A multi-center, double-blind, randomized, placebo-controlled trial protocol to assess Traumeel injection vs dexamethasone injection in rotator cuff syndrome: the TRAumeel in ROtator cuff syndrome (TRARO) study protocol

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Abstract

Background: Shoulder pain is a common musculoskeletal symptom with a wide range of potential causes; however, the majority of conditions can be managed with conservative treatment. The aim of this study is to assess the efficacy and safety of Traumeel injections versus corticosteroid injections and placebo in the treatment of rotator cuff syndrome and bursitis and expand the current evidence base for the conservative treatment of rotator cuff syndrome.

Methods/Design: This is a multi-center, randomized, double-blind, 16-week, three-arm, parallel-group, active- and placebo-controlled trial to assess the efficacy and safety of Traumeel 2 ml injection versus dexamethasone 8 mg injection versus placebo (saline solution). Patients will be randomly allocated to Traumeel, dexamethasone or placebo in a 2:2:1 randomization. After 1 week screening, patients will receive 3 injections at weekly intervals (days 1, 8 and 15) with additional follow-up assessments on day 22, a telephone consultation in week 9 and a final visit at week 15. Male and female patients aged 40 to 65 years, inclusive, will be recruited if they have acute episodes of chronic rotator cuff syndrome and/or bursitis. Patients with calcifications in the shoulder joint or a complete rotator cuff tear will be excluded. At least 160 patients will be recruited. All subacromial injections will be performed under ultrasound guidance utilizing a common technique. The only rescue medication permitted will be paracetamol (acetaminophen), with usage recorded. The primary endpoint is change from baseline in abduction-rotation pain visual analog scale (0–100 mm scale, 0 corresponds to no pain and 100 to extreme pain) at day 22 (Traumeel injections versus dexamethasone injections) for active external rotation. Secondary efficacy parameters include range of motion, disability of arm, shoulder, hand score and patient’s/investigator’s global assessment. Clinical efficacy will be assessed as non-inferiority of Traumeel with respect to dexamethasone regarding the primary efficacy parameter.

Discussion: It is hoped that the results of this trial will expand the treatment options and evidence base available for the management of rotator cuff disease.

Trial registration: ClinicalTrials.gov: NCT01702233. EudraCT number: 2012-003393-12.

Keywords: Rotator cuff syndrome, Shoulder, Bursitis, Traumeel, Dexamethasone, Corticosteroids, Ultrasound, Injections, Pain
Background
Shoulder pain is the third most common musculoskeletal symptom encountered in medical practice, after back and neck pain [1]. It accounts for almost 3 million patient visits each year in the USA [2,3]. A wide range of potential pathoanatomic entities, from simple sprains to massive rotator cuff tears, can give rise to shoulder pain [2].

The majority of these conditions can be managed with conservative treatment [2,4], and conservative therapy can include a number of novel treatments [5]. Rotator cuff dysfunction is a particularly important entity because it occurs frequently, and indicative with complete tear, may necessitate surgical treatment [2,6,7].

The shoulder has the greatest range of motion (ROM) of any joint in the human body. Size mismatch between the smaller glenoid and larger humeral head creates a risk of instability. Stability is provided both statically by the capsule and labrum, and dynamically by the rotator cuff musculature. Dysfunction of any of these structures can lead to pain, weakness, and instability.

The rotator cuff is a musculo-tendinous confluence of four muscles that initiate shoulder motion and maintain the normal relationship between the articular surfaces. The supraspinatus muscle provides abduction, the infraspinatus and teres minor muscles provide external rotation, and the subscapularis muscle provides internal rotation. In addition, the muscles of the rotator cuff balance the forces of other shoulder muscles, most importantly the deltoid muscle. Contraction of the deltoid muscle in the absence of supraspinatus function leads to superior translocation of the humeral head, making wide abduction difficult.

