Traumed - C1502

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

STATISTICAL ANALYSIS PLAN (SAP)

Study code	C1502
Study Protocol	03.02.2020, Final Version 4.0
Study design	Randomised, double-blind, active- and placebo-controlled confirmatory clinical trial
Sponsor /contract party	Biologische Heilmittel Heel GmbH Dr.-Reckeweg-Straße 2-4 D-76532 Baden-Baden Germany

SAP Revision History

Version	Date	Author	Review	Comments
Draft 1.0	07.12.2018	J.C. Vester	V.W. Rahlfs	Initial Draft
Draft-to-Final 1.0	12.04.2021	J.C. Vester	V.W. Rahlfs	Adaption to *Amendment to Protocol version 3.0 (Protocol version 4.0)* *Implementation of final BDRM Decisions*
Final 1.0	20.04.2021	J.C. Vester	V.W. Rahlfs	Switch to American English (AE) Additional operationalization in section 9.4.2. *Stratification* Individual Dataset Assignment in Section 13.2

1. SIGNATURES

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20.4.2021
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3. PRELIMINARY REMARKS

The C1502 Statistical Analysis Plan (SAP) is a detailed technical extension to the C1502 Study Protocol Version 3.0 (1 December 2017), following principles of the Guidelines ICH E3/E6R2/E9, as well as relevant IDV SOPs and/or guidelines as far as applicable to the trial. This plan describes the statistical analysis planned to be performed after all enrolled patients data are available for evaluation. This Statistical Analysis Plan will be finalized and signed after raw database hard lock, but before generation of the final analysis database as well as before unblinding approval. Formal records will be kept of when the Statistical Analysis Plan was finalized as well as when the blind was subsequently broken.

All planned analyses identified in this SAP will be included in the Clinical Trial Report (CTR). Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any *post-hoc* or unplanned analyses not specified in this SAP will be clearly identified as such in the CTR.

The following documents were reviewed when preparing this SAP:

- C1502 Study Protocol Version 4.0 (3 February 2020)
- Amendment Summary Document for Substantial protocol Changes (3 February 2020)
- HE13226_eCRF Specification_v3.0_20180425
- 20210113_C1502_Issue_Overview_FINAL
- C1502_MTG_NOTES_BDRM_09MAR2021_20210324 (Blind Data Review Meeting)
- C1502_LIVE17_Risk Based Centralized Statistical Monitoring_IDV_20210409 (Hardlock)

Readers of this SAP are encouraged to read the Clinical Trial protocol for details on the conduct of this clinical trial and the operational aspects of clinical assessments and timing for completing a patient in this trial.

4. 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	Blind Data Review Meeting
BMI	Body Mass Index
C	Celsius degree
CCSI	Company Core Safety Information
CI	confidence interval
CMH	Cochran-Mantel-Haenszel (pooling)
COX-2	Cyclooxygenase type 2
CRO	Contract Research Organisation
CStat	Chartered Statistician
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EoT	End of Treatment
EU	European Union
FAAM	Foot and Ankle Ability Measure
FAS	Full analysis set
GCP	Good Clinical Practice
GMDS	Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V.
GMP	Good Manufacturing Practice
HSPC	high security PC (personal computer)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LOCF	Last Observation Carried Forward
LPCP	Last Percentile Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/d	Milligrams per day
mm	Millimeter
MMRM	mixed-effect models for repeated measures
MW	Mann-Whitney
N	Number of patients

Abbreviation	Definition
NI	Non-inferiority
NSAID	Non-steroidal anti-inflammatory drug
PP	Per protocol
PRN	When necessary (pro re nata)
QPPV	Qualified person for pharmacovigilance
RICE	Rest, Ice, Compression and Elevation
RSS	Royal Statistical Society
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	Summary Of Changes
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
TGF-β	transforming growth factor beta
TNF-α	tumor necrosis factor alpha
VAS	Visual Analog Scale
VASPM	Pain score on passive movement (VAS)
WMA	World Medical Assembly
WMW	Wilcoxon-Mann-Whitney

5. INTRODUCTION

5.1 Background information

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 trial.

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 authorization 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® gel 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 randomized 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 (tumor 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 clinical trial (TAASS; Gonzalez et al. 2013) was conducted in 449 athletes with grade 1 or grade 2 acute ankle sprain as a multi-center, randomized, blinded, parallel-group, active controlled clinical trial.

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 trial (TRS-ESP/ TAASS trial/ 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 [protocol] 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 [protocol] section 6.1.1 for description.

In the TAASS trial (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 trial 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.

6. EXCERPTS FROM FINAL PROTOCOL

6.1 Protocol Synopsis

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
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		
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 24105 Kiel Germany Phone: +49 431 5002 4485		
Study Duration: First patient first visit: February 2018 Last patient last visit planned: December 2020		**Study Phase:** III
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.		
Methodology: Randomised, double-blind, active- and placebo-controlled confirmatory clinical trial.		
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.		

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 [protocol] 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 [protocol] 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 [protocol] 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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6.2 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).

6.3 Assessment of Efficacy

6.3.1 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 [protocol] section 6.3.2).

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.

6.3.2 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.

6.3.3 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 [protocol] 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 [protocol] section 9.3.2).

7. BLIND DATA TRANSFERS AND QUALITY ASSURANCE

The blind data transfers from the CRO responsible for the eCRF (AMS Advanced Medical Services GmbH) to IDV was performed according to the IDV Data Transfer Guideline Version Final 1.0 from 13 December 2017.

The following data transfers were performed for risk-based centralized statistical monitoring:

- INTERIM TRANSFER:
  1. 28.05.2018 (*TRAUMED-2018-05-28_01*)
  2. 26.06.2018 (*TRAUMED-2018-06-26_02*)
  3. 03.09.2018 (*TRAUMED-2018-09-03_03*)
  4. 08.11.2018 (*TRAUMED-2018-11-08_04*)
  5. 15.01.2019 (*TRAUMED-2019-01-15_05)*
  6. 11.03.2019 (*TRAUMED-2019-03-11_06)*
  7. 12.04.2019 (*TRAUMED-2019-04-12_07)*
  8. 13.05.2019 (*TRAUMED-2019-05-13_08)*
  9. 09.09.2019 (*TRAUMED-2019-09-09_09)*
  10. 18.11.2019 (*TRAUMED-2019-11-18_10)*
  11. 14.01.2020 (*TRAUMED-2020-01-14_11)*
  12. 11.07.2020 (*TRAUMED-2020-07-11_12)*
  13. 11.09.2020 (*TRAUMED-2020-09-11_13)*
  14. 10.11.2020 (*TRAUMED-2020-11-10_14)*
  15. 02.12.2020 (*TRAUMED-2020-12-02_15)*

- SOFTLOCK TRANSFER:
  - 18.01.2021 (*TRAUMED-2021-01-18_16)*
  - 20210113_C1502_Issue_Overview_FINAL

- HARDLOCK TRANSFER:
  - 29.03.2021 (*TRAUMED-2021-03-29_17)*

Based on the hardlock data, patients with major protocol deviations are coded on the base of the definitions in the final Statistical Analysis Plan. The major protocol deviations leading to exclusion from analysis sets as well as the final datasets (analysis populations) are documented on a per patient base in the Appendix of the final Statistical Analysis Plan.

8. CHANGES TO THE PROTOCOL

Preliminary Remark on Substantial Protocol Amendment version 4.0 (February 3, 2020) to Protocol version 3.0

A total of 184 'issue patients', for whom maintenance of blinding procedures may have been compromised, have been identified in 2019 after re-examination of adherence to blinding specifications by the local monitors. Rationale for the re-examination were corresponding findings from site inspections by the German Local Authorities in 2019 (Gesundheitsamt Düsseldorf of German Federal State North Rhine Westphalia, NRW). Re-training and close follow-up control for the sites was implemented to prevent occurrence of further issue cases.

