clinical Study Protocol</td></tr>
<tr><td colspan="2">EudraCT number: 2016-004792-50</td><td>Indication: Acute ankle sprain</td></tr>
<tr><td colspan="3">Study Title:
Multi-centre, Double-blind, Randomised, Active- and Placebo-Controlled, Confirmatory Trial to Demonstrate Efficacy and Safety of Traumed® Gel in Patients having Acute Ankle Sprain</td></tr>
<tr><td colspan="3">Study Sites:
Multi-centre study in Germany (at approximately 35 sites, trauma centres (surgeons), emergency units, sport medicine practices (physicians), general practitioners
Coordinating Investigator: Prof Dr med Thomas Becker
Universitätsklinikum Schleswig-Holstein
Arnold Heller Straße 3
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Phone: +49 431 5002 4485</td></tr>
<tr><td colspan="2">Study Duration:
First patient first visit: February 2018
Last patient last visit planned: December 2020</td><td>Study Phase:
III</td></tr>
<tr><td colspan="3">Study objectives:
The primary objective of the study is to demonstrate the superior efficacy of Traumed® gel versus placebo in patients with acute lateral ankle sprain
The secondary objectives are:
• to assess non-inferiority of Traumed® gel compared to diclofenac gel
• to assess the tolerability and safety of Traumed® gel.</td></tr>
<tr><td colspan="3">Methodology:
Randomised, double-blind, active- and placebo-controlled confirmatory clinical trial.</td></tr>
<tr><td colspan="3">Number of Patients (Planned):
Estimation of sample size is based on the primary efficacy variable area under the curve (AUC) for pain on passive movement as measured by the Visual Analog Scale from baseline to Day 4. A two-sided test of equality of the study drug (Traumed® gel) and the comparator (placebo) at level 0.05 based on an expected raw scale treatment difference of AUC 25 [mm x days] and a common standard deviation of AUC 75 [mm x days] for the response variables (re-expressed for nonparametric evaluation in terms of the robust Mann-Whitney statistic as MW = 0.6), achieves a power of at least 90% for parametric first line analysis as well as for second line non-parametric analysis if the sample size is set to 291 patients for the Traumed® gel group and to 146 patients for the placebo group. Due to an additional safety requirement that AEs with incidence level of 1% for Traumed® gel are found during the study with probability 95%, 299 patients for the Traumed® gel group are required. Assuming a drop-out rate from the Safety Analysis Set of about 4% an amount of 312 randomized patients in the Traumed® gel group is needed. With an allocation ratio of 2:1:1 (Traumed® gel : diclofenac gel : placebo) we obtain 156 patients in the diclofenac and placebo group each, that is, a total of 624 patients with acute unilateral Grade 1 or Grade 2 sprain of the lateral ankle.</td></tr>
</table>

Sponsor: Biologische Heilmittel Heel GmbH	**Name of Medical Product:** Traumed® Gel	**Active Ingredient(s):** Homeopathic preparation, containing herbal and mineral ingredients as described in the Clinical Study Protocol
EudraCT number: 2016-004792-50		**Indication:** Acute ankle sprain

In order to ensure the predefined power of the trial, a sample size enhancement is introduced for compensation of:

- cases for whom maintenance of blinding procedures may have been compromised.

For compensation, the final sample size will be enhanced to 202 patients for the diclofenac and Placebo group each, and to 404 patients for the Traumed® gel group resulting in a new total of 808 patients.

For more details see sections 11.1.3 and 11.4. *(revised per Amendment to protocol version 3.0)*

Diagnosis and Inclusion Criteria:

The patients have to meet all of the following inclusion criteria:

1. Acute unilateral Grade 1 or Grade 2 sprain of the lateral ankle
2. ≥18 years of age
3. Legally competent male or female outpatient
4. Injury occurred within previous 24 hours before first treatment expected
5. Signed Informed Consent
6. After 5 minutes of rest, pain on passive movement by investigator measured by Visual Analog Scale (VAS) >50 mm
7. Not pregnant (as proven by negative pregnancy test in case of woman of childbearing potential before first study drug administration) or breast-feeding. Females of childbearing potential must agree to maintain highly effective birth control throughout the study (see all details in section 9.6). Such methods include:
   - oral, intravaginal, transdermal combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation,
   - oral, injectable, implantable hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (if received medical assessment of the surgical success), sexual abstinence (only if defined as refraining from heterosexual intercourse during the entire period of trial participation)

Sponsor: Biologische Heilmittel Heel GmbH	**Name of Medical Product:** Traumed® Gel	**Active Ingredient(s):** Homeopathic preparation, containing herbal and mineral ingredients as described in the Clinical Study Protocol
EudraCT number: 2016-004792-50		**Indication:** Acute ankle sprain

Exclusion Criteria:

Potential study patients will be excluded if at least one of the following exclusion criteria is present:

1. Similar injury affecting the same joint within the past 6 months
2. Bilateral ankle injury
3. Grade 3 ankle sprain
4. Fracture of the ankle (It should be excluded by using e.g. the Ottawa Ankle Rules. In case of any doubt the exclusion of fracture by x-ray should be considered as per standard of care)
5. Chronic joint disorders such as clinically relevant osteoarthritis or aseptic arthritis
6. Disorders that may lead to joint oedema for other reasons than ankle sprain (such as heart failure, thrombosis, lymphedema and others)
7. Diagnosis requiring bed rest, hospitalization, surgery, or use of any cast during the planned treatment period
8. Debilitating acute or chronic illness
9. Use of systemic and/or topical corticosteroids in the previous 8 weeks, any analgesics (e.g. paracetamol/ acetaminophen) in the previous 24 hours before Screening Visit, or 48 hours in the case of long-acting non-steroidal anti-inflammatory drug (NSAID), cyclooxygenase type 2 (COX-2) specific inhibitors, or tramadol and other opioids. Low dose acetylsalicylic acid (70 – 100 mg per day) for anti-thrombotic therapy is permitted if doses are stable for the month prior to Screening Visit and planned to be stable during the entire study
10. History of sensitivity to any component of the study drugs (including e.g. paracetamol/ acetaminophen intolerance; patients in whom asthma attacks, skin rash or acute rhinitis are triggered by acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs)
11. Unwilling or unable to comply with all the requirements of the study protocol
12. Concurrent injury to proximal structures in ipsilateral lower extremity (i.e. concurrent shin, knee, thigh, or hip injury)
13. History of ligament avulsion, fracture or surgery to the affected lower extremity
14. Presence of infections and/or skin diseases in the area of the study treatment site (including psoriasis)
15. Any previous treatments of the injured ankle, whether topical or systematic, are prohibited except RICE (simultaneous combination of all 4 elements Rest, Ice, Compression and Elevation which is restricted to be used until starting treatment with the investigational drug)
16. Participation in any clinical study within the past 4 weeks
17. Any relationship of dependence with the sponsor or with the investigator

Test Product, Dose, and Mode of Administration:

Traumed® gel, 3 g of gel three times daily for 7 days, to sufficiently cover the area of the ankle, applied by gentle rubbing.

Reference Product, Dose, and Mode of Administration:

Diclofenac 1% gel, 3 g of gel three times daily for 7 days, to sufficiently cover the area of the ankle, applied by gentle rubbing.

Placebo therapy, Dose, and Mode of Administration:

Corresponding placebo gel formulation, 3 g of gel three times daily for 7 days, to sufficiently cover the area of the ankle, applied by gentle rubbing.

Rescue medication, Dose and Mode of Administration:

Paracetamol (acetaminophen), 500 mg/tablet when necessary (*pro re nata*, PRN) for pain with a maximum of 4 tablets or 2000 mg/day (but not more than 2 tablets at a time), is permitted as rescue medication for relieving pain in all three treatment groups. Patients will not be allowed to take paracetamol within 8 hours prior to visit 2. For further visits the restriction is 24 hours. The intake will be recorded by the patients on the patient diary cards.

Supportive therapy:

All patients receive soft support (elastic bandage) at Day 1. All patients will continue using soft support, however patients with Grade 2 will receive a semi-rigid removable brace after the evaluations at Day 7. These semi-rigid braces will be provided to all patients centrally and the investigator team will be trained for correct use at the investigator meeting to ensure standardized circumstances. In addition. using arm crutches will be strongly recommended at least until Day 4.

Criteria for Evaluation:

Primary Efficacy Variable

Area under the curve (AUC)* for pain on passive movement in Visual Analog Scale (VAS) from baseline to Day 4

*All AUC calculations will be based on actual time of measurement

Secondary Efficacy Variables

- AUC for pain at rest in VAS from baseline to Day 4
- AUC for pain on passive movement in VAS from baseline to Day 2, 7 and Final Visit
- AUC for pain at rest in VAS from baseline to Day 2, 7 and Final Visit
- Change from baseline of pain on passive movement in VAS to Day 4, 7 and Final Visit
- Change from baseline of pain at rest in VAS to Day 4, 7 and Final Visit
- Change from baseline to Day 2, 4, 7 and Final Visit in the Foot and Ankle Ability Measure (FAAM) Activities of Daily Living (ADL) subscale
- Amount of rescue medication (doses)
- Time to 50% improvement of pain at rest measured by VAS.

Safety Variables

- Adverse Events (AEs)
- Other observations related to safety (physical examinations and vital signs).

Statistical Methods:

The summaries of the efficacy parameters, the statistical analyses of the primary efficacy variable, and the statistical analyses of the secondary efficacy variables will be performed on the Full Analysis Set (primary set for evaluation of superiority of Traumed® gel versus placebo, secondary set for evaluation of non-inferiority of Traumed® gel compared to diclofenac gel), and on the PP set (primary set for evaluation of non-inferiority of Traumed® gel compared to diclofenac gel, secondary set for evaluation of superiority of Traumed® gel versus placebo).

Missing values for all efficacy parameters will be imputed by the last observation carried forward (LOCF) approach. In addition, a last percentile carried forward approach (LPCF) will be performed as sensitivity analysis (see also section 11.1.4). Further sensitivity analyses resulting from the blind review of the data will be provided in the final Statistical Analysis Plan.

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise. Where appropriate, statistical tests will be supported by presenting estimates and 95% confidence intervals for the respective treatment effects and differences between the treatment groups. These estimates and confidence intervals will be based on the respective statistical models used for the analysis.

Confirmatory analyses

1. AUC for pain on passive movement in VAS from baseline to Day 4 (test for superiority, Traumed® gel versus placebo), Full Analysis Set (FAS)
2. AUC for pain on passive movement in VAS from baseline to Day 4 (test for non-inferiority, Traumed® gel versus diclofenac gel), Per-Protocol Analysis Set (PP)

If the first *a priori* ordered test (superiority) shows statistical significance, the subsequent hypothesis (non-inferiority) can then be tested individually in a confirmatory manner according to the principle of *a priori* ordered hypotheses (for control of alpha using stepwise testing see [Maurer et al. 1995]).

Clinical safety will be addressed by assessing AEs, physical examinations, vital signs and as needed laboratory assessments in a descriptive manner.

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Statistician:	idv Datenanalyse & Versuchsplanung Tassilostrasse 6 D-82131 Gauting/ Germany

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List of Appendices

Glossary of Abbreviations

Abbreviation	Definition
ADL	Activities of Daily Living
AR(s)	Adverse reaction(s)
AE(s)	Adverse event(s)
ANCOVA	Analysis of covariance
AUC	Area under the curve
BDRM	Blinded Data Review Meeting
BMI	Body mass index
C	Celsius degree
CCSI	Company Core Safety Information
CCDS	Company Core Data Sheet
COX-2	Cyclooxygenase type 2
CRO	Contract research organisation
eCRF	Electronic case report form
CTR	Clinical Trial Report
EoT	End of Treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials database of all interventional clinical trials of medicinal products from 1 May 2004 onwards)
ex-gratia	Out of goodwill (Latin)
FAAM-ADL	Foot and Ankle Ability Measure - Activities of Daily Living (21-item self-report questionnaire subscale)
FAS	Full analysis set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (formerly International Conference on Harmonisation)
ICMJE	International Committee of Medical Journal Editors (www.icmje.org).
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
ITT	Intent-to-treat (analysis set)
IUD	Intrauterine device
IUS	intrauterine hormone-releasing system
LPCF	Last Percentile Carried Forward
LOCF	Last Observation Carried Forward

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/day	Milligrams per day
mm	Millimetre
N	Number of patients
NSAID	Non-steroidal anti-inflammatory drug
PP	Per-Protocol (analysis set)
PRN	When necessary (*pro re nata*)
QPPV	Qualified person for pharmacovigilance
RICE	Combination of all 4 elements Rest, Ice, Compression and Elevation
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard deviation
SOP	Standard operating procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGF	Transforming growth factor
TNF	Tumor necrosis factor
VAS	Visual Analog Scale
WHO	World Health Organization
WMA	World Medical Assembly

1. Ethical and Regulatory requirements

1.1. Ethical Conduct of the Study

The study will be conducted in compliance with

- the study protocol,
- ethical principles of the Declaration of Helsinki and its amendments as adopted by the 64th World Medical Assembly (WMA) General Assembly, Fortaleza, Brazil, October 2013,
- the principles of the Good Clinical Practice (GCP) provided in the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for GCP 1996, and
- all applicable national laws and regulations.