Non-operative treatment for shoulder pain due to rotator cuff impingement and tears generally includes appropriate physical therapy, anti-inflammatory medication, corticosteroid injections, and other approaches. Meta-analyses of trials of subacromial injection of corticosteroids for rotator cuff disease have shown a beneficial effect over placebo, while evidence for other interventions is lacking [6,8,9]. The importance of the accuracy of injecting the subacromial bursa with corticosteroids was highlighted by a study by Henkus et al. [10] showing that despite the confidence of physicians, without guidance many subacromial injections hit surrounding structures. However, only injection directly into the subacromial bursa resulted in significant pain relief and increase in functional scores. Marder et al. [11] further supported these findings and found that the rate of accuracy varied with route of injection, and anterior and lateral routes are more accurate than the posterior route. Due to potential variance in accuracy of subacromial injection between physicians, ultrasound-guided injections utilizing a common method have been used for this study.

Traumeel (Tr14) injection solution is a combination formula of 12 botanical and 2 mineral substances with demonstrated anti-inflammatory, anti-edematous, anti-exudative properties. The exact mechanism of action of Tr14 injection solution is still to be fully understood. Various cellular and biochemical pathways appear to be modulated by the ingredients. It has been suggested that Tr14 injection solution does not inhibit cyclo-oxygenase (COX) or lipoxygenase enzyme pathways, as is the case with non-steroidal anti-inflammatory drugs (NSAIDs) [12]. In the rat model of blood-induced inflammation, Tr14 injection solution significantly reduced hind paw induced-edema and decreased IL-6 production. The authors suggested that Tr14 injection solution seems to act by speeding up the healing process instead of blocking the development of edema from the beginning [13]. Additional basic research is currently underway to further elucidate Tr14 injection solution’s mechanism of action.

Tr14 injection solution has been shown to be effective for hemarthrosis of the knee [14], epicondylitis [15], and various musculoskeletal injuries [16]. However, no large study with Tr14 injection solution has been performed so far in patients with rotator cuff syndrome and bursitis. Thus, the aim of this study is to assess the efficacy and safety of Tr14 injection solution injections versus corticosteroid injections in the treatment of rotator cuff syndrome and bursitis and expand the current evidence base for the conservative treatment of the rotator cuff syndrome. It is hoped that the results of this trial will expand the treatment options available to clinicians for the treatment of rotator cuff syndrome, allowing greater patient choice.

Methods/Design
This will be a multi-center, randomized, double-blind, 16-week, three-arm, parallel-group, active- and placebo-controlled trial to assess the efficacy and safety of Tr14 injection solution 2 ml injection versus dexamethasone 8 mg injection versus placebo (Figure 1).

The objective of this study is to evaluate reduction of pain and improvement of functional motion parameters in patients with rotator cuff syndrome and bursitis treated with Tr14 injection solution injections versus corticosteroid injections and versus placebo.

Patients will be randomly allocated to Tr14 injection solution, dexamethasone or placebo in a 2:2:1 randomization. The randomization will be stratified by site. Randomization codes will be generated by a statistician not involved in the study from an algorithm based on the PROC PLAN procedure of SAS, Version 9.1.3. Sealed envelopes containing the individual codes will be sent to the centers and to the study sponsor for the purposes of assigning kits to patients and the managing of adverse events.

All study personnel and patients will be blinded to the treatment being used during the study. The investigator will keep the treatment code envelopes throughout the
The study includes 2 sites in Belgium, 4 in Germany, and 4 in Spain, all based in outpatient clinics. The study has been approved by Competent Authorities in all three countries (Federal Agency for Medicines and Health Products in Belgium, Bundesinstitut für Arzneimittel und Medizinprodukte in Germany and the Agencia Española del Medicamento in Spain), and has received ethical approval from relevant bodies in each country (Commissie voor Medische Ethiek Universitair Ziekenhuis Ghent in Belgium, Ethikkommission der Ärztekammer Hamburg in Germany and Comité Ético de Investigación Clínica Complejo Hospitalario de Toledo in Spain).

The study will be conducted in compliance with the ethical principles of the Declaration of Helsinki and its amendments as adopted by the 59th World Medical Assembly (WMA) General Assembly, Seoul, October 2008; the principles of the GCP provided in the ICH Harmonised Tripartite Guidelines for GCP 1996; and all applicable national laws and regulations.