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) based on the Per-Protocol Analysis Set (PP), a sample size enhancement was introduced by means of Protocol Amendment version 4.0 to Protocol version 3.0 for compensation of cases for whom maintenance of blinding procedures may have been compromised.

As specified in C1502 Study Protocol Version 4.0 (3 February 2020) and in the Amendment Summary Document for Substantial protocol Changes (3 February 2020), detailed handling of these problem cases have to be defined in this update of the Statistical Analysis Plan (SAP).

Based on the Blind Data Review Meeting from March 09, 2021 (C1502_MTG_NOTES_BDRM_09MAR2021_20210324), the operational handling as specified in the following section shall ensure the integrity and validity of the trial.

OLD
(Final C1502 Study Protocol Version 4.0, Amendment to Protocol version 3.0)

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).

NEW
(Final BDRM decision)

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. **All confirmatory and secondary analyses will be based on the group of non-issue patients. Results of issue patients will be provided separately in the Appendix of the Clinical Trial Report (CTR).**

RATIONALE

Blind data review revealed severe deviations of 'issue' cases from 'non-issue' cases, suggesting that compromised cases might constitute a serious risk of bias, preventing pooled analysis.

> The multivariate P-values for the comparison of issue cases vs. non-issue cases regarding the three key domains "Baseline", Efficacy", and "RICE", were throughout below 0.0001, thus, suggesting serious structural differences between issue cases and non-issue cases. The rate of major protocol violations was significantly higher in the group of issue cases (11.4%) as compared to non-issue cases (1.9%; P<0.0001). Also the patient's guess on which treatment he/she received was less balanced in the issue group as compared to the non-issue group (patient's guess for the two active treatments: non-issue cases: 39% Traumed vs. 35% diclofenac, issue cases: 42% Traumed vs. 29% diclofenac).

Final BDRM Decision: In order to preserve the integrity and validity of the trial, issue patients will not be included into the pre-planned confirmatory and secondary analyses of the main part of the Clinical Trial Report. While being evaluated for baseline characteristics, efficacy and safety endpoints in the same way as the non-compromised cases, the compromised cases will be reported separately in the Appendix of the Clinical Trial Report (results to be interpreted with care due to the described issues).

As stated before, the sample size was already proactively increased for compensation in case of an exclusion of the issue patients (Protocol Amendment version 4.0 from February 3, 2020 to Protocol version 3.0). The Reason/ Justification for Change of Protocol Section 11.4 (Protocol Amendment version 4.0 from February 3, 2020 to protocol version 3.0) was provided in the Amendment Summary Document for Substantial Protocol Changes (SOC document from February 3, 2020):

> *The enhancement will ensure planned power and validity for evaluating the pre-defined trial objectives also in case that* ***only non-compromised cases allow valid and unbiased conclusions*** *...*

9. ADDITIONAL SPECIFICATIONS TO THE PROTOCOL

9.1 Standard Procedures

- Within the framework of the idv system, the following standard ensemble of classic and robust summarizing statistics will be provided for data description: mean, standard deviation, standard error of the mean, minimum, lower quartile, median, upper quartile, maximum, valid number. In addition, measures for skewness and kurtosis will be provided for suitable efficacy variables. Where appropriate, the result presentation will include changes from baseline.

- For categorical data, frequency counts will be provided with their associated percentages. Semi-quantitative and quantitative efficacy data will be additionally visualized by boxplot diagrams. All standardized effect sizes (Mann-Whitney) will be visualized with their corresponding 95%-confidence intervals. All standard statistical tables are generated with the standard table layout of the validated statistical package TESTIMATE V6.5.14 (IDV Gauting). Associated meta-data and variable labels are finalized before unblinding. All standard scientific figures are generated with the standard figure layout of the validated scientific package SCIENCEGRAPH V4.9.39 (IDV Gauting).

9.2 Demography and Baseline Characteristics

9.2.1 Operationalizations in Final Protocol

- None.

9.2.2 Additional Operationalizations

- Besides standard descriptive analyses (see section 9.1), formal homogeneity analyses for demographic variables and baseline characteristics will be performed based on the full analysis set (FAS) and the per-protocol set (PP). Robust Mann-Whitney estimators and their 95% confidence intervals will used as standardized summary measures across the relevant demographic-anamnestic variables (demography, physical examination, vital signs, supportive therapy, time and grading of injury) as well as across the efficacy criteria at baseline (VAS pain on passive movement, VAS pain at rest, FAAM). This will be performed in order to check baseline comparability of the three randomized groups in a robust, nonparametric way (minimized assumptions, independent from data type).
- As benchmark for relevant baseline differences, a Mann-Whitney estimator of 0.36 and 0.64 respectively will be applied (referring to a standardized difference of 0.5 according to Cohen, which is regarded as a medium-sized difference).
- In the case of inhomogeneities, stratified analyses will be performed by means of the Peto-Wilcoxon test (2 sided; 95% confidence interval, CI) with adjustment within the framework of the Cochran-Mantel-Haenszel pooling procedure (CMH pooling, also known as van Elteren pooling). For this purpose, depending on the respective data type and distribution, nominal categories, medians or quartiles of the affected baseline criteria will be used for stratification.

9.3 Evaluations and Endpoints – First Line Analysis

9.3.1 Primary Efficacy Variable

9.3.1.1 Operationalizations in Final Protocol

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.

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).

9.3.1.2 Additional Operationalizations

- Visit 4 (Day 7) will be introduced as additional primary endpoint in the chain of *a priori* ordered hypotheses, leading to the following final sequence of confirmatory analyses:

    1. AUC for pain on passive movement in VAS from baseline to Day 4 (test for superiority, Traumed® gel versus placebo)
    2. AUC for pain on passive movement in VAS from baseline to Day 4 (test for non-inferiority, Traumed® gel compared to diclofenac gel)
    3. AUC for pain on passive movement in VAS from baseline to Day 7 (test for superiority, Traumed® gel versus placebo)
    4. AUC for pain on passive movement in VAS from baseline to Day 7 (test for non-inferiority, Traumed® gel compared to diclofenac gel)

    If the preceeding *a priori* ordered test shows statistical significance, the subsequent hypothesis 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]).

    Comment: The original endpoints at Day 4 remain unchanged (hypotheses no. 1 and no. 2), however Day 7 is introduced as additional primary endpoint in the chain of *a priori* ordered hypotheses (hypotheses no. 3 and no. 4). This addition is implemented as per BDRM decision in order to avoid lack of assay sensitivity at the early stage of the ankle joint injury (C1502_MTG_NOTES_BDRM_09MAR2021_20210324).

- Descriptive procedures will be performed according to section 9.1.
- For the analysis of covariance, in addition to the table with descriptive statistics and the analysis of variance of the covariate (test for homogeneity of the groups with respect to the covariate), the following results of the analysis of covariance will be generated:
    - Analysis of covariance of the full model (separate regression lines for each group) with the following information:
        - Test for parallelism and group difference at X_0 as an indication of group differences in case the regression lines are not parallel (for the hypothesis of parallelism a 10%-level will be applied).

        - Model parameter: for each group, the point of intersection of the regression line, the slope and the adjusted mean value of X_0, the common mean value of the covariates for all groups.
    - Analysis of covariance for the reduced regression model (a single regression line for all groups for the assumption that the regression lines are parallel), with the following information:
        - Covariates (within), an indication of the significance and relevance of the covariate for the criterion.
        - Test statistic for adjusted group differences, correct also for groups of unbalanced size.
        - Coefficient of determination R^2 for the amount of variation of the criterion, which is explained by the covariate and the differences between the groups.
        - Model parameter: the y-intercept and slope of the regression lines (slopes are now necessarily identical because of the reduction of the full model), adjusted mean values for a common value X_0 of the covariate.
- The analysis of covariance of the full model will be used for the confirmatory approach (the reduced regression model is provided as supportive information only)
- *Descriptive Procedures*: TESTIMATE V6.5.14; PROC BASIC STATISTICS / SCIENCEGRAPH V4.9.39
- *Test Procedures*: TESTIMATE V6.5.14; PROC ANALYSIS OF COVARIANCE

9.3.2 Secondary Efficacy Variables

9.3.2.1 Operationalizations in Final Protocol

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.