1.2. Independent Ethics Committee

Before initiation of the study at each study site, the protocol, informed consent form, and all other required information will be submitted to the relevant independent ethics committee (IEC) for review and approval, in accordance with applicable regulatory and local requirements. The IEC will also review and approve any advertisements. The IEC's approval will be documented in writing and forwarded to the contract research organisation (CRO) with responsibility for conducting the study.

The investigator will not begin the study until he/she receives written confirmation of approval by the IEC and the sponsor Biologische Heilmittel Heel GmbH (in the Study Protocol referred as Heel) has authorised release of study treatments.

Additionally, the current Summary of Product Characteristics (SmPC; approved in another EU country, Austria) and any updates during the course of the study will be supplied to the IEC. The reported suspected unexpected serious adverse reaction (SUSAR; SAR not expected from review of the above-mentioned relevant safety information) are to be submitted to the IECs according to the national regulatory requirements and international guidelines.

After completion or termination of the study, the study results will be submitted to the IEC after end of the trial (data base lock) within 1 year.

1.3. Patient Information and Informed Consent

The patient informed consent form will be used to explain the risks and benefits of study participation to the patient (in simple terms understandable for the individual patient).

The patient informed consent form will comply with all applicable regulations governing the protection of human patients, including ICH GCP guidelines, the Declaration of Helsinki, patient confidentiality and data protection. The informed consent form and any revision of the patient informed consent form must be approved in written by the independent ethics committee (IEC) prior to use.

Prior to screening, patients will be provided with a copy of the approved patient informed consent form. The principal investigator or an investigator designated by the principal investigator will discuss in the appropriate language with the patient the nature and purpose of the study, the treatments to be administered, the possible risks, expected benefits, and how the data collected in this study will be handled and shared. Patients will have sufficient opportunity to inquire about details of the study and to decide whether or not to participate. They will be instructed that they are free to withdraw their consent to participate in the study at any time and for any reason without prejudice.

The principal investigator or an investigator designated by the principal investigator must obtain the patient's voluntary, personally signed, and personally dated patient informed consent form prior to the performance of any study related procedures - including the administration of study treatments. The original, signed patient informed consent form must be kept in the Investigator Site File. The investigator will provide each patient with a second original of the signed and dated patient informed consent form and document the provision of consent in the patient's medical records.

The investigator will inform patients of any new information that may be relevant to the patients' willingness to continue their participation in the study. The investigator is also obliged to protect the patients' confidentiality.

The patient must agree in the patient informed consent form that his/her data will be processed and stored in a pseudonymous form for evaluation of this study and for any later overviews. Data may also be transferred in an anonymous form to 3rd parties, e.g. other companies or authorities that may be located in other countries with potentially different data protection rules. Data will follow the development of the product and will be used for documentation of the product's efficacy, and safety and tolerability. In addition, pseudonymous data might be accessible in special circumstances for other researchers for additional clinical analysis. The patient informed consent form states that any data obtained will be kept on file or in the database even if consent is withdrawn.

1.4. Protocol Amendments

Substantial amendments to the protocol (any change in the protocol's assessments/ requirements) will not be permitted to be implemented until the coordinating investigator, Heel, Competent Regulatory Authority and the IEC have provided written approval of the

change. Non-substantial amendments (other administrative changes not affecting the scope of the investigation or the scientific quality of the study) can be made following written approval by the coordinating investigator and Heel, however the IEC and Competent Regulatory Authority must be notified of these protocol changes (as appropriate).

The CRO designee will be responsible for the distribution of protocol amendments to the investigator. The investigator will be responsible for implementing any amendments at the study site (including the distribution of amendments to all staff concerned).

1.5. Patient Insurance Coverage and Investigator Indemnity

Heel (sponsor of the study) will provide appropriate insurance coverage for the patients, in accordance with legal requirements. An insurance certificate will be provided for the investigator's site file.

The patients will be informed by the investigator about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the patient. Any deviation from this study protocol caused by patient's fault can lead to the loss of insurance coverage.

Heel indemnifies and holds harmless the study site and its employees and agents against all claims and proceedings (to include any settlements or *ex-gratia* payments made with the consent of the parties hereto and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise):

- By or on behalf of patients taking part in the study (or their dependents) against the investigational site or any of its employees or agents for personal injury (including death) to patients arising out of or relating to the administration of the product under investigation or any clinical intervention or procedure provided for or required by the protocol to which the patients would not have been exposed but for their participation in the study.
- By the study site, its employees or agents or by or on behalf of a patient for a declaration concerning the treatment of a patient who has suffered such personal injury.

The above indemnity by Heel shall not apply to any such claim or proceeding:

- To the extent that such personal injury (including death) is caused by the negligent or wrongful acts or omissions or breach or wilful misconduct of the study site, its employees or agents.
- To the extent that such personal injury (including death) is caused by the failure of the study site, its employees, or agents to conduct the study in accordance with the protocol.

- Unless as soon as reasonably practicable following receipt of notice of such claim or proceeding, the study site shall have notified Heel in writing of it and shall, upon Heel's request, and at Heel's expenses, have permitted Heel to have full care and control of the claim or proceeding using legal representation of its own choosing.
- If the study site, its employees, or agents shall have made any admission in respect of such claim or proceeding or taken any action relating to such claim or proceeding prejudicial to the defense of it without the written consent of Heel such consent not to be unreasonably withheld provided that this condition shall not be treated as breached by any statement properly made by the study site, its employees or agents in connection with the operation of the study site's internal complaint procedures, accident reporting procedures, accident reporting procedures or disciplinary procedures or where such statement is required by law.

1.6. Confidentiality

The investigators, the designated CRO, other third-party vendors and Heel will preserve the confidentiality of all patients taking part in the study, in accordance with ICH GCP and local regulations. The confidentiality of all patient identities will be maintained except during source data verification, when monitors, auditors, and other authorised agents of the sponsor or its designee, the ethics committees approving this research, as well as any other applicable regulatory authorities, will be granted direct access to the study patients' original medical records. No material bearing a patient's name will be kept on file by the designated CRO, other third-party vendors or Heel. The data retained from this study will be protected in accordance with all applicable legal requirements.

1.7. Regulatory Authorities

The study, and any amendments, will only be implemented following compliance with all legally required regulatory requirements.

After completion (data base lock) or termination of the study, the study results will be submitted to the Competent Regulatory Authorities within 1 year.

2. Study Personnel and Study Administration

The study is sponsored and planned by Biologische Heilmittel Heel GmbH.

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3. Introduction and Study Rationale

Ankle sprain injuries are the most common type of joint sprain. The prevalence of ankle joint sprains accounts for 21% of joint injuries in the body. Although somewhat rare, high-ankle or syndesmotic ankle sprains occur in up to 15% of ankle traumas (Childs, 2012).

Lateral ankle sprains are the most prevalent musculoskeletal injury in physically active populations. They also have a high prevalence in the general population and pose a substantial healthcare burden. The injury mechanism is characterised by a high velocity inversion and internal rotation of the ankle/foot complex. The treatment for acute lateral ankle sprain is quite variable, with many patients returning to activity in a short period of time; however, half of the population may never seek initial care (Gribble et al. 2016). Inadequate treatment of ankle sprains can lead to chronic problems such as decreased range of motion, pain, and joint instability (Wolfe et al. 2001; Ivins et al. 2006).
Many patients who suffer from some form of ankle injury do not seek treatment, as a treatment regimen would significantly impact their physical activities, such as training, practicing and competing for a substantial period of time (McKay et al. 2001). A study (Hubbard et al. 2009) showed that natural recovery from ankle sprain takes longer than 8 weeks – a significant time for any athlete to be away from activity.

Some evidence suggests that previous injuries or limited joint flexibility may contribute to ankle sprains. The initial assessment of an acute ankle injury should include questions about the timing and mechanism of the injury. Ankle sprains can be classified as grade 1, grade 2 or grade 3, depending on the severity of the injury (Wexler et al. 1998).

Physicians should apply e.g. the Ottawa ankle rules to determine whether radiography is needed. According to the Ottawa criteria, radiography is indicated if there is pain in the malleolar or midfoot zone, and either bone tenderness over an area of potential fracture (i.e. lateral malleolus, medial malleolus, base of fifth metatarsal, or navicular bone) or an inability to bear weight for four steps immediately after the injury and in the emergency department or physician's office (Tiemstra, 2012).

Clinically, a first approach to soft tissue injuries follows the RICE principle (simultaneous combination of all 4 elements Rest, Ice, Compression and Elevation). The objective of RICE is to stop the injury-induced bleeding into the muscle tissue and thereby minimize the extent of the injury.

In a study in acute ankle sprain, an accelerated intervention with early therapeutic exercise during the first week after ankle sprain improved ankle function compared with RICE, although the groups did not differ at any other time point for pain at rest, pain on activity, or swelling (Bleakley et al. 2010).

Controlled trials of non-steroidal anti-inflammatory drugs (NSAIDs) e.g. diclofenac, piroxicam, celecoxib, naproxen and others in patients with ankle sprain showed that compared with placebo, NSAIDs were associated with improved pain control and function, decreased swelling, and more rapid return to activity. To reduce or even avoid the well-known side effects of systemic NSAIDs topical application is an efficacious alternative (Lin et al. 2004, Mason et al. 2001, Mason et al. 2004, Heumann Pharma, Predel et al. 2004).

Reviews of diclofenac have consistently demonstrated its efficacy in reducing pain and inflammation in acute and chronic conditions compared with placebo. Diclofenac is meanwhile considered to be the gold standard in the treatment of joint sprains and other conditions. Topical diclofenac is well tolerated and is associated with fewer side-effects than other topical NSAIDs, mostly mild, easily resolved local skin irritation (Banning 2008, Zacher et al. 2008, Simon et al. 2009). A systematic review and meta-analysis of blinded, randomized, placebo-, vehicle- or active-controlled trials concluded that topical diclofenac appears to be generally well tolerated for cutaneous use in acute and chronic musculoskeletal conditions (Taylor et al. 2011). For these reasons, diclofenac gel was chosen as a comparator for this study.

Traumeel® is a German non-prescription drug sold for more than 50 years over the counter in pharmacies in Germany, Austria, Switzerland and in more than 50 other countries worldwide in the form of oral drops, tablets, ointment and ampoules. A gel formulation of the product is available in Austria, Belgium, The Netherlands, Poland and Spain in the EU, and in some other countries worldwide for human use as Traumeel® gel. In Germany the gel variant of the product is planned to be submitted for authorisation as Traumed® gel.

Traumeel® (for topical application, either as ointment or a gel) is produced in accordance with the German Homeopathic Pharmacopoeia and the European Pharmacopoeia. The quality of Traumed® is guaranteed both by the use of active substances and excipients that meet the requirements of the Homeopathic Pharmacopoeia and the European Pharmacopoeia and by production in accordance with good manufacturing practice (GMP) guidelines. Local tolerability data of Traumeel® gel are available from a local tolerability trial. Traumeel® is a fixed combination of plant and mineral extracts used for treating inflammation and pain caused by musculoskeletal injuries (Schneider, 2011). Efficacy and tolerability of Traumeel® for musculoskeletal injuries have been reported in randomised controlled trials, which demonstrate reductions in pain and swelling, and improvements in the mobility of joints such as ankle and knee (Zell et al. 1998, Böhmer et al. 1992, Thiel et al. 1994). Traumeel® has proven efficacy which is equivalent to conventional management (Schneider et al. 2008), NSAIDs (Birnesser et al. 2004) and to diclofenac (Schneider et al. 2005) in pain relief and improving joint mobility. Traumeel® is well tolerated, with very few adverse effects (Arora et al 2000, Birnesser et al. 2004, Böhmer et al. 1992, Thiel et al. 1994, Schneider et al. 2005. Schneider et al. 2008, Zenner et al. 1992, Zenner et al. 1994, Zenner et al. 1997).

Evidence for the inflammation regulating action of Traumeel® comes from Porozov et al. 2004 who conducted a study to evaluate the effect of Traumeel® on human leukocyte function. Specifically, the action of Traumeel® was studied on activated human T-cells, monocytes and gut epithelial cells in terms of its effect on the pro-inflammatory mediators IL-1β (interleukin-1β), TNF-α (tumour necrosis factor-α) and IL-8 (interleukin-8) *in vitro*.