**Participants**

Male and female patients aged 40 to 65 years, inclusive, will be recruited if they have acute episodes of chronic rotator cuff syndrome and/or bursitis: tendinopathy of the supraspinatus tendon, bursitis, or partial degenerative tears of the supraspinatus and/or infraspinatus tendon (differentiation by ultrasonography). They must be willing and able to understand and sign an approved informed consent document.

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**Figure 1** Patient flow through the study.

160 patients recruited following 1 week screening

2:2:1 randomization

Dexamethasone group n=64
Tr14 Injection Solution group n=64
Placebo group n=32

Subacromial injections performed at visits 2, 3 and 4, one week apart

Assessment at visit 5 (day 22)

Telephone consultation at week 9

Final follow-up visit at week 15

Tr14 = Traumeel
Table 1 Components of Tr14 injection solution

| Source of extract                        | Quantity per 2 mL injection solution |
|------------------------------------------|--------------------------------------|
| Achillea millefolium (milfoil)           | 0.002 µL                             |
| Aconitum napellus (monkshood)            | 0.012 µL                             |
| Arnica montana (mountain arnica)         | 0.02 µL                              |
| Atropa belladonna (deadly nightshade)    | 0.02 µL                              |
| Bellis perennis (daisy)                  | 0.01 µL                              |
| Calendula officinalis (calendula)        | 0.02 µL                              |
| Matricaria recutita (chamomile)          | 0.002 µL                             |
| Echinacea angustifolia (narrow-leaved cone flower) | 0.005 µL |
| Echinacea purpurea (purple cone flower) | 0.005 µL                             |
| Hamamelis virginiana (witch hazel)       | 0.02 µL                              |
| Calcium sulphide (otherwise: Hepar sulfuris) | 0.000002 µL |
| Hypericum perforatum (St John’s wort)   | 0.006 µL                             |
| Mercurico-amidonitrate (otherwise: Mercurius solubilis Hahnemannii) | 0.000001 µL |
| Symphytum officinale (comfrey)           | 0.000002 µL                          |
| Excipients                               | 0.9% saline solution                 |

Tr14 = Traumeel.
obtained over the lateral edge of the shoulder is used to
guide the injection into the subacromial bursa with the
ultrasound probe used in a long-axis lateral view. A nar-
row gauge needle should be used (22–30 gauge). The nee-
dle is advanced until its tip penetrates the bursal cavity.
Images are taken before and after injection, showing dis-
tension of the bursa following injection of the product.
For the first 48 hours after injection, the patient is allowed
to continue all routine activities of daily living, but is
advised not to overuse the treated shoulder.

Concomitant care
Previous treatment with NSAIDs, analgesics, and COX
type 2 (COX-2) inhibitors is allowed, with a washout
period of 1 week before baseline; paracetamol can be
taken until 48 hours before baseline visit. This also in-
cludes all kinds of applications, i.e. topical, oral or paren-
teral. Patients have to be instructed that for the duration
of the study they must not take any pain relief medica-
tion other than paracetamol (which will be used as res-
cue medication and can be taken during the study except
48 hours before the study visits). No chondroprotective
medication is allowed (e.g. among others, glucosamine,
chondroitin sulfate, hyaluronic acid, diacerein, native
collagen and so-called USA-300 preparation).

Treatment with anticoagulants is not permitted during
the study. Low-dose (70–100 mg/d) aspirin for anti-
thrombotic therapy is permitted if doses are stable for the
month prior to screening and remain stable throughout
the study period. Also, treatment with corticosteroid injec-
tions or intake of oral corticosteroids in the 3 months
prior to the study or during the study is not permitted.

Physiotherapy is forbidden within 30 days prior to screen-
ing, but will be allowed as non-drug rescue treatment from
Day 23 until Week 15. Acupuncture, TENS and shock-
wave therapy are also forbidden within 30 days prior to
screening and during the course of the study until week 15.