9.3.2.2 Additional Operationalizations

- AUC for pain on passive movement in VAS from baseline to Day 7 is defined as additional primary endpoint (see section 9.3.1.2), and, thus, removed from secondary efficacy variables.
- Descriptive procedures for secondary efficacy variables (1) to (7) will be performed according to section 9.1. Descriptive procedures for secondary efficacy variable 'time to 50% improvement' will be performed by means of frequency counts based on patient visits (50% improvement of pain at rest), as well as by Kaplan-Meier curves for time-to-event (including censored values). In addition to pain at rest (measured by VAS at patient visits), also pain on passive movement will be evaluated applying the same procedures.
- Test procedures for secondary efficacy variables (1) to (6) will be performed for the FAS and PP analysis sets as specified for the primary efficacy variable by analysis of covariance (see section 9.3.1.2), applying the associated baseline pain VAS as covariate. The test procedure for the secondary efficacy variable (7) will be performed for the FAS and PP analysis sets as specified for the primary efficacy variable by analysis of covariance (see section 9.3.1.2), applying baseline pain on passive movement in VAS as covariate. The secondary efficacy variable (8) will be analyzed by means of the Peto-Logrank test (time-to-event (logrank) test).
- *Descriptive Procedures* (Secondary Efficacy Variables (1) to (7)): TESTIMATE V6.5.14; PROC BASIC STATISTICS / SCIENCEGRAPH V4.9.39

- *Descriptive Procedures* (Secondary Efficacy Variable (8)): TESTIMATE V6.5.14; PROC KAPLAN-MEIER FUNCTION / SCIENCEGRAPH V4.9.39
- *Test Procedures* (Secondary Efficacy Variables (1) to (7): TESTIMATE V6.5.14; PROC ANALYSIS OF COVARIANCE
- *Test Procedures* (Secondary Efficacy Variable (8): TESTIMATE V6.5.14; PROC PETO-LOGRANK-TEST

9.4 Evaluations and Endpoints – Second Line Analysis

9.4.1 Nonparametric Analysis

9.4.1.1 Operationalizations in Final Protocol

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 [protocol] 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.

9.4.1.2 Additional Operationalizations

- The nonparametric procedures will be performed for the FAS and PP analysis set as sensitivity analyses for the primary parametric approach. The univariate analysis will be performed by means of the Wilcoxon-Mann-Whitney (WMW) test for the area under the curve (AUC) of pain on passive movement in Visual Analog Scale (VAS) from baseline to Day 4. The repeated measurement analyses will combine the repeated observations of pain on passive movement (VAS) at Day 2, 4, 7 and Final Visit by means of the generalised Wilcoxon-Mann-Whitney test (Wei-Lachin procedure, directional test).
- *Descriptive Procedures*: TESTIMATE V6.5.14; PROC BASIC STATISTICS / SCIENCEGRAPH V4.9.39
- *Test Procedures*: TESTIMATE V6.5.14; PROC WILCOXON-MANN-WHITNEY-U-TEST / SCIENCEGRAPH V4.9.39 / PROC MULTIVARIATE COMPARISONS - WEI-LACHIN – DIRECTIONAL

9.4.2 Stratification

9.4.2.1 Operationalizations in Final Protocol

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)*

9.4.2.2 Additional Operationalizations

- The robust stratified analyses will be performed for the FAS and PP analysis set as sensitivity analyses for the primary parametric approach by means of the Cochran-Mantel-Haenszel (CMH) pooling procedure with Wilcoxon scores (Peto-Wilcoxon test).
    - Adjustment for centers by means of the CMH pooling procedure will be performed for the area under the curve (AUC) of pain on passive movement in Visual Analog Scale (VAS) from baseline to Day 4 with centers as strata. Small centers will technically be pooled. According to protocol, the final pooling benchmark is to be decided at the time of the blind review of the soft lock data with documentation in the final Statistical Analysis Plan (see ICH Guidance E9 §3.2 "any case decisions concerning this approach should always be taken blind to treatment, for example at the time of the blind review"). Based on the softlock data, the pooling benchmark for small centers is set to N<20 (virtual center labelled as "center 99"). This way, the sensitivity analysis will be based on 12 center strata and one virtual center, which is regarded as reasonable procedural size for the sensitivity analysis.
    - Adjustment for patients with and without delayed "Day 4" assessments (Day 4+1) will be performed for the area under the curve (AUC) of pain on passive movement in Visual Analog Scale (VAS) from baseline to Day 4.
- Due to serious risk of bias, the "problematic" cases will be evaluated separately and will not be part of the confirmatory or secondary analyses (for details, see section 8 *Changes to the Protocol*).
- *Test Procedures*: TESTIMATE V6.5.14; PROC PETO-WILCOXON-TEST.

9.5 Accounting for Missing Data

9.5.1.1 Operationalizations in Final Protocol

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 this final Statistical Analysis Plan.

The frequency and type of missing values will be documented in the Clinical Trial Report.

9.5.1.2 Additional Operationalizations

- The imputation by means of Last Observation Carried Forward [LOCF] will be applied to all first line analyses (confirmatory and exploratory) with the exception of the secondary efficacy variables no. 7 and 8 (see section 9.3.2). Imputation of missing values is performed using the last existing follow-up value. The imputation by means of Last Percentile Carried Forward [LPCF] will be omitted due to the marginal number of missing efficacy values.
- The number of non-missing values will be documented in the Clinical Trial Report for all variables and evaluations (valid number). The frequency and type of missing values will be documented in the Clinical Trial Report for the primary efficacy variable (area under the curve, AUC) of pain on passive movement in Visual Analog Scale (VAS) from baseline to Day 4.
- The standard ensemble of classic and robust summarizing statistics (see section 9.1) will be provided for the pre-specified imputation as well as for *data as available*, i.e. without imputation.

9.6 Evaluations and Endpoints – Safety

9.6.1.1 Operationalizations in Final Protocol

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 analyzed.

9.6.1.2 Additional Operationalizations

- Descriptive procedures will be performed according to section 9.1.

9.7 Analysis Populations

9.7.1.1 Operationalizations in Final Protocol

Safety Analysis Set: Randomized 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 trial 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 minutes.

9.7.1.2 Additional Operationalizations

- In order to preserve validity and integrity of the trial, all confirmatory and secondary analyses will be based on the group of *non-issue* patients (for details see section 8 *Changes to the Protocol*). As stated in the 'Amendment Summary Document for Substantial Protocol Changes', the sample size was proactively enhanced *to ensure planned power and validity for evaluating the pre-defined trial objectives also in case that* ***only non-compromised cases allow valid and unbiased conclusions***. Results of *issue patients* will be provided separately in the Appendix of the Clinical Trial Report (CTR).
- FAS: VAS availability at Day 4 is referring to LOCF (primary analysis).
- PP: premature discontinuations due to "lack of efficacy", "adverse event", or "lack of efficacy" and "adverse event" (i.e. drug-related premature discontinuations) will not be excluded from the PP analysis, regardless of any existing protocol deviation. Benchmarks for „Major Protocol Deviation" (final BDRM decisions):
    - Grade 3 determination after Visit 3
    - VASPM V1 < 50
    - Missing VASPM at V1 or V3 (Related to ‚Data as Available')
    - Visit 2 <> Day 2 (Protocol Day 2)
    - Visit 3 < Day 4 or > Day 5 (Protocol Day 4 + 1 Day)
    - Visit 4 < Day 6 or > Day 9 (Protocol Day 7 ± 1 day)
    - Compliance < 80% at V3 or V4
    - Premature Discontinuation (not drug-related)
- The analysis populations (Safety, FAS, and PP) are listed individually in the Appendix of the final Statistical Analysis Plan.