The researchers found that Traumeel® modulates the secretion of IL-1ß, TNF-α and IL-8 in resting as well as in activated immune cells. It was observed that T-cell and monocyte proliferation was not affected. The researchers concluded that Traumeel® reduces pro-inflammatory cytokines in resting and activated immunocytes *in vitro*, as well as in resting and activated colon epithelial cells, suggesting that the first-line and mobile arm of immune defence is activated by Traumeel®. The study concluded that the results support the characterization of Traumeel® as an inflammation-regulating medication.

Traumeel® acts differently to NSAIDs, its anti- inflammatory effect results from the synergistic interaction between its components on the different phases of the inflammatory response (Lussignoli et al. 1999).

In vitro studies (Wexler et al. 1998) showed that the ingredients of Traumeel® are non-cytotoxic to granulocytes, lymphocytes, platelets and endothelial cells, indicating that the normal defensive and homeostatic functions of these cells are preserved during treatment with Traumeel®. Additional data alluding to the mode of action of Traumeel® comes from basic research (Heine et al. 2002) which has shown that the organic components of Traumeel® stimulate lymphocytes to synthesize and secrete the cytokine TGF-β (transforming growth factor-β) in whole blood cultures. TGF-β reduces pro-inflammatory substances such as TNF-α, Interferon-gamma, IL-1 and IL-2.

Traumeel® seems to modulate the healing process to assist resolution of symptoms including pain.

For homeopathic substances, pharmacokinetic investigations are not relevant regarding the efficacy of a substance or a combination of different substances. An expert's opinion on toxicology states that the material available and clinical experience provides no indication of toxicological risks associated with ingredients of the homeopathic drug Traumeel® when the product is applied as recommended.

A Traumeel® ointment and gel non-inferiority study (TAASS; Gonzalez et al. 2013) was conducted in 449 athletes with grade 1 or grade 2 acute ankle sprain as a multi-centre, randomized, blinded, parallel-group, active controlled study.

The baseline medians of the pain Visual Analog Scale (VAS) scale were lying between 52.6 mm and 55.7 mm (minimum 29.9 mm, maximum 94.8 mm). All groups showed strong pain decrease with a final median of 0 mm (total pain relief) after 6 weeks. At the

primary endpoint day 7 the median was 21.6 (Traumeel® ointment), 16.0 (Traumeel® Gel) and 17.5 (diclofenac gel).

Total pain relief at day 7 (-100.0%) was reached in 8.5% of the patients in the Traumeel® ointment group, in 5.0% of the patients in the Traumeel® gel group and in 5.9% of the patients in the diclofenac gel group.

The baseline medians of the Foot and Ankle Ability Measure (FAAM) Activities of daily living (ALD) score were lying between 51.2 and 56.0 (minimum 2.4, maximum 98.3). All groups showed strong increase of FAAM-ADL with a final median of 100 (best score) after 6 weeks. At the primary endpoint day 7 the median was 81.0 (Traumeel® ointment), 85.1 (Traumeel® gel) and 79.8 (diclofenac gel). Thus, the best median score was observed in the Traumeel® gel group, followed by the Traumeel® ointment group and the diclofenac gel group.

Altogether, 31 out of 447 patients of the safety population (6.9%) suffered from 43 AEs. At least one AE was experienced by 9 patients out of 152 patients (5.9%) of the Traumeel® ointment group, by 14 patients out of 148 patients (9.5%) of the Traumeel® Gel group and by 8 patients out of 147 patients (5.4%) of the diclofenac gel group. The proportion of treated patients with AEs was therefore below 10% in all treatment groups. The most common AE was headache, reported in 13 cases. None of these 13 headaches was assessed by the investigator as “possible” or “probable” related to investigational medication. Serious AEs were experienced by no patient and in no treatment group. There were no serious or fatal AEs.

Pharmacovigilance data on Traumeel® Gel show 9 non-serious adverse reactions (ARs), assessed with “possible” or “probable” causal relationship to the treatment, in the time period between 01.01.2008 and 01.01.2016. Two of the cases reporting skin reactions were received from a clinical study (TRS-ESP/ TAASS - Study/ EudraCT number: 2008-007939-4). One case reported eye hypersensitivity symptoms and can be considered as an isolated case. The other cases related to hypersensitivity skin conditions, which are already listed in the respective label (allergic reactions). The units sold on Traumeel® gel during this period are 2.047.579 packages. Thus, the incidence ratio for the non-serious ADRs is 7 cases per 2.047.579 packages, which means an event rate of 1 : 292.511.

No AEs indicative of Traumeel® overdose, either for ointment or gel, have been reported. Based on the available data, the overall safety profile of Traumeel® medications is considered being very good.

According to the SmPC of Diclofenac Heumann Gel (HEUMANN PHARMA GMBH & CO. GENERICA KG, N., 2013) its use is contraindicated in case of sensitivity to any components of the gel (e.g. paracetamol, isopropanol, ethanol; see section 6.1.1 for description of other ingredients), for patients in whom asthma attacks, skin rash or acute rhinitis are triggered by acetylsalicylic acid or NSAIDs, treatment for open wound,

infections or inflammation of the skin (e.g. eczema) or application on the mucosa. Possible side effects are also described in the SmPC.

Diclofenac Heumann Gel is only recommended in first and second trimester of pregnancy if absolutely required. Systemic administration of diclofenac inhibited the ovulation in rabbits and the implantation and embryogenesis in rats. Teratogenicity was investigated in rats, cats and rabbits. Based on the available non-clinical data, diclofenac is considered non-teratogenic. (HEUMANN PHARMA GMBH & CO. GENERICA KG, N., 2013).

Placebo is contraindicated in case of sensitivity to any components of the gel, see section 6.1.1 for description.

In the TAASS study (Gonzalez et al. 2013) topical treatment with Traumeel® or diclofenac resulted in reduction of pain and restoration of function in patients with grade 1 or grade 2 ankle sprain. The current study is designed to demonstrate the superior efficacy of Traumed® gel versus placebo and to assess the non-inferiority of Traumed® gel compared to diclofenac gel.

4. Study Objectives

The primary objective of the study is to demonstrate the superior efficacy of Traumed® gel versus placebo in patients with acute lateral ankle sprain.

The secondary objectives are:

- to assess the non-inferiority of Traumed® gel compared to diclofenac gel
- to assess the tolerability and safety of Traumed® gel.

5. Investigational Plan

5.1. Overall Design and Plan of the Study

This is a multicentre, double-blind, randomised, active- and placebo-controlled, parallel-group study.

After evaluation of entry criteria patients with grade 1 or 2 unilateral ankle sprain will be randomised to study treatment. The treatment will be 3 g of Traumed® gel or diclofenac gel or matching placebo gel, administered locally to sufficiently cover the area of the injury, 3 times daily for 7 days. The first treatment will be administered following the baseline study procedures and after randomisation of the patient on Day 1.

After end of investigational treatment patients will be followed up for another 7 days. Consequently, the entire duration of the study for each patient will be 14 days.

Patients will receive paracetamol (acetaminophen) 500 mg/tablet as rescue medication to be taken for pain relief when necessary (*pro re nata*, PRN) during the entire duration of the trial, see section 6.1.9 for further details. In addition, patients will not be allowed to take any pain relief medication other than the provided paracetamol, see section 6.2 for details.

All patients will receive soft support (elastic bandage) on Day 1. There will be a re-evaluation of grading of the disease at Day 4. Patients whose classification will be changed to Grade 3 will be withdrawn from the study. Grade 1 and grade 2 patients will continue using the soft support during the entire study, if required. Grade 2 patients will additionally receive a semi-rigid removable brace on Day 7, see section 6.1.10 for detailed description. It will be strongly recommended to all patients to use arm crutches during the entire trial and with a special importance until Day 4. The patients should only partly weight the sprained ankle when using crutches.

The study will start with the recruitment of the first patient. End of trial is defined as completion of the data base lock.

The study was originally planned to be started in Q1/2018. The first patient was screened on February 26th, 2018. The extended duration of the recruitment period will be approximately 35 months and will be completed when at least 808 eligible patients have been enrolled. *(revised per Amendment to protocol version 3.0)*

5.1.1. Study Schedule

The (planned) study schedule includes the following milestones:

First patient first visit (FPFV):	February 2018
Last patient last visit (LPLV):	December 2020 planned
Database hardlock:	Q1 2021 planned

(revised per Amendment to protocol version 3.0)

Heel ensures that an end of trial notification will be submitted to the concerned Competent Regulatory Authorities and Independent Ethics Committees (IEC) according to regulatory requirements.

5.2. Discussion of Study Design

A multicentre, double-blind, randomised, active- and placebo-controlled, Phase III study is a well-established design and the duration of the treatment and follow-up period is appropriate. Patients are allowed to take rescue medication which protects also the placebo

patients. Using elastic bandages and semi-rigid braces ensures that all patients will receive the necessary mechanical support of the injured ankle.

5.3. Selection of Study Population

Patients with acute unilateral Grade 1 or Grade 2 sprain of the lateral ankle will be enrolled. Grade 3 patients are not eligible as for them topical gel treatment is not appropriate.

Ankle sprains are classified by 3 grades of sprains:

- Grade 1 sprain (mild): Slight stretching and some damage to the fibres (fibrils) of the ligament. The joint is stable.
- Grade 2 sprain (moderate): Partial tearing of the ligament. If the ankle joint is examined and moved in certain ways, abnormal looseness (laxity) of the ankle joint occurs. Clinically partial instability.
- Grade 3 sprain (severe): Complete tear of the ligament. If the investigator pulls or pushes on the ankle joint in certain movements, gross instability occurs. The joint is instable.

Fracture of the ankle should be excluded by using e.g. the Ottawa Ankle Rules. In case of any doubt the exclusion of fracture by x-ray should be considered as per standard of care. After excluding fracture the investigator will evaluate the stability of the ankle joint using the anterior drawer test, the inversion stress manoeuvre and the external rotation test.

The mechanism of the injury and the clinical symptoms (edema, hematoma, location of pain at palpation) will be documented to support the grading.

The high pain and swelling might influence the outcome of the grading at Day 1, therefore a confirmatory check of the grading will be performed at Day 4. Patients who are classified having Grade 3 ankle sprain after randomisation and up to Day 4 will be withdrawn from the study and their data will not be part of the efficacy analysis but will be part of the safety analysis.

The investigators will be trained during the investigator meeting to ensure a consistent assessment and grading between investigators.

5.3.1. Inclusion Criteria

Potential study patients must meet the following inclusion criteria:

1. Acute unilateral Grade 1 or Grade 2 sprain of the lateral ankle
2. ≥18 years of age
3. Legally competent male or female outpatient

4. Injury occurred within previous 24 hours before first treatment expected
5. Signed Informed Consent
6. After 5 minutes of rest, pain on passive movement by investigator measured by Visual Analog Scale (VAS) >50 mm
7. Not pregnant (as proven by negative pregnancy test in case of woman of childbearing potential before first study drug administration) or breast-feeding. Females of childbearing potential must agree to maintain highly effective birth control throughout the study (see all details in section 9.6). Such methods include:
   - oral, intravaginal, transdermal combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation,
   - oral, injectable, implantable hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (if received medical assessment of the surgical success), sexual abstinence (only if defined as refraining from heterosexual intercourse during the entire period of trial participation).

5.3.2. Exclusion Criteria

Potential study patients will be excluded if at least one of the following exclusion criteria is present:

1. Similar injury affecting the same joint within the past 6 months
2. Bilateral ankle injury
3. Grade 3 ankle sprain
4. Fracture of the ankle (It should be excluded by using e.g. the Ottawa Ankle Rules. In case of any doubt the exclusion of fracture by x-ray should be considered as per standard of care)
5. Chronic joint disorders such as clinically relevant osteoarthritis or aseptic arthritis
6. Disorders that may lead to joint oedema for other reasons than ankle sprain (such as heart failure, thrombosis, lymphedema and others)
7. Diagnosis requiring bed rest, hospitalization, surgery, or use of any cast during the planned treatment period
8. Debilitating acute or chronic illness
9. Use of systemic and /or topical corticosteroids in the previous 8 weeks, any analgesics (e.g. paracetamol/ acetaminophen) in the previous 24 hours before

Screening Visit, or 48 hours in the case of long-acting NSAID, cyclooxygenase type 2 (COX-2) specific inhibitors, or tramadol and other opioids. Low dose acetylsalicylic acid (70 – 100 mg per day) for anti-thrombotic therapy is permitted if doses are stable for the month prior to Screening Visit and planned to be stable during the entire study

10. History of sensitivity to any component of the study drugs (including e.g. paracetamol/ acetaminophen intolerance; patients in whom asthma attacks, skin rash or acute rhinitis are triggered by acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs)
11. Unwilling or unable to comply with all the requirements of the study protocol
12. Concurrent injury to proximal structures in ipsilateral lower extremity (i.e. concurrent shin, knee, thigh, or hip injury)
13. History of ligament avulsion, fracture or surgery to the affected lower extremity
14. Presence of infections and/or skin diseases in the area of the study treatment site (including psoriasis)
15. Any previous treatments of the injured ankle, whether topical or systematic, are prohibited except RICE (simultaneous combination of all 4 elements Rest, Ice, Compression and Elevation, which is restricted to be used until starting treatment with the investigational drug)
16. Participation in any clinical study within the past 4 weeks
17. Any relationship of dependence with the sponsor or with the investigator.