After screening, only paracetamol (500 mg when ne-
cessary) is permitted during the study as rescue medica-
tion for pain relief. At screening, after ensuring patient
eligibility, paracetamol rescue medication and a patient
diary will be provided to the patients. Patients will be
instructed to document the paracetamol consumption
every day and to bring the diary to the site at each visit,
where paracetamol usage will be documented. Paracet-
amol consumption is limited to 2000 mg (4 tablets) per
day. Patients are instructed that they must not take para-
cetamol within the 48 hours prior to a study visit.

Criteria for withdrawal of patient from study
Study completion or discontinuation will be documented
with the reason for any discontinuation. Reasons for a
patient discontinuing participation in the study include:

- Inefficacy of the study therapy;
- Increase of visual analog scale (VAS) by at least
  30 mm in comparison to baseline during 2
  consecutive visits
- Any other medical condition requiring – in the
  opinion of the investigator – a change of the
  therapy for the baseline condition
- Occurrence of a medical condition requiring use of
  prohibited medications (NSAIDs, analgesics other
  than paracetamol, COX-2 inhibitors, chondroprotec-
tive medications, anticoagulants other than low-dose
  aspirin or corticosteroids other than study therapy)
- Medical condition affecting assessment of the
  primary endpoint (e.g. any injuries or conditions
  causing shoulder pain or requiring analgesic
treatment)
- Medical conditions affecting patient safety if
  participation with the study therapy is continued:
  conditions and adverse events (AEs) causing safety
  concerns with intra-articular steroids therapy or
  with injection to the shoulder joint area OR any other
  AE or condition that – in the opinion of the investiga-
tor – endangers patient safety if the participation in
  the study is continued
- Withdrawal of consent
- Lost to follow-up
- Death.

In case of an AE, the patient is to be followed up until
resolution of the AE. Patients who discontinue prema-
turely from the study will not be replaced.

Adherence to protocol
Protocol adherence will be documented and judged by
patient reporting (diary) and attendance at clinic visits
according to schedule.

Outcomes
The primary endpoint is change from baseline in
abduction-rotation pain VAS (0–100 mm scale, 0 cor-
responds to no pain and 100 to extreme pain) at visit
5 (day 22) (Tr14 injection solution injections versus
dexamethasone injections) for active external rotation.
The abduction-rotation will be done with an internal
rotation and external rotation and both actively and
passively. However, the primary parameter is active ro-
tation abduction with external rotation and only for
this movement the VAS will be measured. During the
shoulder examination, the active external abduction
rotation must be the first movement during evaluation
for pain VAS determination.

Secondary efficacy parameters include ROM, disabili-
ty of arm, shoulder, hand (DASH) score and patient's/
investigator’s global assessment. For ROM the following movements will be analyzed [18,19]:

- Abduction rotation (active external, active internal, passive external, passive internal) measured by goniometry.
- Hand-back range and hand-neck range both measured in cm.
- Jobe (also known as ‘empty can’) test with measurement of pain and weakness (positive/negative). This will be examined as active movement.
- Painful arc after visit 4 (last injection) with measurement of pain (positive/negative). This will be examined as active movement.

Safety parameters include local tolerability, laboratory monitoring, vital signs and AEs. AEs will be standardized for termination and classification, using Medical Dictionary for Regulatory Activities (MedDRA) (the latest available version will be used). Concomitant medications will be classified by site of action and therapeutic and clinical characteristics using the World Health Organization (WHO) DRUG dictionary (the latest available version will be used).

Statistical methods
Clinical efficacy will be assessed as non-inferiority of Tr14 injection solution with respect to dexamethasone regarding the primary efficacy parameter. A one-sided t-test of non-inferiority of Tr14 injection solution with respect to dexamethasone at level 0.025 will be computed using an analysis of covariance (ANCOVA) model with treatment group and center as qualitative factors and the baseline value of the abduction rotation pain VAS for active external rotation as a covariate.