10. SOFTWARE APPLIED

Unblinded clinical trial evaluation will be performed on high security PCs (HSPC) within a validated working environment at the department 'Clinical Research/Biometry' in the institute IDV Data Analysis and Study Planning under supervision of Volker W. Rahlfs, PhD., C. Stat. (RSS), with a 'Certificate Biometry in Medicine GMDS'.

Software packages to be used for unblinded analyses and generation of Clinical Trial Report (CTR):

- TESTIMATE V6.5.14 (statistical analyses)
- SCIENCEGRAPH V4.9.39 (scientific figures)
- ICH-Study-Report-Manager V2.4.3 (Clinical Trial Report)

11. POST HOC CHANGES TO PLANNED ANALYSES (POST UNBLINDING)

Any major changes to this plan after final sign-off will be specified in the Clinical Trial Report of the final analyses with corresponding scientific rationales.

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13. APPENDIX

13.1 BDRM Decisions

13.1.1 Problem Cases

Besides the 'issue' cases addressed in C1502 Study Protocol Version 4.0 (3 February 2020) and in the Amendment Summary Document for Substantial protocol Changes (3 February 2020), no other problem cases were identified. For details see section 8 *Changes to the Protocol*.

13.1.2 Other Decisions

Day 7 was introduced as additional endpoint in the chain of *a priori* ordered hypotheses (hypotheses no. 3 and no. 4). This addition was implemented as per BDRM decision in order to avoid lack of assay sensitivity at the very early stage of the ankle joint injury (C1502_MTG_NOTES_BDRM_09MAR2021_20210324).

13.2 Individual Dataset Assignment

The following table shows the individual dataset assignment based on the hardlock transfer for 'non-issue' patients (in Table 1) and 'issue' patients (in Table 2) (see section 8 *Changes to the Protocol*).

Table 1: Dataset Assignment, Status: Hardlock Transfer, 'Non-issue' Patients (n = 625)