5.3.3. Discontinuation of Treatment

Patients who meet any of the discontinuation criteria will discontinue investigational treatment and will be followed up only for AEs until Day 14.

Study investigators may request the patient to discontinue investigational treatment in case of:

- Diagnosis of Grade 3 ankle sprain
- Any other medical condition requiring in the opinion of the investigator a change of the therapy for the baseline condition
- Occurrence of a medical condition requiring use of prohibited medications or treatment
- Medical condition affecting assessment of the primary endpoint
- Medical conditions affecting patient safety if the investigational therapy is continued: conditions and AEs causing safety concerns with investigational treatment to the ankle

joint area OR any other AE or condition that - in the opinion of the investigator – endangers patient safety if the investigational therapy is continued

- Lack of efficacy as considered by the investigator.

Discontinuation of investigational treatment and its reason will be documented in the medical records and recorded in the eCRF. If a patient discontinues investigational treatment, the discontinuation of treatment visit should be performed. Further treatment of the ankle sprain will be at discretion of the investigator and will not be recorded in the eCRF. In case the patient will be treated in another hospital or practice, the investigator will make efforts to collect and record AEs the patient might have had until Day 14. This can be done during an onsite visit of or a phone call with the patient or with the treating physician at the other hospital or practice. Patients who discontinue prematurely from the study will not be replaced, except patients with Grade 3 sprain confirmed at any day up to Day 4 ('replacement' referring to the total number of patients to be enrolled, see also definitions in section 11.4).

5.3.4. Withdrawal of Patients from the Study

Reasons for premature withdrawal (drop out) from the study:

- Diagnosis of Grade 3 ankle sprain at any day up to Day 4
- The patient does not fulfil all inclusion criteria and/or meets any of the exclusion criteria but was randomised by error
- Pregnancy
- Lost to follow up
- Death
- Withdrawal of consent.

Withdrawal from study including its reason will be documented in the medical records and entered into the eCRF. In case the reason for withdrawal from study is withdrawal of consent, the patient will be asked why he/she withdrew his/her consent. The specified reason will be also recorded in the medical records and entered into the eCRF. No further investigational treatment will be used and/or assessments will be performed for withdrawn patients. In case of an ongoing AE, the patient is to be followed up according to the local medical practice.

5.3.5. Study Site Discontinuation by the Sponsor.

The Sponsor may prematurely close a study site at any time for any of the following reasons:

- occurrence of AEs or other safety issues requiring early withdrawal of at least 25% of enrolled patients (if 20 or more of planned patients are enrolled)
- failure to enroll patients, i.e. no patients enrolled after 3 months from site initiation
- persisting occurrence of significant protocol violations affecting patient safety in already enrolled patients
- inaccurate or incomplete data affecting evaluability of patients in final analysis
- significant administrative problems including GCP violations or misconduct of the study which may jeopardize the quality of study.

The reasons for the discontinuation of the study at a study site have to be communicated in writing to the IEC of the relevant site. Afterwards the close-out site visit has to be performed.

5.3.6. Premature Termination or Temporary Suspension of the Study

Heel reserves the right to terminate this clinical study prematurely if, in the opinion of the investigator or Heel, an excessive risk exists or if continuation of the study does not appear to be reasonably justified (i.e. the study is not qualified to show efficacy or harmlessness of the IMP).

If the trial is prematurely terminated or suspended for any reason, the investigator must follow the instructions of the sponsor to stop the trial. The investigator should promptly inform all affected patients and should assure appropriate therapy and follow-up. Furthermore, the investigator should promptly inform the involved personnel of the institutions, where applicable.

In both cases, Heel will promptly inform the Competent Regulatory Authority and IEC and provide them with a detailed written explanation of the termination or suspension.

If the Competent Regulatory Authority or IEC terminates or suspends its approval or favorable opinion of a trial, the sponsor will inform the investigators and institutions and provide them with a detailed written explanation of the termination or suspension.

Suspended trials can only be restarted after re-approval or positive opinion from Competent Regulatory Authority and IEC.

If the investigator or institution terminates or suspends the trial at his/her site without prior agreement of the sponsor, the investigator or institution should promptly inform the sponsor and should provide the sponsor with a detailed written explanation of the termination or suspension. Depending on this communication the sponsor will inform IEC and Competent Regulatory Authority, in accordance with applicable regulations.

6. Study treatment

6.1.1. Description of Study Medication

Study medication will be provided by the Production Operations Department of Biologische Heilmittel Heel GmbH.

Investigational Medicinal Product (IMP)

Ingredient	Traumed® gel, 100 g contains
Arnica montana D3	1.500 g
Calendula officinalis Ø[1]	0.450 g
Hamamelis virginiana Ø	0.450 g
Echinacea Ø	0.150 g
Echinacea purpurea Ø	0.150 g
Matricaria recutita Ø	0.150 g
Symphytum officinale D4	0.100 g
Bellis perennis Ø	0.100 g
Hypericum perforatum D6	0.090 g
Achillea millefolium Ø	0.090 g
Aconitum napellus D1	0.050 g
Atropa belladonna D1	0.050 g
Mercurius solubilis Hahnemanni D6	0.040 g
Hepar sulfuris D6	0.025 g
Excipients	contains purified water, ethanol, carbomers, sodium hydroxide solution
Ethanol content	24,4 % (V/V)
Bulk Number	9934

Ingredient	placebo gel, 100 g contains
Excipients	contains purified water, ethanol, carbomers, sodium hydroxide solution
Ethanol content	24,4 % (V/V)
Bulk Number	78980

The composition of the Diclofenac Heumann Gel (in the Study Protocol referred as `diclofenac gel`) is described in the "Fachinformation" as follows:

Ingredient	Diclofenac Heumann Gel, (1%), 100 g contains
Diclofenac sodium salt	1,00 g
Excipients	contains purified water, ethanol, isopropanol, carbomers, ammonia solution

[1] Ø Homeopathic mother tincture

6.1.2. Assigning Patients to Treatment Groups

Patients will be randomly allocated to Traumed® gel or diclofenac gel or placebo gel in 2:1:1 randomisation. A corresponding random code list is prepared using the random permuted block scheme. In accordance with the ICH Biostatistics Guideline, the block size is intentionally not given in the trial protocol [ICH E9 § 2.3.2, "Investigators and other relevant site staff should generally be blind to the block length"]. The sealed random code list and the sets of sealed envelopes are prepared using the validated program RANCODE in a validated working environment at idv Data Analysis and Study Planning, Gauting, Germany.

Patients will be randomised based on the 4-digit randomisation number recorded on the investigational medication (IMP). The next patient eligible for randomisation will be allocated to the lowest available randomisation number at the site. IMP will be provided to all sites in pre-defined shipment blocks and shipment blocks will contain appropriate distribution of randomisation codes belonging to the 3 treatment arms.

6.1.3. Dosage and Administration of IMP

Randomised patients will receive either Traumed® gel or diclofenac gel or placebo gel. The treatment regimen is 3 g of study drug applied by gentle rubbing to sufficiently cover the area of the injury 3 times daily for 7 days. Patients will use dosing card to administer an appropriate amount of the study drug.

The selection of dose and timing for each patient dosage and administration of IMP is in line with established clinical practice.

The team member responsible exclusively for handling the study medication will apply the first and last IMP dose during Screening/ Baseline Visit (Day 1) and End of Treatment (EoT) Visit 4 (Day 7), train all patients how to use the IMP with special regard to the dosage and how to use the dosing card and will ensure that they are trained for the application of the study medication.

6.1.4. Blinding

This is a double-blind, randomised study. Study personnel will be blinded during the study. The investigator will keep the sealed treatment (emergency) code envelopes throughout the course of the study and must not break the code without a valid reason (e.g. in case of emergency). Emergency unblinding is to be done only when absolutely necessary for the management of an individual patient and where stopping the blinded medication is not sufficient in the judgement of the investigator. The justification for the unblinding has to be discussed by telephone with the Sponsor`s responsible person to

ascertain whether unblinding is necessary and that appropriate steps for patient management are taken.

To further support the blinding each investigational site will have a team member responsible exclusively for handling the study medication and soft support/ semi-rigid brace, and who will not be involved in any other study procedures related to the patient (in the Study Protocol referred as team member responsible exclusively for handling the study medication). He/she will apply the first dose of investigational treatment and will train the patient how to use the dosing card and how to apply the study medication and the elastic bandage/ semi-rigid brace. The team member responsible exclusively for handling the study medication will remove the bandage at each visit before the investigator makes the investigations and will apply the IMP and replace the elastic bandage/ semi-rigid brace (as required as of Visit 4).

It will be ensured that only the team member responsible exclusively for handling the study medication will be present at the IMP gel applications and at removing and replacing the bandage/ semi-rigid brace. No other member of the investigator team will have any contact with the IMP for the entire duration of the study.

Disposable dosing cards will be used for each application. These cards will indicate the amount of IMP gel for each application and in addition due to the camouflage design they will also support the blinding of the patients.

The returned IMP will be stored in zipped bags closed by the team member responsible exclusively for handling the study medication until return to the sponsor for destruction.

Site staff of all investigational sites will receive a comprehensive training for these procedures at the investigator meeting as well as at the Site Initiation Visits. In addition, an agreement will be signed by all site personnel (principal investigator, investigator(s), study nurse(s) and team member(s) responsible exclusively for handling the study medication as a minimum) to ensure the procedures are understood and followed.

6.1.5. Manufacturing, Packaging and Labelling

Manufacturing including packaging and labelling will be carried out in accordance with the GMP guidelines (including their Annexes), ICH GCP requirements, sponsor approved standard operating procedures, The European Union (EU) Clinical Trial Directive and all applicable local laws.

Final labelling and packaging of the products will be performed by the Production Operations Department of Biologische Heilmittel Heel GmbH in accordance with their standard operating procedures (SOPs) and international requirements. Product labels comply with the relevant GCP requirements including national regulatory requirements and languages.

6.1.6. Shipment and Storage of IMP

IMP will be supplied to the sites together with the relevant documentation. The site staff will acknowledge the receipt of all shipments via fax or email.

IMP will be handled by the team member responsible exclusively for handling the study medication. He/she will be appointed by the principal investigator.

IMP has to be stored in an appropriate secure area (e.g. a locked cabinet) not above 25°C and not frozen, as indicated in the packaging.

The IMP is to be dispensed only under the restricted conditions defined in the present protocol (see 6.1.5).

All returned IMP will be stored in zipped bags until destruction.

6.1.7. IMP Accountability and Destruction

Each center will be responsible for maintaining an accurate log and inventory of IMP received, dispensed and returned. The designated CRO will provide the framework for documenting study drug accountability throughout the study. The team member responsible exclusively for handling the study medication has to record the shipment, dispense, and return of IMP on the *drug accountability form*. The *drug accountability form* needs to be available for inspection at any time. Data of the investigational product dispense, use and return will be entered into the eCRF.

The designated CRO representatives will verify drug accountability during routine site monitoring visits and at the completion of the trial. An explanation of any discrepancies has to be provided by the responsible team member.

Detailed drug accountability has to be performed for remaining unused and returned used IMP. Remaining and returned IMP tubes and copies of the completed *drug accountability forms* will be sent back to Heel for destruction by the team member responsible exclusively for handling the study medication after last patient last visit. Certificates of returns have to be signed by the responsible person(s).

6.1.8. Treatment Compliance

The compliance with investigational treatment will be ensured by weighing the gel tubes returned by the patient at Day 4 and finally at Day 7. Afterwards the team member responsible exclusively for handling the study medication will seal the used tubes in zipped bags.

6.1.9. Rescue Medication

Randomised patients will receive Paracetamol (acetaminophen) 500 mg/tablets as a rescue medication to be taken for pain relief when necessary (*pro re nata*, PRN), with a maximum dose of four tablets or 2000 milligrams per day (mg/d), and not more than 2 tablets at a time. Patients will not be allowed to take paracetamol within 8 hours prior to visit 2. For further visits the restriction is 24 hours, consequently taking paracetamol will not be allowed within 24 hours prior to visit 3, visit 4 and visit 5. Other allowed and prohibited concomitant medications are described in section 6.2.

Randomised patients will also receive a patient diary and will be instructed to document the time and dose of each intake of the rescue medication (paracetamol) in a patient diary every day and to bring the patient diary to the site at each patient visit. Site staff will check the patient diary at all visits if rescue medication has been taken at all, and if yes, according to the requirements.