All continuous efficacy parameters will be analyzed by suitable analysis of ANCOVA models, whereas the dichotomous Jobe and painful arc test data will undergo suitable logistic regression model analyses. The ordered categorical responses of the patients’ and examiners’ global assessment will be evaluated by Cochran-Mantel-Haenszel (CMH) tests that account for stratification by center. Clinical safety will be addressed by assessing AEs, physical examinations, laboratory assessments, and vital signs results in a descriptive manner. All statistical analyses in this study will be exploratory in nature.

Analyses will be based on the safety analysis, full analysis, and the per-protocol sets. 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 per-protocol set. These summaries and analyses will be supported by corresponding summaries and exploratory statistical analyses performed on the full analysis set. Missing values for all efficacy parameters will be imputed by the last observation carried forward (LOCF) approach. All 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, shown in Table 3.

Sample size calculation
Estimation of sample size is based on the primary efficacy variable, change from baseline in abduction rotation pain VAS for active external rotation. A one-sided t-test of non-inferiority at level 0.025 based on a non-inferiority margin of 13 mm and a standard deviation of 25 mm for the response variables achieves a power of 80% computed for equal treatment effects if the sample size is set to 60 patients per active treatment group in the per protocol set. Assuming a dropout rate of 6.25%, at least 160 patients should be randomized (i.e. 64 patients per active treatment group and 32 in the placebo group).

Discussion
The corticosteroids most commonly used in clinical trials for problems with the rotator cuff are methylprednisolone acetate and triamcinolone acetonide [8]. However, as crystalline corticosteroids, the appearance of these products in the vial is considerably different to Tr14 injection solution. Dexamethasone was chosen as the comparator corticosteroid as visually the solution is similar to Tr14 injection solution, thus aiding blinding of those administering the injections. The dose of dexamethasone was chosen to provide equivalence to 40 mg methylprednisolone acetate or 40 mg triamcinolone acetonide [20]. This dose of dexamethasone also provided a 2 ml injection, which was the same as the quantity of Tr14 injection solution to be used, again assisting blinding. A once-weekly dosing interval was chosen as an appropriate time interval to allow comparison with other injection therapies. A total of three injections was chosen as, in clinical practice, if there are no signs of improvement after 3 weeks of injections, it is unlikely that treatment would be continued.

To the best of our knowledge, dexamethasone has only been investigated in shoulder injuries on two previous occasions, first by Plafki et al. [21] using 4 mg dexamethasone-21-palmitat (equivalent to 2.5 mg dexamethasone) injected into the subacromial bursa once with ultrasound guidance for the treatment of subacromial impingement. This study was hindered by the need to stop the local anesthetic only
### Table 2 Schedule of study procedures and events

| Procedure/Event | Visit 1 Screening (max. –7 days) | Visit 2 Baseline Day 1 | Visit 3 Day 8 ± 1 day | Visit 4 Day 15 ± 1 day | Visit 5 Day 22 ± 1 day | Telephone Week 9 ± 3 days | Visit 7 Week 15 ± 3 days |
|-----------------|----------------------------------|------------------------|-----------------------|------------------------|------------------------|-------------------------|-------------------------|
| Informed consent| X                                |                        |                       |                        |                        |                         |                         |
| Inclusion/exclusion review | X                              |                        |                       |                        |                        |                         |                         |
| Body weight and height | X                              |                        |                       |                        |                        |                         |                         |
| Physical examination | X                              |                        |                       |                        | X                      |                         |                         |
| Vital signs | X                                | X                      | X                     | X                      | X                      | X                       |                         |
| Medical history | X*                              |                        |                       |                        |                        |                         |                         |
| Randomization | X                                |                        |                       |                        |                        |                         |                         |
| Shoulder ultrasonography | X                            | X                      | X****                 | X****                  | X****                  |                         |                         |
| Urine for pregnancy test | X                              |                        |                       |                        |                        |                         |                         |
| Clinical laboratory tests | X                            |                        |                       |                        |                        |                         | X                       |
| Telephone visit | X                                |                        |                       |                        |                        |                         |                         |
| Shoulder examination including*** |                                |                        |                       |                        |                        |                         | X                       |
| ○ VAS score | X                                | X                      | X                     | X                      | X                      | X                       |                        |
| ○ DASH score | X                                |                        |                       |                        |                        |                         |                         |
| ○ Range of motion***** |                                |                        |                       |                        |                        |                         |                         |
| ○ Jobe/painful arc test |                                |                        |                       |                        |                        |                         |                         |
| Patient’s global assessment |                                |                        |                       |                        | X                      | X                       |                         |
| Investigator’s global assessment |                                |                        |                       |                        | X                      | X                       |                         |
| Shoulder injections | X                                | X                      | X                     | X                      |                        |                         |                         |
| Previous and concomitant treatments* | X*                            | X                      | X                     | X                      | X                      | X                       | X                       |
| Rescue medication dispensation | X                              | X                      | X                     | X                      |                        |                         |                         |
| Patient diary dispensation | X                              |                        |                       |                        |                        |                         | X                       |
| Rescue medication consumption** |                                | X                      | X                     | X                      | X                      | X                       |                         |
| Patient diary collection |                                |                        |                       |                        | X                      |                         |                         |
| Study drug accountability |                                | X                      | X                     | X                      | X                      | X                       | X                       |
| AEs | X                                | X                      | X                     | X                      | X                      | X                       | X                       |