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4902-001	1073	1	1	1
4902-002	1074	1	1	1
4902-003	1075	1	1	1
4902-004	1076	1	1	1
4902-005	1077	1	1	1
4902-006	1078	1	1	1
4902-007	1079	1	1	0
4902-008	1080	1	1	1
4902-009	1217	1	1	1
4902-010	1218	1	1	1
4902-011	1219	1	1	1
4902-012	1220	1	1	1
4902-013	1221	1	1	1
4902-014	1222	1	1	1
4902-015	1223	1	1	1
4902-016	1224	1	1	1
4902-017	1561	1	1	0
4902-018	1562	1	1	1
4902-019	1563	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4902-020	1564	1	1	1
4902-021	1565	1	1	1
4902-022	1568	1	1	1
4902-023	1566	1	1	1
4902-024	1567	1	1	1
4902-025	1729	1	1	1
4902-026	1730	1	1	1
4903-001	1089	1	1	0
4903-002	1090	1	1	1
4903-003	1091	1	1	1
4903-004	1092	1	1	1
4903-005	1093	1	1	1
4903-006	1094	1	1	1
4905-009	1457	1	0	0
4905-010	1458	1	1	1
4906-001	1049	1	1	1
4906-002	1050	1	1	1
4906-003	1051	1	1	1
4906-004	1052	1	1	1
4906-005	1053	1	1	1
4906-006	1054	1	1	1
4906-007	1055	1	1	1
4906-008	1056	1	1	1
4906-009	1233	1	1	1
4906-010	1234	1	1	1
4906-011	1235	1	1	1
4906-012	1236	1	1	1
4906-013	1237	1	1	1
4906-014	1238	1	1	1
4906-015	1239	1	1	1
4906-016	1240	1	1	1
4906-017	1385	1	1	1
4906-018	1386	1	1	1
4906-019	1387	1	1	1
4906-020	1388	1	1	1
4906-021	1389	1	1	1
4906-022	1390	1	1	1
4906-023	1391	1	1	1
4906-024	1392	1	1	1
4906-025	1441	1	1	1
4906-026	1442	1	1	1
4906-027	1443	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4906-028	1444	1	1	1
4906-029	1445	1	1	1
4906-030	1446	1	1	1
4906-031	1447	1	1	1
4906-032	1448	1	1	1
4906-033	1577	1	1	1
4906-034	1578	1	1	1
4906-035	1579	1	1	1
4906-036	1580	1	1	1
4906-037	1581	1	1	1
4906-038	1582	1	1	1
4906-039	1583	1	1	1
4906-040	1584	1	1	1
4906-041	1649	1	1	1
4906-042	1650	1	1	1
4906-043	1651	1	1	1
4906-044	3009	1	1	1
4906-045	3010	1	1	1
4906-046	3011	1	1	1
4906-047	3012	1	1	1
4906-048	3109	1	1	1
4906-049	3110	1	1	1
4906-050	3111	1	1	1
4906-051	3112	1	1	1
4906-052	3149	1	1	1
4907-001	1009	1	1	1
4907-002	1010	1	1	1
4907-003	1011	1	1	1
4907-004	1012	1	1	1
4907-005	1013	1	1	1
4907-006	1014	1	1	1
4907-007	1015	1	1	1
4907-008	1016	1	1	1
4907-009	1161	1	1	1
4907-010	1162	1	1	1
4907-011	1163	1	1	1
4907-012	1164	1	1	1
4907-013	1165	1	1	1
4907-014	1166	1	1	1
4907-015	1167	1	1	1
4907-016	1168	1	1	1
4907-017	1329	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4907-018	1330	1	1	1
4907-019	1331	1	1	1
4907-020	1332	1	1	1
4907-021	1333	1	1	1
4907-022	1334	1	1	1
4907-023	1335	1	1	1
4907-024	1336	1	1	1
4907-025	1489	1	1	1
4907-026	1490	1	1	1
4907-027	1491	1	1	1
4907-028	1492	1	1	1
4907-029	1493	1	1	1
4907-030	1494	1	1	1
4907-031	1495	1	1	1
4907-032	1496	1	1	1
4907-033	1537	1	1	1
4907-034	1538	1	1	1
4907-035	1539	1	1	1
4907-036	1540	1	1	1
4907-037	1541	1	1	1
4907-038	1542	1	1	1
4907-039	1543	1	1	1
4907-040	1544	1	1	1
4907-041	1673	1	1	1
4907-042	1674	1	1	1
4907-043	1675	1	0	0
4907-044	1676	1	1	1
4907-045	1677	1	1	1
4907-046	1678	1	1	1
4907-047	1679	1	1	1
4907-048	3105	1	1	1
4907-049	3106	1	1	1
4907-050	3107	1	1	1
4907-051	3108	1	1	1
4907-052	3309	1	1	1
4908-001	1145	1	1	1
4908-002	1146	1	1	1
4908-003	1147	1	1	1
4908-004	1148	1	1	1
4908-005	1149	1	1	1
4908-006	1151	1	1	1
4908-007	1150	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4908-008	1152	1	1	1
4908-009	1345	1	1	1
4908-010	1346	1	1	1
4908-011	1347	1	1	1
4908-012	1348	1	1	1
4908-013	1349	1	1	1
4908-014	1350	1	1	1
4908-015	1351	1	1	1
4908-016	1352	1	1	1
4908-017	1585	1	1	1
4908-018	1586	1	1	1
4908-019	1587	1	1	1
4908-020	1588	1	1	1
4908-021	1589	1	1	1
4908-022	1590	1	1	1
4908-023	1591	1	1	1
4908-024	1592	1	1	1
4908-025	1633	1	1	1
4908-026	1634	1	1	1
4908-027	1635	1	1	1
4908-028	1636	1	1	1
4908-029	1637	1	1	1
4908-030	1638	1	1	1
4908-031	1639	1	1	1
4908-032	1640	1	1	1
4908-033	3073	1	1	1
4909-001	1041	1	1	1
4909-002	1042	1	1	1
4909-011	1155	1	1	1
4909-012	1156	1	1	1
4909-015	1159	1	1	1
4909-016	1160	1	1	1
4909-017	1417	1	1	1
4909-018	1418	1	1	1
4909-019	1419	1	1	1
4909-036	1660	1	1	1
4909-037	1661	1	1	1
4909-038	1662	1	1	1
4909-039	1663	1	1	1
4909-040	1664	1	1	1
4909-041	3013	1	1	1
4909-042	3014	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4909-043	3015	1	1	1
4909-044	3016	1	1	1
4909-045	3133	1	1	1
4909-046	3134	1	1	1
4909-047	3135	1	1	1
4910-046	1646	1	1	1
4910-047	1647	1	1	1
4910-048	1648	1	1	1
4910-049	1737	1	1	1
4910-050	1738	1	1	1
4910-051	1739	1	1	1
4910-052	1740	1	1	1
4910-053	1741	1	1	1
4910-054	1742	1	1	1
4910-055	1743	1	1	1
4910-056	1744	1	1	1
4910-057	3077	1	1	1
4910-058	3078	1	1	1
4910-059	3079	1	1	1
4910-060	3080	1	1	1
4910-061	3153	1	1	1
4910-062	3154	1	1	1
4910-063	3155	1	1	1
4910-064	3156	1	1	1
4910-065	3189	1	1	1
4910-066	3190	1	1	1
4910-067	3191	1	1	1
4910-068	3192	1	1	1
4910-069	3193	1	1	1
4910-070	3194	1	1	1
4910-071	3195	1	1	1
4910-072	3196	1	1	1
4910-073	3209	1	1	1
4910-074	3210	1	1	1
4910-075	3211	1	1	1
4910-076	3212	1	1	1
4910-077	3261	1	1	1
4910-078	3262	1	1	1
4910-079	3263	1	1	1
4910-080	3264	1	1	1
4910-081	3265	1	1	1
4910-082	3266	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4910-083	3267	1	1	1
4910-084	3268	1	1	1
4910-085	3293	1	1	1
4910-086	3294	1	1	1
4910-087	3295	1	1	1
4910-088	3296	1	1	1
4910-089	3297	1	1	1
4910-090	3298	1	1	1
4911-006	3053	1	1	1
4911-007	3054	1	1	0
4911-008	3055	1	1	1
4911-009	3056	1	1	1
4911-010	3085	1	1	1
4911-011	3086	1	1	1
4911-012	3087	1	1	1
4912-001	1017	1	1	1
4912-002	1018	1	1	1
4912-003	1019	1	1	1
4915-001	1025	1	1	1
4915-002	1026	1	1	1
4915-003	1027	1	1	1
4915-004	1028	1	1	1
4915-005	1029	1	1	1
4915-006	1030	1	1	1
4915-007	1031	1	1	1
4915-008	1032	1	1	1
4915-009	1169	1	1	1
4915-010	1170	1	1	1
4915-011	1171	1	1	1
4915-012	1172	1	1	1
4915-013	1173	1	1	1
4915-014	1174	1	1	1
4915-015	1175	1	1	1
4915-016	1176	1	1	1
4915-017	1193	1	1	1
4915-018	1194	1	1	1
4915-019	1195	1	1	1
4915-020	1196	1	1	1
4915-021	1197	1	1	1
4915-022	1198	1	1	1
4915-023	1199	1	1	1
4915-024	1200	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4915-025	1201	1	1	1
4915-026	1202	1	1	1
4915-027	1203	1	1	1
4915-028	1204	1	1	1
4915-029	1205	1	1	1
4915-030	1206	1	1	1
4915-031	1207	1	1	1
4915-032	1208	1	1	1
4915-033	1225	1	1	1
4915-034	1226	1	1	1
4915-035	1227	1	1	1
4915-036	1228	1	1	1
4915-037	1229	1	1	1
4915-038	1230	1	1	1
4915-039	1231	1	1	1
4915-040	1232	1	1	1
4915-041	1305	1	1	1
4915-042	1306	1	1	1
4915-043	1307	1	1	1
4915-044	1308	1	1	1
4915-045	1309	1	1	1
4915-046	1310	1	1	1
4915-047	1311	1	1	1
4915-048	1312	1	1	1
4915-049	1401	1	1	1
4915-050	1402	1	1	1
4915-051	1403	1	1	1
4915-052	1404	1	1	1
4915-053	1405	1	1	1
4915-054	1406	1	1	1
4915-055	1407	1	1	1
4915-056	1408	1	1	1
4915-057	3121	1	1	1
4915-058	3122	1	1	1
4915-059	3123	1	1	1
4915-060	3124	1	1	1
4915-061	3126	1	1	1
4915-062	3125	1	1	1
4915-063	3127	1	1	1
4915-064	3128	1	1	1
4915-065	3129	1	1	1