In addition, it is essential that time and dose of <u>all</u> paracetamol tablet intakes (rescue medication) are documented by the site staff in the eCRF.

The site will record the total number of tablets taken by the patient from one visit to the next on the *rescue medication accountability form*. Patient Diary 1 will be used between visits at Day 1 and Day 4, it will be collected by the site staff on Day 4 and will be replaced with Patient Diary 2, which will be used until end of the study.

6.1.10. Supportive Therapy

All patients will receive soft support (elastic bandage) on Day 1. The team member responsible exclusively for handling the study medication will train all patients how to use the elastic bandage and - if needed - for the usage of the semi-rigid brace.

Re-evaluation of grading will be performed at Day 4. Grade 1 patients will continue using the soft support during the entire trial, as required *(revised per Amendment to protocol version 3.0)*. Grade 2 patients will receive a semi-rigid removable brace on Day 7. Grade 3 patients will be withdrawn from the trial and further treatment will be at the discretion of the investigator. The semi-rigid braces will be provided to all patients centrally and the investigator team will be trained for correct use at the investigator meeting and/or at Site Initiation Visits and/or during regular Monitoring Visits to ensure standardized circumstances. In addition, it will be strongly recommended to all patients to use arm crutches during the entire trial and with a special importance until Day 4. The patients should only partly weight the sprained ankle when using crutches.

Use of arm crutches and semi-rigid braces will be recorded on the medical records and entered into the eCRF.

The use of RICE (simultaneous combination of all 4 elements rest, ice, compression, and elevation) is restricted to the time immediately after the event, and before starting treatment with the investigational drug. After start of study treatment and during the entire course of the trial use of RICE is prohibited. If it occurs, it will be recorded on medical records and entered into the eCRF.

6.2. Prior and Concomitant Medications

Use of local or systemic corticosteroids is not allowed 8 weeks before screening and during the study. Long-acting NSAIDs, COX-2 specific inhibitors, tramadol or other opioids are not allowed within 48 hours, and any other analgesics (e.g. acetaminophen) are not allowed within 24 hours prior to the screening /baseline visit and during the study. Disallowed medication includes all forms of those medications, i.e. topical, oral or parenteral.

Low dose (70-100 mg/day) acetylsalicylic acid for anti-thrombotic therapy is permitted if doses are stable for the month prior to screening and expected to remain stable throughout the study period.

Patients have to be instructed that they must not take any pain relief medication other than the provided paracetamol rescue medication during the entire study period, see section 6.1.9 for details. Any intake of pain medications other than the rescue medication will be recorded in the patient diary and entered into the eCRF.

Antithrombotic treatment may be given at the discretion of the investigator in accordance with currently valid guidelines.

Medications required for treatment of symptoms/diseases that are totally unrelated to the treated indication and related disorders are permitted during the trial and have to be documented in the eCRF (including name of the medication, date of administration and its duration, and indication for use).

7. Study Procedures

7.1. Schedule of Study Procedures

A schedule of study procedures and events is provided in Table 1.

Table 1 Schedule of Study Procedures

	Initial Visit Screening/Baseline	**Treatment Visits Visit 2**	**Visit 3**	**EoT Visit Visit 4**	**Final Visit Visit 5**
	Day 1	Day 2	Day 4 + 1 day	Day 7 +/- 1 day	Day 14 +/- 1 day
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Demographics	X				
Pregnancy test (if applicable)	X			X	
Medical history	X				
Time and grading of injury	X				
Height/Weight (BMI) [1]	X				X[1]
Physical examination including blood pressure and pulse	X				X
Randomization	X				
Dispense patient diary[2]	X		X		
FAAM-ADL[3]	X	X	X	X	X
Pain at rest by Visual Analog Scale (VAS)[3]	X	X	X	X	X
Pain on passive movement by Visual Analog Scale (VAS)[3]	X	X	X	X	X
IMP tubes dispensed	X				
Investigational treatment	X	X	X	X	
Application of soft support (elastic bandage)	X	X	X	X (as required)	X (as required)
Rescue medication dispensed	X		X (if needed)	X (if needed)	
Diary reviewed		X	X	X	X
Diary returned			X		X
IMP tubes weighted			X	X	
Rescue medication reviewed		X	X	X	X
IMP tubes returned and sealed				X	
Rescue medication returned					X
Check use of other pain medication and record if any	X	X	X	X	X
Record previous/concomitant medication	X	X	X	X	X
Record Adverse Events[4]	X	X	X	X	X
Record use of arm crutches	X	X	X	X	X
Confirmatory check of grading			X		
Application of semi-rigid brace for Grade 2				X	X
Question to patients which treatment they assume to have received					X

[1] At Visit 5 (day 14) only the weight will be measured.
[2] The first patient diary will be collected on Day 4. The patient will receive second diary on the same day. [3] The time point of each visits/ measurements of patients shall be ideally the same at each visit (+/- 1 hour). [4] Including adverse events observed at the site of administration of the IMP (lateral ankle).

7.2. Description of Patient Visits

7.2.1. Screening / Baseline Visit (Day 1)

Day 0 is defined as the day of injury. The day of inclusion to the study is Day 1. If the patient is included into the study on the same day when the injury has occurred, Day 0 and Day 1 are identical. The date and time of injury and date and time of the first treatment with investigational drug has to be documented in the eCRF to ensure that the time difference between both events does not exceed 24 hours.

Suitable outpatients will be asked by the investigator about their willingness to be included in the clinical trial. The patient is to be informed verbally and in writing in the appropriate language about the nature and purpose of the study, the treatments to be administered, the possible risks and discomfort, the benefits to be expected, and how data collected in this trial will be handled and shared. The patient informed consent form is to be signed and dated by the patient and countersigned by the investigator prior to proceeding with the Screening/ Baseline Visit procedures. The investigator will provide each patient with a second original of the signed and dated informed consent form. See section 1.3 for more details.

Patients who have signed the patient informed consent form will be assessed if they meet all inclusion but none of the exclusion criteria.

Only patients who fulfil all entry criteria will be enrolled and will receive a unique 7-digit patient number (in former protocol versions referred to as ‘E-code’).

The following study procedures are to be performed:

- Check of inclusion/ exclusion criteria
- Record medical history and demographics
- Review and record previous/ concomitant treatments for the sprained ankle including use of RICE (i.e., the simultaneous combination of all 4 elements rest, ice, compression and elevation) or of parts of these 4 measures
- Review and record previous/concomitant treatments for any other clinical condition(s) also with respect to disallowed medication
- Ankle sprain-related measurements:
    - FAAM-ADL

- VAS for evaluating pain at rest for baseline. VAS for pain on passive movement by investigator for inclusion and for baseline. Date and time of assessment will be recorded. Each pain assessments should take place at the same time (+/- 1 hour related to baseline assessment time) at each visit whenever possible

- Physical examination of cardiovascular, respiratory, musculoskeletal and gastrointestinal systems, head and eyes
- Measurement of body weight and height, (for body mass index), blood pressure and heart rate
- Pregnancy test (urine dipstick) for women of childbearing potential.

7.2.2. Randomization

- Patients who fulfil all the inclusion criteria and do not meet any of the exclusion criteria will be randomised to the investigational treatment and will receive Traumed® gel or diclofenac gel or placebo gel. (See section 6.1.2)
- The team member responsible exclusively for handling the study medication will dispense IMP to the patient, will apply the first dose and will train the patient how to use the dosage card and the IMP.
- The team member exclusively responsible for handling the study medication will train the patient how to use the elastic bandage and place the elastic bandage (soft support)
- Paracetamol (500 mg/tablet) will be dispensed as rescue medication for pain relief with a maximum dose of four tablets or 2000 mg/day, but not more than 2 tablets at a time. Patients are to be instructed to refrain from taking any analgesic medication other than the provided rescue medication and that they are not allowed to take paracetamol neither within 8 hours prior to visit 2. (For further visits the restriction will be 24 hours, consequently taking paracetamol will not be allowed within 24 hours prior to visit 3, visit 4 and visit 5).
- Patient diary will be distributed to the patient. The patient will be instructed to document the date, time and amount of paracetamol intake every day and to bring the diary to the site at each visit. In addition, the patient will be requested to document other concomitant medications in the diary and to record how many times he/she has applied the IMP on each day. The site staff will transfer the paracetamol consumption since last patient visit (including date, time, and amount of consumed tablets) and the IMP use from the diary into the eCRF.
- The patient will be strongly suggested to use arm crutches during the entire trial and with a special importance until Day 4

- Evaluation of any AEs experienced after informed consent has been signed, including AEs observed at the site of administration of the IMP (lateral ankle). SAE evaluation and reporting if applicable
- Patients will be instructed to return to the next visit (+/- 1 hour related to baseline assessment time) and return patient diary, IMP and remaining rescue medication

7.2.3. Treatment Visit 2 (Day 2)

The following observations/ procedures are to be performed and checked:

- FAAM-ADL (+/- 1 hour related to baseline assessment time whenever possible)
- Removal of the elastic bandage by the team member responsible exclusively for handling the study medication
- Ankle sprain-related measurements: VAS for evaluating pain at rest and pain on passive movement (+/- 1 hour related to baseline assessment time whenever possible)
- Review of rescue medication usage recorded in the patient diary and transfer data into the eCRF
- Check other (prohibited) pain medication and/or whether RICE was used with the patient (RICE is prohibited, i.e. the simultaneous combination of all 4 elements rest, ice, compression and elevation; parts of these 4 measures are acceptable), record on medical records and enter into the eCRF if any
- Record any change in other concomitant medications
- Record use of arm crutches
- Evaluation and recording of any AEs the patient has experienced since the last visit including possible re-injury of the ankle and adverse events observed at the site of administration of the IMP. SAE evaluation and reporting if applicable
- Application of IMP and elastic bandage by the team member exclusively responsible for handling the study medication
- Drug accountability for rescue medication
- Instruct the patient that he/she is further not allowed to take any analgesic medication other than the rescue medication provided by the study site staff (paracetamol) with a maximum dose of four tablets or 2000 mg/day, but not more than 2 tablets at a time. He/she will not be allowed to take any tablets of it within 24 hours prior to visit 3.
- Instruct the patients to return to next visit (+/- 1 hour related to baseline assessment time) and return patient diary, IMP and remaining rescue medication.

*7.2.4. Treatment Visit 3 (***Day 4 +1/- 0 day***)*

The following observations/ procedures are to be performed and checked:

- FAAM-ADL (+/- 1 hour related to baseline assessment time whenever possible)
- Removal of the elastic bandage by the team member exclusively responsible for handling the study medication
- Ankle sprain-related measurements: VAS for evaluating pain at rest and pain on passive movement (+/- 1 hour related to baseline assessment time whenever possible)
- Review of rescue medication and IMP usage recorded in the patient diary and transfer data into the eCRF
- Check other pain medication and/or RICE use with the patient (both are prohibited), record on medical records and enter into the eCRF if any
- Record any change in other concomitant medications
- Record use of arm crutches
- Evaluation and recording of any AEs the patient has experienced since the last visit including a possible re-injury of the ankle and adverse events observed at the site of administration of the IMP. SAE evaluation and reporting if applicable
- Collection of patient diary used from Day 1 to Day 4 and dispense patient diary to be used from Day 4 to Day 14
- Confirmatory check of grading. Patients with severity Grade 3 will be withdrawn from the study. No further data will be collected from these patients. Further treatment and taken care will be at discretion of the investigator according to the local medical practice.
- Drug accountability for IMP by weighing of study drug tube by the team member exclusively responsible for handling the study medication
- Application of IMP (and elastic bandage, if still required) by the team member exclusively responsible for handling the study medication
- Drug accountability for rescue medication
- Dispense 500 mg paracetamol tablets (one box containing 20 tablets) as rescue medication for pain relief (if needed). Instruct the patient that he/she is further not allowed to take any analgesic medication other than the rescue medication (paracetamol) provided by the study site staff with a maximum dose of four tablets or 2000 mg/day, but not more than 2 tablets at a time. He/she will not be allowed to take any paracetamol tablets within 24 hours prior to visit 4.

- Instruct patients to return to next visit (+/- 1 hour related to baseline assessment time) and return patient diary, IMP and remaining rescue medication.