*Patients are to be instructed to discontinue their current pain medication (NSAIDs, analgesics, COX-2 inhibitors) one week prior to baseline visit. No chondroprotective medication is allowed (e.g., among others, glucosamine, chondroitin sulfate, hyaluronic acid, dicyclic, native collagen and so-called USA-300 preparation).

**The usage of study rescue medication is generally not allowed within 48 hours before a study visit. At each visit, the patient has to bring the diary with documentation of daily consumption to the site.

***Bilateral shoulder examination at screening (VAS in target shoulder only).

****Ultrasound-guidance of subacromial periarticular study drug injections.

*****Range of motion includes abduction rotation (active external, active internal, passive external, passive internal) measured by goniometry and hand-back range and hand-neck range both measured in cm. The active external abduction rotation must be the first movement during shoulder examination for pain VAS determination.

AE = adverse event; COX-2 = cyclo-oxygenase type 2 inhibitors; DASH = Disability of arm, shoulder, hand; NSAID = non-steroidal anti-inflammatory drug; VAS = visual analog scale.
injuries, with authors suggesting that this could translate into humans, so caution should be exercised [23-25]. However, a study by Bhatia et al. [26] suggests that corticosteroid use in patients with subacromial impingement should not be considered a causative factor in rotator cuff tears. This retrospective, case-controlled study compared patients with subacromial impingement syndrome according to the number of subacromial corticosteroid injections they had received (less than three versus three or more). Analysis by magnetic resonance imaging (MRI) showed no significant difference between the two groups in the incidence of rotator cuff tear (p < 1.0).

These concerns serve to highlight the potential need for an effective and safe treatment for rotator cuff syndrome that is not associated with potential detrimental effects on the rotator cuff tendon. In a previous non-randomized, observational study, Tr14 injection solution injections were found to be non-inferior to NSAID injections (mainly diclofenac) for the treatment of epicondylitis [15]. Although the study was designed to demonstrate non-inferiority, markedly greater improvements in pain at rest, change in extensional joint mobility and change in torsional joint mobility were observed, along with greater satisfaction and better tolerability reports from patients for Tr14 injection solution versus NSAID injections. This current study has been designed to investigate whether Tr14 injection solution could provide an effective alternative to corticosteroids with the potential for a better safety profile. This could expand the range of treatments available to clinicians for the treatment of rotator cuff syndrome, providing greater patient choice.