4915-066	3130	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4915-067	3131	1	1	1
4915-068	3132	1	1	1
4915-069	3177	1	1	1
4915-070	3178	1	1	1
4915-071	3179	1	1	1
4915-072	3180	1	1	1
4915-073	3181	1	1	1
4915-074	3182	1	1	1
4915-075	3183	1	1	1
4915-076	3184	1	1	1
4915-077	3185	1	1	1
4915-078	3186	1	1	1
4915-079	3187	1	1	1
4915-080	3188	1	1	1
4915-081	3245	1	1	1
4915-082	3246	1	1	1
4915-083	3247	1	1	1
4915-084	3248	1	1	1
4915-085	3249	1	1	1
4915-086	3250	1	1	1
4915-087	3251	1	1	1
4915-088	3252	1	1	1
4915-089	3253	1	1	1
4915-090	3254	1	1	1
4915-091	3255	1	1	1
4915-092	3256	1	1	1
4915-093	3317	1	1	1
4915-094	3318	1	1	1
4915-095	3319	1	1	1
4915-096	3320	1	1	1
4915-097	3321	1	1	1
4915-098	3322	1	1	1
4915-099	3323	1	1	1
4915-100	3324	1	1	1
4918-015	1319	1	1	1
4918-016	1320	1	1	1
4918-017	1513	1	1	1
4918-019	1515	1	1	1
4918-020	1516	1	1	1
4918-021	1517	1	1	1
4918-022	1518	1	1	1
4918-023	1519	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4918-024	1520	1	1	1
4918-025	1601	1	1	1
4918-026	1602	1	1	1
4918-027	1603	1	1	1
4918-028	1604	1	1	1
4918-029	1605	1	1	1
4918-030	1606	1	1	1
4918-031	1607	1	1	1
4918-032	3017	1	1	1
4918-033	3018	1	1	1
4918-034	3019	1	1	1
4918-035	3020	1	1	1
4918-036	3113	1	1	1
4919-001	1033	1	1	1
4919-002	1034	1	1	1
4919-003	1035	1	1	1
4919-004	1036	1	1	1
4919-005	1037	1	1	1
4919-006	1038	1	1	1
4919-007	1039	1	1	1
4919-008	1040	1	1	1
4919-009	1185	1	1	1
4919-010	1186	1	1	1
4919-011	1187	1	1	1
4919-012	1188	1	1	1
4919-013	1189	1	1	1
4919-014	1190	1	1	1
4919-015	1191	1	1	1
4919-016	1192	1	1	1
4919-017	1209	1	1	1
4919-018	1210	1	1	1
4919-019	1211	1	1	1
4919-020	1212	1	1	1
4919-021	1213	1	1	1
4919-022	1214	1	1	1
4919-023	1215	1	1	1
4919-024	1216	1	1	1
4919-025	1257	1	1	1
4919-026	1258	1	1	1
4919-027	1259	1	1	1
4919-028	1260	1	1	1
4919-029	1261	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4919-030	1262	1	1	1
4919-031	1263	1	1	1
4919-032	1264	1	1	1
4919-033	1281	1	1	1
4919-034	1282	1	1	1
4919-035	1283	1	1	1
4919-036	1284	1	1	1
4919-037	1285	1	1	1
4919-038	1286	1	1	1
4919-039	1287	1	1	1
4919-040	1288	1	1	1
4919-041	1409	1	1	1
4919-042	1410	1	1	1
4919-043	1411	1	1	1
4919-044	1412	1	1	1
4919-045	1413	1	1	1
4919-046	1414	1	1	1
4919-047	1415	1	1	1
4919-048	1416	1	1	1
4919-049	1481	1	1	1
4919-050	1482	1	1	1
4919-051	1483	1	1	1
4919-052	1484	1	1	1
4919-053	1485	1	1	1
4919-054	1486	1	1	1
4919-055	1487	1	1	1
4919-056	1488	1	1	1
4919-057	3093	1	1	1
4919-058	3094	1	1	1
4919-059	3095	1	1	1
4919-060	3096	1	1	1
4919-061	3097	1	1	1
4919-062	3098	1	1	1
4919-063	3099	1	1	1
4919-064	3100	1	1	1
4919-065	3101	1	1	1
4919-066	3102	1	1	1
4919-067	3103	1	1	1
4919-068	3104	1	1	1
4919-069	3161	1	1	1
4919-070	3162	1	1	1
4919-071	3163	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4919-072	3164	1	1	1
4919-073	3165	1	1	1
4919-074	3166	1	1	1
4919-075	3167	1	1	1
4919-076	3168	1	1	1
4919-077	3169	1	1	1
4919-078	3170	1	1	1
4919-079	3171	1	1	1
4919-080	3172	1	1	1
4919-081	3233	1	1	1
4919-082	3234	1	1	1
4919-083	3235	1	1	1
4919-084	3236	1	1	1
4919-085	3237	1	1	1
4919-086	3238	1	1	1
4920-001	1121	1	1	1
4920-002	1122	1	1	1
4920-003	1123	1	1	1
4920-004	1124	1	1	1
4920-005	1125	1	1	1
4920-006	1126	1	1	1
4920-007	1127	1	1	1
4920-008	1128	1	1	1
4920-009	1297	1	1	1
4920-010	1298	1	1	1
4920-011	1299	1	1	1
4920-012	1300	1	1	1
4920-013	1301	1	1	1
4920-014	1302	1	1	1
4920-015	1303	1	1	1
4921-002	1106	1	1	1
4921-011	1291	1	1	1
4921-012	1292	1	1	1
4921-013	1293	1	1	1
4921-016	1296	1	1	1
4921-020	1373	1	1	1
4921-021	1374	1	1	1
4921-022	1369	1	1	1
4921-023	1375	1	1	1
4921-024	1376	1	1	1
4921-025	1465	1	1	1
4921-027	1467	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4921-029	1469	1	1	1
4921-039	1575	1	1	1
4921-048	1624	1	1	1
4921-049	1689	1	1	1
4921-050	1690	1	1	1
4921-055	1695	1	1	1
4921-056	1696	1	1	1
4921-057	3021	1	1	1
4921-058	3022	1	1	1
4921-059	3023	1	1	1
4921-060	3024	1	1	1
4921-061	3145	1	1	1
4921-062	3146	1	1	1
4921-063	3147	1	1	1
4921-064	3148	1	1	1
4923-030	1630	1	1	1
4923-031	1631	1	1	1
4923-032	1632	1	1	1
4923-033	1721	1	1	1
4923-034	1722	1	1	1
4923-035	1723	1	1	1
4923-036	1724	1	1	1
4923-037	1725	1	1	1
4923-038	1726	1	1	1
4923-039	1727	1	1	1
4923-040	1728	1	1	1
4923-041	1769	1	1	1
4923-042	1770	1	1	1
4923-043	1771	1	1	1
4923-044	1772	1	1	1
4923-045	1773	1	1	1
4923-046	1774	1	1	1
4923-047	3025	1	1	1
4923-048	3028	1	1	1
4923-049	3026	1	1	1
4923-050	3027	1	1	1
4923-051	3197	1	1	1
4923-052	3198	1	1	1
4923-053	3199	1	1	1
4923-054	3200	1	1	1
4923-055	3205	1	1	0
4923-056	3206	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4923-057	3207	1	1	1
4923-058	3208	1	1	1
4923-059	3273	1	1	1
4923-060	3274	1	1	1
4923-061	3275	1	1	1
4923-062	3276	1	1	1
4923-063	3277	1	1	1
4923-064	3278	1	1	1
4926-001	1521	1	1	1
4926-002	1522	1	1	1
4926-007	1527	1	1	1
4928-001	1273	1	1	1
4928-002	1274	1	1	1
4928-003	1275	1	1	1
4928-004	1276	1	1	1
4928-005	1277	1	1	1
4928-006	1278	1	1	1
4928-007	1279	1	1	1
4928-008	3033	1	1	1
4929-001	1433	1	1	1
4929-002	1434	1	1	1
4929-003	1435	1	1	1
4929-004	1436	1	1	1
4929-005	1437	1	1	1
4930-009	1665	1	1	0
4930-010	1666	1	1	1
4930-011	3040	1	1	1
4932-001	1265	1	1	1
4932-002	1266	1	1	1
4932-003	1267	1	1	1
4932-004	1268	1	1	1
4932-005	1269	1	1	1
4932-006	1270	1	1	1
4932-007	1271	1	1	1
4932-008	1272	1	1	1
4932-009	1681	1	1	1
4932-010	1682	1	1	1
4932-011	3041	1	1	1
4932-012	3042	1	1	1
4934-001	1609	1	1	1
4934-002	1610	1	1	1
4934-003	1612	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4934-004	1611	1	1	1
4934-005	1613	1	1	1
4934-006	1614	1	1	1
4934-007	1615	1	1	1
4934-008	1616	1	1	1
4934-009	1713	1	1	1
4934-010	1714	1	1	1
4934-011	1715	1	1	1
4934-012	1716	1	1	1
4934-013	1717	1	1	1
4934-014	3045	1	1	1
4934-015	3046	1	0	0
4934-016	3047	1	1	1
4934-017	3048	1	1	1
4936-001	3081	1	1	1
4936-002	3082	1	1	1
4936-003	3083	1	1	1
4936-004	3084	1	1	1
4936-005	3157	1	1	1
4936-006	3158	1	1	1
4936-007	3159	1	1	1
4936-008	3160	1	1	1
4936-009	3225	1	1	1
4936-010	3226	1	1	1
4936-011	3227	1	1	1
4936-012	3228	1	1	1
4936-013	3229	1	1	1
4936-014	3230	1	1	1
4936-015	3231	1	1	1
4936-016	3232	1	1	1
4936-017	3281	1	1	1
4936-018	3282	1	1	1
4936-019	3283	1	1	1
4936-020	3284	1	1	1
4936-021	3285	1	1	1
4936-022	3286	1	1	1
4936-023	3287	1	1	1
4936-024	3288	1	1	1
4936-025	3313	1	1	1
4936-026	3314	1	1	1
4936-027	3315	1	1	1
4936-028	3316	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4936-029	3325	1	1	1
4936-030	3326	1	1	1
4936-031	3327	1	1	1
4936-032	3328	1	1	1
4936-033	3333	1	1	1
4936-034	3334	1	1	1
4936-035	3335	1	1	1
4936-036	3336	1	1	1
4936-037	3337	1	1	1
4936-038	3338	1	1	1
4936-039	3339	1	1	1
4937-001	3137	1	1	1
4937-002	3138	1	1	1
4938-001	3141	1	1	1
4938-002	3142	1	1	0
4939-001	3217	1	1	1
4939-002	3218	1	1	1
4939-003	3219	1	1	1