7.2.5. End of Treatment Visit (Visit 4; Day 7 +/- 1 day) or Discontinuation of Treatment Visit if applicable

The following observations/procedures are to be performed and checked:

- FAAM-ADL (+/- 1 hour related to baseline assessment time whenever possible)
- Removal of the elastic bandage by the team member exclusively responsible for handling the study medication
- Ankle sprain-related measurements: VAS for evaluating pain at rest and pain on passive movement (+/- 1 hour related to baseline assessment time whenever possible)
- Pregnancy test (urine dipstick) for women of childbearing potential
- Review of rescue medication and IMP usage recorded in the patient diary and transfer data into the eCRF
- Check other pain medication and/or RICE use with the patient (both are prohibited), record on medical records and enter into the eCRF if any
- Record any change in other concomitant medications
- Record use of arm crutches
- Evaluation and recording of any AEs the patient has experienced since the last visit including possible re-injury of the ankle and adverse events observed at the site of administration of the IMP. SAE evaluation and reporting if applicable
- Last application of IMP by the team member exclusively responsible for handling the study medication.
- Application of elastic bandage for patients with Grade 1 ankle sprain (if still required), and semi-rigid brace for patients with Grade 2 ankle sprain by the team member exclusively responsible for handling the study medication (grading based on confirmation check of grading performed at Day 4)
- Drug accountability for IMP, weighting and collection of study drug tube by the team member exclusively responsible for handling the study medication
- Drug accountability for rescue medication
- Dispense 500 mg paracetamol tablets (one box containing 20 tablets) as rescue medication for pain relief (if needed). Instruct the patient that he/she is further not allowed to take any analgesic medication other than the rescue medication (paracetamol) provided by the study site staff with a maximum dose of four tablets or

2000 mg/day, but not more than 2 tablets at a time. He/she will not be allowed to take any paracetamol tablets within 24 hours prior to visit 5

- Patients will be instructed to return to the next visit (+/- 1 hour related to baseline assessment time) and return patient diary and remaining rescue medication.

7.2.6. Final Visit (Visit 5; Day 14+/-1 day)

- FAAM-ADL (+/- 1 hour related to baseline assessment time whenever possible)
- Removal of the elastic bandage/semi rigid brace
- Ankle sprain-related measurements: VAS for evaluating pain at rest and on passive movement, (+/- 1 hour related to baseline assessment time whenever possible)
- Review of rescue medication usage recorded in the patient diary and transfer data into the eCRF
- Check other pain medication and/or RICE use with the patient (both are prohibited), record on medical records and enter into the eCRF if any
- Record any change in other concomitant medications
- Record use of arm crutches
- Evaluation and recording of any AEs the patient has experienced since the last visit including possible re-injury of the ankle. SAE evaluation and reporting if applicable
- Application of elastic bandage (if still required)/ semi-rigid brace
- Physical examination of cardiovascular, respiratory, musculosceletal and gastrointestinal systems, head and eyes
- Measurement of body weight, blood pressure and heart rate
- Collection of Patient Diary used from Day 4 till Day 14
- Collect returned rescue medication and enter details into the eCRF
- Final drug accountability for rescue medication
- Collect answer from patients regarding their guess on which treatment they were receiving (Traumed® or diclofenac or placebo)
- Discuss further treatment and care with the patient according to the local medical practice.

8. Assessment of Efficacy

8.1. Primary Efficacy Parameter

Pain assessment on VAS for evaluating pain on passive movement

Ankle pain will be measured using a 100 mm VAS starting with no pain (0 mm) and ending with most severe imaginable pain the patient may imagine in relation to his/her ankle sprain (100 mm).

First the patients will be asked after 5 minutes rest to assess their pain themselves on a VAS scale for a secondary efficacy assessment (for details see section 8.2).

Than while the patient is still at rest the investigator should perform 10° dorsal- and 30° plantar flexion on the injured ankle and the patients will assess their pain themselves on a VAS scale (primary efficacy assessment). The range of movement will be controlled by using a goniometer. It is very important that no lateral move of the ankle joint will be made. The pain to be assessed is the pain on passive movement.

To ensure a consistent assessment between investigators, investigators will be trained together at the investigator meeting.

The date and time of assessment will be recorded. Pain assessments should take place +/- 1 hour related to baseline at each visit for the individual patient, whenever possible.

8.2. Secondary Efficacy Parameters

Pain assessment on VAS for evaluating pain at rest

Ankle pain will be measured using a 100 mm VAS starting with no pain (0 mm) and ending with most severe imaginable pain the patient may imagine in relation to his/her ankle sprain (100 mm).

The patients will be asked after 5 minutes rest to assess their pain themselves on a VAS scale.

Foot and Ankle Ability Measure (FAAM), Activities of Daily Living (ADL)

The FAAM is a validated questionnaire and was developed to meet the need for a self-reported evaluative instrument that comprehensively assesses physical function of individuals with musculoskeletal disorders of the leg, foot, and ankle.

It is a well-established and widely used responsive multidimensional outcome measure with a sensitivity capable of detecting subject-relevant symptoms and clinically significant changes in health in ankle sprain.

The FAAM-ADL/S consists of an ADL (21-item scale) and a sports (S) subscale (8 items) asking study participants to rate their ability to perform specific tasks. The FAAM-ADL/S is a valid and reliable instrument in the public domain (Martin 2005, Carcia et al. 2008).

The possible responses for each item are the following: no difficulty, slight difficulty, moderate difficulty, extreme difficulty, unable to do and not applicable.

In this clinical trial FAAM-ADL will be used. The scoring of the FAAM-ADL will be performed according to the recommendations of Martin et al. 2005.

The response to each item on the FAAM-ADL subscale will be recorded from 4 to 0, with 4 being 'no difficulty' and 0 being 'unable to do'. Responses marked as not applicable will not counted. The scores on each of the items will be added together to get the item score total. The total number of items with a response is multiplied by 4 will get the highest potential score. If all 21 items are answered, the highest potential score will be 84. If one item is not answered the highest potential score will be 80, if two are unanswered the highest potential score will be 76. The total item score will be divided by the highest potential score and then multiplied by 100 to produce the FAAM-ADL score that ranges from 0 to 100. According to the above recommendations the final scores of the FAAM-ADL subscale is to be standardized to a 0 - 100 scale (0 = worst score, 100 = best score).

Time to 50 % improvement of pain measured by VAS

The time to 50 % improvement will be calculated from VAS assessments on pain at rest performed at all patient visits using the percent changes from baseline (recorded at Day 1).

Rescue medication

The rescue medication use will be documented in the eCRF based on the information given in the patient diary and the drug accountability for rescue medication during the study.

8.3. Safety Assessments

In this study topical medications are applied for a local disorder where systemic effects are neither expected from the disorder nor from any of the investigational medications given. Due to these reasons, no safety laboratory testing is planned for this study.

Adverse Events

Definition, collection and reporting of adverse events are described in section 9.

Vital Signs

Vital signs (heart rate, systolic/ diastolic blood pressure) will be collected and evaluated by comparison of the results obtained pre- and post-treatment.

Physical examination

At screening/ baseline and at final visit a physical examination will be performed. Physical status of cardiovascular, respiratory musculoskeletal and gastrointestinal systems, head and eyes and in addition other abnormalities if applicable will be recorded in the eCRF.

Any clinically significant change observed at the final evaluation of vital signs and physical examination in comparison with baseline has to be evaluated carefully, recorded as AE if abnormal, and a possible causality will be evaluated (see section 9.3.2).

Appropriateness of Measurements

All clinical procedures that will be used in this study are standard and generally accepted.

9. Safety Reporting

9.1. Definitions

9.1.1. Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an (investigational) medicinal product, whether or not considered related to the (investigational) medicinal product.

9.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose

- results in death
- is life-threatening (note: the term “life-threatening” refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe)
- requires patient hospitalisation or prolongation of existing hospitalisation (for the purpose of this study, a hospitalisation is defined as a hospital stay of at least 8 hours and/or an overnight stay)
- results in persistent or significant disability/incapacity

- is a congenital anomaly/ birth defect

or

- other medically important condition.

Other medically important conditions are defined as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one or more of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalisation, or development of drug dependency or drug abuse.

However, medical judgement has to be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not-serious is made independently of any attribution of causality.

Events requiring treatment on an emergency outpatient basis (not resulting admission to hospital) and not fulfilling any of the definitions of serious given above are NOT considered to be SAE.

9.1.3. Medical Events not to be Considered Adverse Events or SAEs

The following events should not be recorded as an AE/ SAE if recorded at the Screening/ Baseline Visit and/or the basic examination of a clinical trial:

- A pre-planned procedure, e.g. surgery and invasive procedures, unless the condition for which the procedure was planned has worsened since baseline. Complications to pre-planned procedures should be recorded as AEs.
- A pre-existing condition found as a result of Screening/ Baseline Visit procedures.
- Variations in chronic disease symptoms and in related investigational results if similar variations were observed earlier. These include symptoms and their intensity that are requested and documented in the eCRF, Diary or Questionnaire at the respective visits.
- Compromised or biologically implausible test results, e.g. mechanical or physical effects on blood samples or values incompatible with life, respectively.
- Pregnancy is not considered to be an AE.

Note: Any worsening in severity or frequency of a concomitant illness or any new illness diagnosed in the study period has to be regarded as AEs/SAEs.

In this clinical trial deterioration of ankle sprain symptoms will not be recorded as an AE/SAE.

9.1.4. Adverse Reaction

An Adverse Reaction (AR) is any untoward and unintended response to an IMP that is considered to have a reasonable possibility of a causal relationship with the treatment, i.e. the relationship cannot be ruled out.

9.1.5. Unexpected Adverse Reaction

An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the information available on the IMP reference safety information, (i.e. the actual IB for an unauthorized IMP; an SmPC/ CCSI/ CCDS for an authorized product.

9.1.6. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious AR, the nature or severity of which is not consistent with the applicable reference safety information, (i.e. the actual IB for an unauthorized IMP; an SmPC/ CCSI/ CCDS for an authorized product.

9.2. Recording of Adverse Events

All AEs that occur during the entire course of the study after the patient has signed the informed consent are to be collected and reported in the eCRF, regardless of whether they are reported by the patient, elicited by investigator questioning, detected through physical examination, or by other means. These should include AEs observed at the site of administration of the IMP (lateral ankle) as well. AEs of Screening Failures will be documented on the paper *AE Reporting Form* as they will not be entered in the eCRF.

9.3. Evaluation of Adverse Events

As far as possible, each AE is described by:

- duration (start and end dates)
- start/end of investigational medication and/or non-investigational medication including – but not limited to – rescue medication
- intensity (mild, moderate, severe)
- investigator causality (relationship to the investigational medicinal product)

- action(s) taken (dose change of investigational medication and/or non-investigational medication including – but not limited to – rescue medication, treatment of AE etc.) including start and end of respective action
- concomitant diseases and respective medication in general
- start, end and dosage of rescue medication
- outcome.

9.3.1. Adverse Event Intensity

AE intensity determined by the clinical investigator on the basis of his/her direct observations or the patient's reporting:

- Mild: causes no limitation of usual activities; the patient may experience slight discomfort
- Moderate: causes some limitation of usual activities; the patient may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

9.3.2. Adverse Event Causality (Relationship Guide)

Any AE has to be judged for causality (relationship to investigational medication and/or to non-investigational medication including – but not limited to – rescue medication and relationship to study procedure). The investigator will assess causal relationship between IMP and all AEs whether there is a reasonable possibility that the investigational medication caused the event.

The assessment will be based on the question `Do you consider that there is a reasonable possibility that the AE may have been caused by the IMP?`

The evaluated answer will be `yes` or `no`.

In case the reasonable possibility can`t be excluded, reasonable possibility of causal relationship should be considered until further evidence will be available to exclude it.

For AEs the causal relationship to other medications and study procedures will also be assessed. In case of reasonable possibility that the AE may has been caused by study procedures or other medication the evaluated answer will be `yes`.

9.4. Handling of Adverse Events

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the investigational product and/or non-investigational product including – but not limited to – rescue medication has to be discontinued if appropriate. Follow-up evaluations of the patient are to be performed until the patient recovers or until the clinical investigator considers the situation to be no longer clinically significant.

Investigators monitor and register all AEs on the *AE form* of the eCRF at each visit. For any AE a specific diagnosis rather than signs or symptoms have to be given in the eCRF. In absence of a specific diagnosis, an individual *AE form* has to be filled in for each, sign or symptom to allow proper MedDRA coding.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of monitoring of persistent AEs will be provided in the Data Handling Manual/ Data Validation Plan. If an AE is still not resolved at the end of the study for the individual patient, this will be documented as ongoing at study completion.

For recurrent AEs, i.e. AEs of the same nature, but with a different date of onset, an individual *AE form* has to be completed for each of them.

AEs occurring after the termination of the study for the individual patient and/or of the study in total are to be reported to Biologische Heilmittel Heel GmbH even after the clinical trial has been completed if, in the judgement of the investigator, there is an association between the event and the previous use of the product under investigation.

9.5. Reporting of Serious Adverse Events

If the AE is classified as serious, the clinical investigator has to complete and also sign the SAE module in the eCRF. It is the responsibility of the investigator to send the SAE report out of the eCRF to the Drug Safety Department and Study Team of the designated CRO within **24 hours** after being aware of it, and print the report out of the eCRF and file it in the Investigator Site File. At the earliest possible date, the *SAE report form* has to be followed by a detailed report and any documentation that may became available, e.g. hospital records, autopsy reports, and/or other pertinent documents.