The American Academy of Orthopaedic Surgeons (AAOS) guidelines on ‘Optimizing the Management of Rotator Cuff Problems’ state that they cannot recommend for or against the use of subacromial corticosteroid injections in the treatment of rotator-cuff-related symptoms in the absence of full thickness tear [27]. This is due to a lack of compelling evidence resulting in an unclear balance between benefits and potential harm. There is even less evidence about the efficacy of natural medications. It is hoped that the results of this trial will assist in providing more evidence to support physicians in their management of rotator cuff disease. Investigation of the efficacy and place in therapy of Tr14 injection solution is ongoing with further randomized-controlled trials underway.

**Abbreviations**

AAOS: American academy of orthopaedic surgeons; AE: Adverse event; ANCOVA: Analysis of covariance; CMH: Cochran-Mantel-Haenszel; COX: Cyclo-oxygenase; COX-2: Cyclo-oxygenase type 2; DASH: Disability of arm, shoulder, hand; EU: European union; GCP: Good clinical practice; GMP: Good manufacturing practice; HbA1c: Glycosylated fraction of hemoglobin; ICH: International conference on harmonization; IUD: Intrauterine device; LOCF: Last observation carried forward; MedDRA: Medical dictionary for regulatory activities; MRI: Magnetic resonance imaging; NSAID: Non-steroidal anti-inflammatory drug; ROM: Range of motion; TENS: Transcutaneous

| Table 3 Statistical analyses to be performed |
|---------------------------------------------|
| **ANCova with treatment group and center as qualitative factors and baseline value as covariate** |
| Applicable for analyses at visits 5 and 7 for both treatment comparisons Tr14 injection solution against the comparators dexamethasone and placebo, respectively. |
| • Changes from baseline in abduction-rotation pain VAS for active external rotation. |
| • Changes from baseline in ROM for abduction-rotation in degrees (active external, active internal, passive external, passive internal rotation). |
| • Changes from baseline in ROM for hand-back range and hand-neck range as distance measurement in cm. |
| • Changes in DASH. |
| **Repeated measurements ANCOVA with treatment group, center, visit and treatment-by-visit interaction as qualitative factors and baseline value as covariate** |
| Visits 5 and 7 included in analysis; both treatment comparisons Tr14 injection solution against the comparators dexamethasone and placebo, respectively. |
| • Changes from baseline in abduction-rotation pain VAS for active external rotation. |
| **Logistic regression model with treatment group, center and baseline value (positive/negative) as qualitative factors** |
| Applicable for analyses at visits 5 and 7 for both treatment comparisons Tr14 injection solution against the comparators dexamethasone and placebo, respectively. |
| • Jobe. |
| • Painful arc. |
| **Cochran-Mantel-Haenszel (CMH) test for ordered categorical responses stratified by center** |
| Applicable for analyses at visits 5 and 7 for both treatment comparisons Tr14 injection solution against the comparators dexamethasone and placebo, respectively. |
| • Patient’s global assessment. |
| • Investigator’s global assessment. |

**ANCOVA** = analysis of covariance; **DASH** = disability of arm, shoulder, hand; **ROM** = range of motion; **TENS** = Transcutaneous electrical nerve stimulation.
Contributions

Luc Vanden Bossche (LVB) is a consultant/advisor to the Traumeel Scientific Advisory Board for Biologische Heilmittel Heel GmbH. LVB is receiving honorarium for work on this study. LVB has received honoraria for giving scientific talks on behalf of Biologische Heilmittel Heel GmbH. Guy Vanderstraeten (GV) is a consultant/advisor to Biologische Heilmittel Heel GmbH.

Authors’ contributions

LVB is principal investigator; LVB contributed to the overall design of the study and helped draft the protocol. GV is the medical advisor in the study. GV contributed to the overall design of the study and helped draft the protocol. All authors revised the manuscript critically for important intellectual content and have given final approval of the version to be published.

Authors’ information

LVB I have been treating patients with musculoskeletal injuries for over 10 years. In this time the number of patients presenting to me who are unable to use NSAIDs, corticosteroids or other traditional medications has increased. This is often due to contraindications and intolerance to the products. As a physician, I would like to offer my patients an alternative option that is both safe and effective. I have participated in this trial in the hope that TR14 injection solution may provide such an option.

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