Table 2: Dataset Assignment, Status: Hardlock Transfer, 'Issue' Patients (n = 184)

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4905-001	1129	1	1	1
4905-002	1130	1	1	1
4905-003	1131	1	0	0
4905-004	1132	1	0	0
4905-005	1133	1	1	1
4905-006	1134	1	1	0
4905-007	1135	1	1	1
4905-008	1136	1	1	0
4905-011	1459	1	1	1
4905-012	1460	1	1	0
4909-003	1043	1	1	1
4909-004	1044	1	1	1
4909-005	1045	1	1	1
4909-006	1046	1	1	1
4909-007	1047	1	1	0
4909-008	1048	1	1	0
4909-009	1153	1	1	0
4909-010	1154	1	1	0
4909-013	1157	1	1	1
4909-014	1158	1	1	1
4909-020	1420	1	1	1
4909-021	1421	1	1	1
4909-022	1422	1	1	1
4909-023	1423	1	1	1
4909-024	1424	1	1	1
4909-025	1553	1	1	1
4909-026	1554	1	1	1
4909-027	1555	1	1	1
4909-028	1556	1	1	1
4909-029	1557	1	1	1
4909-030	1558	1	1	1
4909-031	1559	1	1	1
4909-032	1560	1	1	1
4909-033	1657	1	1	1
4909-034	1658	1	1	1
4909-035	1659	1	1	1
4910-001	1057	1	1	1
4910-002	1058	1	1	1
4910-003	1059	1	1	1
4910-004	1060	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4910-005	1061	1	1	1
4910-006	1062	1	1	1
4910-007	1063	1	1	1
4910-008	1064	1	1	1
4910-009	1177	1	1	1
4910-010	1178	1	1	1
4910-011	1179	1	1	1
4910-012	1180	1	1	1
4910-013	1181	1	1	1
4910-014	1182	1	1	1
4910-015	1183	1	1	1
4910-016	1184	1	1	1
4910-017	1321	1	1	1
4910-018	1322	1	1	1
4910-019	1323	1	1	1
4910-020	1324	1	1	1
4910-021	1325	1	1	1
4910-022	1326	1	1	1
4910-023	1327	1	1	1
4910-024	1328	1	1	1
4910-025	1425	1	1	1
4910-026	1426	1	1	1
4910-027	1427	1	1	1
4910-028	1428	1	1	1
4910-029	1429	1	1	1
4910-030	1430	1	1	1
4910-031	1431	1	1	1
4910-032	1432	1	1	1
4910-033	1497	1	1	1
4910-034	1498	1	1	1
4910-035	1499	1	1	1
4910-036	1500	1	1	1
4910-037	1501	1	1	1
4910-038	1502	1	1	1
4910-039	1503	1	1	1
4910-040	1504	1	1	1
4910-041	1641	1	1	1
4910-042	1642	1	1	1
4910-043	1643	1	1	1
4910-044	1644	1	1	1
4910-045	1645	1	1	1
4911-001	1137	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4911-002	1138	1	1	1
4911-003	1139	1	1	0
4911-004	1140	1	1	1
4911-005	1141	1	1	1
4917-001	1249	1	1	1
4917-002	1250	1	0	0
4917-003	1251	1	1	1
4918-001	1081	1	1	1
4918-002	1082	1	1	1
4918-003	1083	1	1	1
4918-004	1084	1	1	1
4918-005	1085	1	1	1
4918-006	1086	1	1	1
4918-007	1087	1	1	1
4918-008	1088	1	1	1
4918-009	1313	1	1	1
4918-010	1314	1	1	1
4918-011	1315	1	1	1
4918-012	1316	1	1	1
4918-013	1317	1	1	1
4918-014	1318	1	1	1
4918-018	1514	1	1	1
4921-001	1105	1	1	1
4921-003	1107	1	1	1
4921-004	1108	1	1	1
4921-005	1109	1	1	1
4921-006	1110	1	1	1
4921-007	1111	1	1	1
4921-008	1112	1	1	1
4921-009	1289	1	1	0
4921-010	1290	1	1	1
4921-014	1294	1	1	1
4921-015	1295	1	1	1
4921-017	1370	1	1	1
4921-018	1371	1	1	1
4921-019	1372	1	1	1
4921-026	1466	1	1	0
4921-028	1468	1	1	1
4921-030	1470	1	1	1
4921-031	1471	1	1	1
4921-032	1472	1	1	0
4921-033	1569	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4921-034	1570	1	1	1
4921-035	1571	1	1	1
4921-036	1572	1	1	1
4921-037	1573	1	1	1
4921-038	1574	1	1	1
4921-040	1576	1	1	1
4921-041	1617	1	1	1
4921-042	1618	1	1	1
4921-043	1619	1	1	1
4921-044	1620	1	1	1
4921-045	1621	1	1	1
4921-046	1622	1	1	1
4921-047	1623	1	1	1
4921-051	1691	1	1	1
4921-052	1692	1	1	1
4921-053	1693	1	1	1
4921-054	1694	1	1	1
4923-001	1505	1	1	1
4923-002	1506	1	1	1
4923-003	1507	1	1	1
4923-004	1508	1	1	1
4923-005	1509	1	1	0
4923-006	1510	1	1	1
4923-007	1511	1	1	1
4923-008	1512	1	1	1
4923-009	1529	1	1	1
4923-010	1530	1	1	1
4923-011	1531	1	1	1
4923-012	1532	1	1	1
4923-013	1533	1	1	1
4923-014	1534	1	1	1
4923-015	1535	1	1	1
4923-016	1536	1	1	1
4923-017	1545	1	1	1
4923-018	1546	1	1	1
4923-019	1547	1	1	1
4923-020	1548	1	1	1
4923-021	1549	1	1	1
4923-022	1551	1	1	1
4923-023	1550	1	1	0
4923-024	1552	1	1	1
4923-025	1625	1	1	1

PATID	RANDOM NUMBER	SAFETY	FAS	PP
4923-026	1626	1	1	1
4923-027	1627	1	1	1
4923-028	1628	1	1	1
4923-029	1629	1	1	1
4926-003	1523	1	1	1
4926-004	1524	1	1	1
4926-005	1525	1	1	1
4926-006	1526	1	0	0
4930-001	1593	1	1	1
4930-002	1594	1	1	1
4930-003	1595	1	1	1
4930-004	1596	1	1	1
4930-005	1597	1	0	0
4930-006	1598	1	1	0
4930-007	1599	1	1	0
4930-008	1600	1	1	0
4931-001	1377	1	1	1
4931-002	1378	1	1	1

13.3 Table of Contents for Data Displays (Items of eCRF)

All items of the eCRF will be presented in individual participant data listings and in appropriate summary tables. Standard descriptive summary statistics will be calculated for continuous and semi-continuous variables (i.e., arithmetic mean, standard deviation, standard error of the mean, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values). In addition, measures for skewness and kurtosis will be provided for suitable efficacy variables. Categorical data will be presented in frequency tables using counts and their associated percentages. Individual participant data listings will be presented per eCRF item and will be sorted appropriately. Summary tables will be displayed by treatment conditions and visit (if applicable). Where appropriate, the presentation will include changes from baseline. Semi-quantitative and quantitative efficacy data will be additionally visualized by boxplot diagrams. All standardized effect sizes (Mann-Whitney) will be visualized with their corresponding 95%-confidence intervals. All standard statistical tables will be generated applying the standard table layout of the validated statistical package TESTIMATE V6.5.14 (IDV Gauting). Associated meta-data and variable labels are finalized before unblinding All standard scientific figures are generated applying the standard figure layout of the validated scientific package SCIENCEGRAPH V4.9.39 (IDV Gauting).