All the above documents in addition to the SAE report will be sent by fax to the Drug Safety Department of the designated CRO within 24 hours (see fax number below) and the original documents will be filed in the Investigator Site File. Personal data of the patient should be deleted or blackened, the 7-digit patient number (formerly named ‘E-code’) and study code (C1502) to be used for patient identification.

For reporting SAEs in the event of technical failure of eCRF, a paper form of *SAE Report* need to be completed and faxed within 24 hours using the following contact:

AMS Safety Department (CRO)

Fax no.: +49 (0) 621 700 95 950

At the earliest possible date, the SAE report form has to be completed in the eCRF and procedures described in the first paragraph should be followed. A detailed follow-up report and any documentation that may be available, e.g. hospital case records, autopsy reports, and/or other pertinent documents will be sent via fax.

The primary person responsible for Safety at the Pharmacovigilance Department of Biologische Heilmittel Heel GmbH is:

Franziska Wörner
Biologische Heilmittel Heel GmbH
Dr.-Reckeweg-Straße 2-4
76532 Baden-Baden, Germany
Phone: +49 (0) 7221 501- 361
Fax: +49 (0) 7221 501-3099
Email: drugsafety@heel.com

Availability in emergency patient safety situation (24 hours in 7 days/week)
Mobile: +49 (0) 160 / 88 29 373

The Qualified Person for Pharmacovigilance (QPPV) at Biologische Heilmittel Heel GmbH is:

Dr Norbert Skuballa
Biologische Heilmittel Heel GmbH
Dr.-Reckeweg-Straße 2-4
76532 Baden-Baden, Germany
Phone: +49 (0) 7221 501-3225
Fax: +49 (0) 7221 501-3099

Heel complies with applicable regulatory requirement(s) related to the reporting of SAEs and SUSARs to the Competent Regulatory Authority, ECs and investigators. In addition, Heel or designated CRO will prepare an annual Development Safety Update Report (DSUR) according to regulatory requirements.

9.6. Pregnancy

Females who are pregnant or breast-feeding are not allowed to participate in this clinical trial. Pregnancy test will be performed for woman of childbearing potential before first study drug administration to exclude pregnancy. Woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

In the Summary of Product Characteristics for Diclofenac Heumann Gel (HEUMANN PHARMA GMBH & CO. GENERICA KG, N., 2013), administration of Diclofenac Heumann Gel is under 4.6 only recommended during the first and second trimester of pregnancy if absolutely required.

Females of childbearing potential must agree to maintain highly effective birth control throughout the study. Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[1]
- intrauterine device (IUD) [1],
- intrauterine hormone-releasing system (IUS) [1]
- bilateral tubal occlusion[1]
- vasectomised partner[1,2]
- sexual abstinence[3].

[1] Contraception methods that in the context of this guidance are considered to have low user dependency.

[2] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child bearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[3] In the context of the guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

All pregnancies observed during the course of the study and their outcomes should be reported to CRO and/or the Sponsor. If a patient becomes pregnant the investigational product should be discontinued immediately and the patient should be withdrawn from the study. The Investigator or other site personnel informs the CRO and/or the Sponsor within 24 hours of when he or she becomes aware of the pregnancy.

Pregnancy Report Form should be used for reporting and to be sent via fax to:

AMS Safety Department (CRO)

Fax no.: +49 (0) 621 700 95 950

The designated CRO and/or Sponsor representative works with the Investigator to ensure that all relevant information is provided within 24 hours in case of SAE and within 30 days for pregnancies without any complications.

Pregnancy itself is not considered as AE, but any complications e.g. congenital abnormalities, birth defects, and spontaneous miscarriages should be handled and reported as SAEs.

The outcome of pregnancy should be followed up, documented and reported to CRO and/ or Sponsor within the same timeframe as described above.

10. Data Quality Assurance

10.1. Data Collection, Monitoring, and Auditing

Detailed procedures will be separately provided in the data management, monitoring, and quality plans.

10.1.1. Data Collection

All clinical study data of randomized patients are to be recorded in the eCRF/ Clinical Data Management System Clincase®.

All patient data have to be reported in the eCRFs in a pseudonymous fashion. Patients are identified by a unique 7-digit patient identification number (patient number, in previous protocol versions referred to as 'E-code') generated in the eCRF.

The investigator will be responsible for the completeness, accuracy, and legibility of the information in the eCRF and other study documents. For documents other than eCRF, only ballpoint pen is to be used and any change of data is to be done by striking out the incorrect data with a single line and dating and initialling the changes made.

The study monitors then have to check the eCRF entries against the source documents (100% source data verification) for accuracy and validity as per the Monitoring Plan as applicable.

The patient diary will remain as source at the site and will only be reviewed by the monitors but not collected. The diary data will be transcribed into appropriate sections of the eCRF by site personnel. Source data will include FAAM-ADL questionnaires, VAS recordings, medical records, diary data and drug accountability of IMP tubes and rescue medication blisters.

Upon completion of the examination timely completion of the eCRF (within 24 hours for Visit 1, all other patient visits within 72 hours) is expected from the site personnel to ensure quality of data and to have oversight on patient safety. Once eCRF entries for a patient (visit) are completed, they will be available for review by the monitor and the designated CRO Clinical Data Management department. Completed eCRFs will be reviewed remotely for completeness, logical discrepancies and clinical consistency. The monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

Electronic copies of the site-specific eCRFs including audit trails have to be archived by the investigator together with the study documents, source data, and laboratory records (if applicable) for the time required by relevant guidelines and national regulations. Any evaluations documented on paper will be entered into the eCRF. The original entries on paper documents, including those completed by the patient, will be considered source data.

10.1.2. Confidentiality/ Property

Adequate records have to be maintained for the study, including patient medical records, eCRFs, laboratory reports, worksheets, nursing notes, signed informed consent forms, product forms, SAE paper forms (to be used in case the eCRF is not available), and

information regarding patient discontinuation and reasons for discontinuation. The confidentiality of each record with patient identification (unique 7-digit patient number) is to be guaranteed by the clinical investigator.

This study protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The investigator agrees to use this information only in conducting this study and is not allowed to use it for any other purposes without written consent from the Sponsor. Results obtained from this study are the property of the Sponsor.

10.1.3. Retention of Records

The investigator agrees to retain electronic copies of the eCRFs of his/her trial patients, the Investigator Site File and other relevant study-related documents (e.g. the protocol and any protocol amendments, the IMP reference safety information, CA and IEC approval, signed patient informed consent forms, and source documents for each patient in the study [e.g. all study-related demographic and medical information, medication disposal, patient diaries and patient reported outcomes]) in a secure place as long as needed to comply with national and international regulations (generally for 15 years). These records have to be made available for audits or inspections upon reasonable request by a representative of the Sponsor or regulatory authorities. Before the investigator destroys any of the above-mentioned documents (only after 15 years or as regulated), he informs Heel in writing.

In case the investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records has to be transferred to any other person who accepts responsibility for the records, e.g. another investigator, or an external archive contracted by the Sponsor. Notice of such transfer has to be given in writing to the sponsor.

10.1.4. Routine Monitoring

To ensure compliance a site visit will be held prior to initiation of patient recruitment (Site Initiation Visit). The protocol, eCRFs, study treatment supplies, handling of study medication, the role of the team member responsible for study medication and other study procedures will be explained in detail.

A monitor assigned by the designated CRO will conduct regular site visits for the purpose of study monitoring.

The purpose of the regular monitoring visits is to ensure that the rights and wellbeing of human patients are protected; that study data are accurate, complete, and verifiable with

source data; and that the study is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigator must agree to allow the study monitor and authorised representatives of the designated CRO and/or Heel to inspect all eCRFs and corresponding source documents (e.g. original medical records, patient records and other relevant records); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The investigator should provide adequate time and facilities for monitoring visits.

The monitor will query any missing or spurious data with the investigator, which should be resolved in a timely manner. A monitoring log will be maintained to record each monitor visit, the reason for the visit, the monitor's signature, and the investigator's or designee's confirmation signature.

10.1.5. Site Audits

Biologische Heilmittel Heel GmbH or its designee may carry out an audit at any time. Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP and applicable regulatory requirements, that the rights and well-being of the patients enrolled have been protected, and that the data relevant for the evaluation of the investigational product have been captured, processed and reported in compliance with the planned arrangements. The investigator will permit direct access to all study documents, drug accountability records, medical records, and source data.

Regulatory authorities may perform an inspection of the study, even up to several years after its completion. If an inspection is announced, Heel must be informed immediately.

10.2. Database Management and Quality Control

The designated CRO will be responsible for the activities associated with the data management of this study, including the production of an eCRF, setting up a relevant database, along with appropriate validation of data and resolution of queries. All data will be entered into an eCRF. Automated and manual checks will be made against the data to ensure completeness and consistency. Resolution of queries will be implemented in the database.

AEs will be standardised for terminology and classification, using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary (the latest available version at study start will be used for the entire duration of the study).

Concomitant medical conditions and Medical History terms will be standardised for terminology and classification, using Medical Dictionary for Regulatory Activities

(MedDRA) Dictionary (the latest available version at study start will be used for the entire duration of the study).

Concomitant drugs will be standardised for terminology and classification using WHO Drug Dictionary.

11. Statistical Methods and Determination of Sample Size

11.1. Statistical and Analytical Plans

Clinical efficacy will be assessed as superiority of Traumed® gel versus placebo and as non-inferiority of Traumed® gel compared to diclofenac gel regarding the primary efficacy parameter indicated below.

Clinical safety will be addressed by assessing AEs, physical examinations and vital signs results in a descriptive manner.

All items of the eCRF will be presented in individual patient data listings and in appropriate summary tables. Standard descriptive summary statistics will be calculated for continuous variables (i.e. arithmetic mean, standard deviation, minimum value, median, maximum value, number of non-missing values). Categorical data will be presented in frequency tables using counts and percentages. Individual patient data listings will be presented per parameter and will be sorted appropriately. Summary tables will be displayed by treatment group and visit (if applicable). Where appropriate the presentation will include changes from baseline and shift tables.

Further details of the planned analyses will be given in the statistical analysis plan (SAP), which will be developed by the designated biostatistician for approval by Heel GmbH well in advance before unblinding the study.

11.1.1. Data Sets to be Analysed

Analyses will be based on the Safety Analysis, Full Analysis, and the Per-Protocol analysis sets. The definitions of the analysis sets follow those given in the ICH E9 guideline (CMP/ICH/363/96).

Safety Analysis Set: Randomised patients who receive at least one dose of investigational medication will form the Safety Analysis Set. The Safety Analysis Set will be used for all analyses of safety, tolerability, and background characteristics. For this set, the exposure to IMP will be also analysed.

Full Analysis Set (FAS): The Full Analysis Set is a subset of the Safety Analysis Set consisting of all patients with acute unilateral Grade 1 or Grade 2 sprain of the lateral

ankle, for whom both baseline and Day 4 VAS values of pain are available. The Full Analysis Set will be used for the Intent-to-Treat (ITT) analysis.

Per-Protocol (PP) Set: Patients in the Full Analysis Set without major protocol deviations will form the PP Set. The PP Set will be used for the per-protocol analysis of the efficacy parameters. The same efficacy evaluations as in the FAS are planned. Relevant differences between the FAS and PPS will be evaluated in the clinical trial report.

Protocol deviations will be collected during the entire study and will be classified as minor or major at the Blind Data Review Meeting (BDRM). Protocol deviations that may affect the efficacy outcome of participants will be classified as major. The decision about major protocol deviations and assignments to populations will be documented in the BDRM meeting minutes.

11.1.2. Baseline and Background Characteristics

All screening and baseline summaries will be based on the Safety Analysis Set unless otherwise indicated.

Ongoing and previous diseases in medical history will be summarised separately by system organ class and preferred term. Coding will be based on MedDRA (the latest available version at study start will be used).

Previous and concomitant medications will only be listed.

11.1.3. Analysis of Efficacy Parameters

The summaries of the efficacy parameters, the statistical analyses of the primary efficacy variable, and the statistical analyses of the secondary efficacy variables will be performed on the Full Analysis Set (primary set for evaluation of superiority of Traumed® gel versus placebo, secondary set for evaluation of non-inferiority of Traumed® gel compared to diclofenac gel), and on the PP set (primary set for evaluation of non-inferiority of Traumed® gel compared to diclofenac gel, secondary set for evaluation of superiority of Traumed® gel versus placebo).

Missing values for all efficacy parameters will be imputed by the last observation carried forward (LOCF) approach. In addition, a last percentile carried forward approach (LPCF) will be performed as sensitivity analysis (see also section 11.1.4). Further sensitivity analyses resulting from the blind review of the data will be provided in the final SAP.

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise. Where appropriate, statistical tests will be supported by presenting estimates and 95% confidence intervals for the respective treatment effects and differences between the treatment groups. These estimates and confidence intervals will be based on the respective statistical models used for the analysis.

In the study of Schomacher (Schomacher 2008), the clinically relevant difference between VAS scores showed varying results. In the case of low baseline VAS scores the clinically relevant reduction in VAS values starts at 5 to10 of 100 mm whereas with higher baseline VAS scores minimal change of 20 mm or 30% may be indicated. Nevertheless, the review of Schomacher was not limited to pain of joints of extremities.

In the study of Tubach et al. (Tubach et al. 2005 a/b) the MCII (minimal clinically important improvement) of pain for knee and hip osteoarthritis was evaluated. The absolute (and relative) changes were, respectively, (a) –19.9 mm (–40.8%) and –15.3 mm (–32.0%) for pain.

Based on these, a treatment difference of 16.6 mm seems to be appropriate to show a clinically important improvement for a study with moderate or severe ankle pain. A difference of 16.6 mm on a 0-100 mm VAS scale can be recomputed into a 25 mm x days difference in AUC for pain in VAS score from Day 1 (Baseline) to Day 4 by elementary geometric considerations. In order to assess non-inferiority of Traumed® gel with respect to diclofenac gel the non-inferiority margin for comparing the AUCs will be set to 25 mm x days.

Primary Efficacy Variable

Area under the curve (AUC)* for pain on passive movement in Visual Analog Scale (VAS) from baseline to Day 4

*All AUC calculations will be based on actual time of measurement.

Secondary Efficacy Variables

- AUC for pain at rest in VAS from baseline to Day 4
- AUC for pain on passive movement in VAS from baseline to Day 2, 7 and Final Visit
- AUC for pain at rest in VAS from baseline to Day 2, 7 and Final Visit
- Change from baseline of pain on passive movement in VAS to Day 4, 7 and Final Visit
- Change from baseline of pain at rest in VAS to Day 4, 7 and Final Visit
- Change from baseline to Day 2, 4, 7 and Final Visit in the FAAM-ADL subscale
- Amount of rescue medication (doses)
- Time to 50% improvement of pain at rest measured by VAS at patient visits.

Confirmatory Analyses

1. AUC for pain on passive movement in VAS from baseline to Day 4 (test for superiority, Traumed® gel versus placebo), Full Analysis Set. The null and alternative hypotheses for the comparison of Traumed® gel versus placebo can be formulated as follows:

H_0: $\mu_T = \mu_P$
H_A: $\mu_T \neq \mu_P$
H_0: Null-hypothesis; H_A: Alternative Hypothesis; T: Test Treatment; P: Placebo Treatment; μ: mean of population (AUC)

2. AUC for pain on passive movement in VAS from baseline to Day 4 (test for non-inferiority, Traumed® gel compared to diclofenac gel), Per-Protocol Analysis Set (PP). For the comparison of Traumed® gel versus diclofenac gel the null and alternative hypothesis can be formulated as follows:

H_0: $\mu_T - \mu_R > 25$ [mm x days]
H_A: $\mu_T - \mu_R \leq 25$ [mm x days]
H_0: Null-hypothesis; H_A: Alternative Hypothesis; T: Test Treatment; R: Reference Treatment; μ: mean of population (AUC)

Hypothesis no. 1 (superiority) is based on the FAS analysis set, while hypothesis no. 2 (non-inferiority) is based on the PP analysis set. This way, both hypotheses are based on the more conservative data set.

If the first *a priori* ordered test (superiority) shows statistical significance, the subsequent hypothesis (non-inferiority) can then be tested individually in a confirmatory manner according to the principle of *a priori* ordered hypotheses (for control of alpha using stepwise testing see [Maurer et al. 1995]).

The confirmatory analyses will be performed using an analysis of covariance (ANCOVA) with baseline pain VAS as covariate. Due to the expected small number of patients per center, an additional inclusion of center as covariate will not be performed (see also EMA Guideline on adjustment for baseline covariates, section 4.2.3., EMA/295050/2013).

Exploratory Analyses

Details for analyzing the secondary efficacy parameters will be given in the SAP. Since all analyses of secondary efficacy parameters are exploratory in nature, no adjustment for multiplicity will be performed. Unless specified otherwise, treatment comparisons for the

secondary efficacy parameters are performed only for Traumed® gel versus placebo gel and Traumed® gel compared to diclofenac gel, respectively.

Sensitivity Analyses

Several pre-defined sensitivity analyses will be performed in order to demonstrate the robustness of the confirmatory results:

Data Sets

The two primary hypotheses (superiority, non-inferiority) will be evaluated additionally using the corresponding alternative data set (hypothesis no. 1: PP, hypothesis no. 2: FAS). The results of the sensitivity analyses will be compared with the confirmatory results.

Nonparametric Analysis

As a sensitivity analysis to the primary parametric approach, a nonparametric analysis will be performed for the two primary hypotheses.

The nonparametric procedures will be performed by means of the Wilcoxon-Mann-Whitney test. The Wilcoxon-Mann-Whitney test (WMW test) is the well-known robust test attributed to Wilcoxon (Wilcoxon 1945) and Mann and Whitney (Mann et al. 1947); for details of the test see e. g. Armitage, Berry, and Matthews (Armitage et al. 2002), or Sprent and Smeeton (Sprent et al. 2001).

The Mann-Whitney estimator (MW) is the associated effect size measure for the Wilcoxon-Mann-Whitney test (WMW test). It is a robust but highly sensitive effect size measure to determine the magnitude and direction of the treatment effects. It is recommended by many authors for its sensitivity and robustness in all data situations (Agresti et al. 1984, Brunner et al. 2000, Munzel et al. 2003, D`Agostino et al. 2006, Brunner et al. 2013, Kieser et al. 2013) for ordinal scales in non-inferiority trials it is even regarded as the ‘gold standard’ see, e.g. Design and Analysis of Non-Inferiority Trials (Rothmanns et al. 2011). Technically, the MW gives the probability that a randomly chosen subject of the test group is better off than a randomly chosen subject of the comparison group (with the probability ranging from 0 to 1, with 0.5 indicating equality); it is statistically defined as: $P(X<Y) + 0.5\,P(X=Y)$.

The relevant benchmarks for the Mann-Whitney effect size measure (MW) are as follows (Colditz et al. 1988):

0.29	large inferiority
0.36	medium sized inferiority
0.44	small inferiority
0.50	equality
0.56	small superiority
0.64	medium sized superiority
0.71	large superiority

Under the assumption of a normal distribution the defined non-inferiority margin AUC 25 mm x days with common standard deviation 75 mm x days, (see section 11.4) can be re-expressed in terms of the Mann-Whitney statistic: the raw scale margin results in a standardized mean difference of 25/75 = 0.33, which can be directly transformed to a Mann-Whitney margin of 0.407 (Rahlfs et al. 2014). This margin is consistent with the nonparametric NI bound of 0.40 in a previous NI trial (Gonzalez et al. 2013).

In addition, a non-parametric repeated measurement analysis will be performed by means of the generalized Wilcoxon-Mann-Whitney test (Wei-Lachin procedure), combining the repeated observations by a simultaneous, directional test.

Stratification

In order to control for center effects, a robust stratified analysis will be performed for the primary efficacy criterion applying the Cochran-Mantel-Haenszel procedure with adjustment for centers (CMH pooling, also known as van Elteren pooling). This procedure is robust also with very low sample sizes per center and group.

In order to control for effects of delayed “Day 4” assessments (Day 4+1), a robust stratified analysis (CMH) will be performed for patients with and without delay.

In order to ensure the data integrity of the trial and to exclude potential bias introduced by partial unblinding, a separate analysis of problematic and non-problematic cases will be conducted with subsequent meta-analytic pooling and test for overall effect and heterogeneity.

Further details will be defined in an update of the Statistical Analysis Plan (SAP). *(revised per Amendment to protocol version 3.0)*

11.1.4. Accounting for Missing Data

Missing data represent a potential source of bias in a clinical trial. For the clinical trial at hand two general approaches are pursued:

- Avoidance of drop-outs
- Using sensitivity analyses in order to demonstrate the robustness of the results of the first line analyses.

The pre-planned analysis procedures are as follows:

1. Last Observation Carried Forward [LOCF] (Applied to all Efficacy Analyses)

A LOCF analysis (Last Observation Carried Forward) will be performed as first line analysis. LOCF will be applied for missing values regardless of the reason for discontinuation.

2. Last Percentile Carried Forward [LPCF] (Applied as Sensitivity Analysis to the First Line Efficacy Analyses)

The LPCF method carries forward the change information, using the percentile value with back transformation to raw scale, instead of last value carried forward. This approach was recently developed and recommended by O´Brien, Zhang and Bailey in 2005 (O`Brien et al. 2005). The results of this method are well comparable to the mixed-effect models for repeated measures (MMRM), without making the corresponding parametric assumptions. According to their simulation study the calculated estimators should be negligibly biased by missing data.

Additional sensitivity analyses resulting from the blind review of the data and further technical details will be provided in the final statistical analysis plan.

The frequency and type of missing values will be documented in the clinical study report.

11.1.5. Analysis of Safety Parameters

Safety variables are:

- AEs
- other observations related to safety (physical examinations, vital signs).

All safety summaries will be performed on the Safety Analysis Set if not indicated otherwise. For vital signs, no formal testing will be applied to detect imbalances between the treatment groups.

AEs will be presented by MedDRA Preferred Term and System Organ Class in different categories.

Incidence rates of AEs, SAEs and AEs related to investigational product will be reported. The duration of exposure to IMP and the amount of IMP used for the three treatment groups (Traumed® gel, diclofenac gel and placebo gel) will be analysed.

11.2. Subgroup Analyses

Subgroup analysis might be performed based on the study results on exploratory manner.

11.3. Interim Analyses

No interim analysis is planned.

11.4. Determination of Sample Size

Estimation of sample size is based on the primary efficacy variable. A two-sided test of equality of the study drug (Traumed® gel) and the comparator (placebo) at level 0.05 based on an expected raw scale treatment difference of AUC 25 [mm x days] and a common standard deviation of AUC 75 [mm x days] for the response variables (re-expressed for nonparametric evaluation in terms of the Mann-Whitney statistic as MW = 0.6 (see section 11.1.3), achieves a power of at least 90% for parametric first line analysis as well as for second line nonparametric analysis if the sample size is set to 291 patients for the Traumed® gel group and to 146 patients for the placebo group.

Due to an additional safety requirement that AEs with incidence level of 1% for Traumed® gel are found during the study with probability 95%, 299 patients for the Traumed® gel group are required. Assuming a drop-out rate from the Safety Analysis Set of about 4% an amount of 312 randomized patients in the Traumed® gel group is needed. With an allocation ratio of 2:1:1 (Traumed® gel : diclofenac gel : placebo) 156 patients are obtained in the diclofenac gel and placebo group each, that is, a total of 624 patients with acute unilateral Grade 1 or Grade 2 sprain of the lateral ankle.

In order to ensure the pre-defined power of the trial for the trial objectives including the confirmatory test for non-inferiority (Traumed® gel compared to diclofenac gel), which is based on the Per-Protocol Analysis Set (PP), a sample size enhancement is introduced for compensation of:

- cases for whom maintenance of blinding procedures may have been compromised and, thus, are representing a major protocol violation (exclusion from PP analysis).

For compensation, the final sample size will be enhanced to 202 patients for the diclofenac and Placebo group each, and to 404 patients for the Traumed® gel group resulting in a new total of 808 patients. *(revised per Amendment to protocol version 3.0)*

12. Study Report and Publication Policy

An integrated study report in accordance with the ICH Harmonized Tripartite Guideline (E3) (Structure and content of clinical study reports) will be developed.

All data and records provided by the Sponsor or generated during the study (other than patient's medical records) and all data and inventions discovered in the course of conducting the study, whether patentable or not, are the sole and exclusive property of the Biologische Heilmittel Heel GmbH (Sponsor).

Any publication of the results, either in part or in total will require the written agreement of the Coordinating Investigator and the Sponsor. With this written agreement the Coordinating Investigator and Sponsor will engage to form a Publication Steering Committee to the extent it is necessary, composed of all relevant stakeholders, the Coordinating Investigator, Sponsor and other parties as needed. The Publication Steering Committee will determine the publication strategy and plan, and also will assign the Authorship Team. The Authorship Team will draft and approve the congress abstracts, manuscripts and/or other publications. The members of Publication Steering Committee should be aware of Good Publication Practice (GPP3) principles for industry-sponsored clinical trials (Battisti et al. 2015) and International Committee of Medical Journal Editors (ICMJE) guidelines (www.icmje.org).

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