Data displays will be provided for the following analysis sets:

Chapter Title	Analysis set
Study Patients	A: All patients randomized
Demographic and Other Baseline Characteristics	B: Safety analysis set C: Full analysis set D: Per-protocol analysis set
Treatment Compliance	B: Safety analysis set C: Full analysis set D: Per-protocol analysis set
Visits	B: Safety analysis set C: Full analysis set D: Per-protocol analysis set
Analysis of Efficacy	C: Full analysis set D: Per-protocol analysis set
Analysis of Concomitant/ Supportive Therapies	B: Safety analysis set C: Full analysis set D: Per-protocol analysis set
Analysis of Safety	B: Safety analysis set

13.3.1 Tables

Study Patients

Sections
Disposition of Patients
End of Study / End of Treatment
Inclusion/Exclusion Criteria
Major Protocol Violations
Analysis Sets

Demographic and Other Baseline Characteristics

Chapter Title
Demography
Pregnancy Test
Medical History
Physical Examination / Vital Signs
Prior and Concomitant Medications
Time and Grading of Injury / Confirmatory Check of Grading
Supportive Therapy
VAS
FAAM

Treatments

Chapter Title
Study Drug Administration
Compliance

Visits

Chapter Title
Visits Intervals

Efficacy Analysis

Chapter Title
VAS Pain on Passive Movement at Visits
AUC for VAS Pain on Passive Movement at Visits
VAS Pain at Rest at Visits
AUC for VAS Pain at Rest at Visits
Time to 50% Improvement for VAS Pain at Rest at Visits
Rescue Medication

Concomitant/ Supportive Therapies

Chapter Title
Other Pain Medication
Supportive Therapy
Concomitant Medications

Safety Analysis

Chapter Title
Extent of Exposure
Adverse Events
Physical Examination / Vital Signs

13.3.2 Listings

Study Patients

Sections
Disposition of Patients
End of Study / End of Treatment
Inclusion/Exclusion Criteria
Major Protocol Violations
Analysis Sets

Demographic and Other Baseline Characteristics

Chapter Title
Demography
Pregnancy Test
Medical History
Physical Examination / Vital Signs
Prior and Concomitant Medications
Time and Grading of Injury / Confirmatory Check of Grading
Supportive Therapy
VAS
FAAM

Treatments

Chapter Title
Study Drug Administration
Compliance

Visits

Chapter Title
Visits Intervals

Efficacy Analysis

Chapter Title
VAS Pain on Passive Movement at Visits
AUC for VAS Pain on Passive Movement at Visits
VAS Pain at Rest at Visits
AUC for VAS Pain at Rest at Visits
Time to 50% Improvement for VAS Pain at Rest at Visits
Rescue Medication

Concomitant/ Supportive Therapies

Chapter Title
Other Pain Medication
Supportive Therapy
Concomitant Medications

Safety Analysis

Chapter Title
Extent of Exposure
Adverse Events
Physical Examination / Vital Signs

13.3.3 Figures

Efficacy analysis

Chapter Title	Type of Figure
VAS Pain on Passive Movement at Visits	Boxplots across all points in time (per group and visit); Means with standard deviation across all points in time (per group and visit); Standardized effect sizes (MW) with CI across all points in time (per group and visit)
AUC for VAS Pain on Passive Movement at Visits	Boxplots across all points in time (per group and follow-up visit); Means with standard deviation across all points in time (per group and follow-up visit); Standardized effect sizes (MW) with CI across all points in time (per group and follow-up visit); Scattergram for primary endpoint at Day 4 with regression lines (baseline VAS as covariate)
VAS Pain at Rest at Visits	Boxplots across all points in time (per group and visit); Means with standard deviation across all points in time (per group and visit); Standardized effect sizes (MW) with CI across all points in time (per group and visit)
AUC for VAS Pain at Rest at Visits	Boxplots across all points in time (per group and follow-up visit); Means with standard deviation across all points in time (per group and follow-up visit); Standardized effect sizes (MW) with CI across all points in time (per group and follow-up visit)

Time to 50% Improvement for VAS Pain at Rest at Visits	Kaplan Meier Curves per group.
Rescue Medication	Boxplots for Day 1 to 4 Totals per group, Boxplots for Day 1 to Final Day Totals per group; Standardized effect sizes (MW) for Day 1 to 4 Totals and Day 1 to Final Day Totals with CI per group.

13.4 Clinical Trial Report (CTR) Specifications

13.4.1 Core CTR Specifications

The Core Clinical Trial Report (CTR) will be generated by means of the idv ICH-Study-Report-Manager V2.4.3 within the validated working environment at the department 'Clinical Research/ Biometry' in the institute IDV Data Analysis and Study Planning. The generation is based on the idv CTR template according to idv SOP KLIFO-16.04, the template being finalized before breaking the blind. The following specifications will apply to the CTR:

- Layout is DIN A4 format
- Body text font is Times New Roman 12 pt
- Language is American English (AE)
- CTR Structure is following the idv template according to idv SOP KLIFO-16.04
- CTR protocol sections are cited in original wording (unchanged or in past tense), the same applies to CTR SAP sections
- Scientific tables will be imported with full audit trail via validated pathway of module *idv-Tabellen/-Text*, remaining unchanged after import (original table)
- Scientific figures will be imported with full audit trail via validated pathway of module *idv Science-Graph-Tools*, remaining unchanged after import (original figure)
- Separate tables of content for core text, tables, and figures; generation by ICH-Study-Report-Manager V2.4.3
- CTR Versions:
    - Draft 0.1 (IDV Mock Report, generated before unblinding)
    - Draft 1.0 (initial IDV CTR version after unblinding)
    - Draft 1.X (follow-up CTR version after external review)
    - Draft to Final (IDV)
    - Final (IDV)

13.4.2 Appendices:

- Title pages generated according to title page of Core Report
- Appendix 1: Individual Patient Listing ('Non-Issue' Cases)
    - Listing of analysis data (validated XLI-export from TESTIMATE V6.5.14 analysis database with variable description by means of TESTIMATE V6.5.14 metadata)
- Appendix 2: Tables and Figures ('Non-Issue' Cases)
    - Tables will be imported with full audit trail via validated pathway of module *idv-Tabellen/-Text*, remaining unchanged after import (original scientific table)
    - Figures will be imported with full audit trail via validated pathway of module *idv Science-Graph-Tools*, remaining unchanged after import (original scientific figure)
- Appendix 3: 'Issue" Cases
    - A. Individual Patient Listing (for specs see Appendix 1)
    - B. Tables and Figures (for specs see Appendix 2)
- Appendix 4: Listing of Original Raw Data Files (sas7bdat eCRF Domains) with variable description by means of latest version 4.0 of HE13226_eCRF Specification (02 June 2020), sorting as shown in Table 3.

Table 3: Sorting of Individual Patient Data (sas 7bdat raw data)

DOMAIN	DOMAIN TITLE	SORT BY
ADMIN	Study Drug Administration	SEQNO
AE	Adverse Events	SEQID
AEGO	Adverse Events flags	
CCG	Confirmatory check of Grading	VISITNO
COMMENTS	Comments	
DA	Rescue Medication Accountability	VISITNO
DIARYHO	Diary Handout	VISITNO
DM	Demography	
DOV	Visits	VISITNO
DS	Informed Consent	
EC	Exclusion Criteria	EXC
EOS	End of Study	
EOT	End of Treatment	
EVALP	Question to Patients about their treatment	VISITNO
FAAM	Foot and Ankle Ability Measure (FAAM) / Activities of Daily Living (ADL) Subscale	VISITNO
GDD	Date of Confirmation of Grade 3 - Discontinuation of Treatment	
GRAD	Time and Grading of Injury	VISITNO
IC	Inclusion Criteria	INC
LINK	Link list	
MH	Medical History	SEQNO
MHGO	Medical History flags	VISITNO
NA	Not Applicable	SEQNO
OPM	Other Pain Medications	STUDDCD
PARAC	Rescue Medication	STUDDCD
PCM	Prior and Concomitant Medications	CMSEQ

DOMAIN	DOMAIN TITLE	SORT BY
PCMGO	Prior and Concomitant Medications flags	
PE	Physical Examination	SEQNO
PEGO	Physical Examination flags	VISITNO
PREG	Pregnancy Test (only for female patients with childbearing potential)	VISITNO
RAND	Randomization	
SUPT	Supportive Therapy	VISITNO
TAEC	Occurence of Adverse Events	VISITNO
TCMC	Occurence of Concomitant Medications	VISITNO
UNBLIND	Medical Code Broken	
VAS	Visual Analogue Scale	VISITNO
VS	Vital Signs	VISITNO