ORIGINAL ARTICLE

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Traumeel vs. diclofenac for reducing pain and improving ankle mobility after acute ankle sprain: A multicentre, randomised, blinded, controlled and non-inferiority trial

C. González de Vega,[1] C. Speed,[2] B. Wolfarth,[3] J. González[4]

SUMMARY

Background: Acute ankle sprains are common and activity limiting injuries, and topical diclofenac gel has proven efficacy in alleviating pain and restoring function. This trial aimed to compare a topical natural agent, Traumeel with topical diclofenac gel (1%) in the management of acute ankle sprain. **Methods:** This prospective, multicentre, randomised, blinded, active-control and non-inferiority study involved 449 physically active adults sustaining unilateral grade 1 or 2 ankle sprain within the past 24 h. Participants were randomised to receive 2 g of Traumeel ointment (T-O) (n = 152) or Traumeel gel (T-G) (n = 150) or diclofenac gel (D-G) (n = 147), administered topically to the ankle three times a day for 14 days, with 6-weeks follow up. **Results:** Day 7 median percentage reductions in Visual Analogue Scale pain score were 60.6%, 71.1% and 68.9% for the T-O, T-G and D-G groups, respectively. Total pain relief was reported by 12 (8.5%), 7 (5.0%) and 8 (5.9%) participants in each group, respectively. Median improvements in Foot and Ankle Ability Measure Activities of Daily Living subscale score were 26.2, 26.2 and 25.0 points for T-O, T-G and D-G groups, respectively. Mann–Whitney effect sizes and lower bound confidence intervals demonstrated non-inferiority of Traumeel vs. diclofenac for reducing pain and functional improvement. At 6 weeks, participants reported total pain relief and normal functioning. Adverse events (n = 43) were reported by 31/447 participants (6.9%). Treatments were equally well tolerated. **Conclusions:** T-O and T-G decreased pain and improved joint function to the same extent as D-G in acute ankle sprain, and were well tolerated.

What's known

- A range of therapeutic interventions is available for reducing pain and swelling and restoring stability in patients with lateral ankle injuries.
- Topical diclofenac is one of the most widely used non-steroidal anti-inflammatory drugs, and is superior to placebo in providing pain relief.
- Based on its efficacy and tolerability, Traumeel has been used for many years in the management of musculoskeletal disorders.

What's new

- The natural medications, Traumeel ointment and Traumeel gel are as effective as diclofenac gel 1% in reducing pain and restoring function in individuals with mild-to-moderate ankle sprain.
- In a large multicentre study, topical Traumeel was well tolerated, with a low risk of adverse effects.
- Traumeel can be considered an effective first-line, local treatment option and an alternative to topical diclofenac for treating acute ankle sprain.

[1]MEDYR Clinic, Sports Medicine & Rehabilitation, Madrid, Spain
[2]Rheumatology, Sport & Exercise Medicine, Cambridge Centre for Health and Performance, Cambridge, UK
[3]Preventive and Rehabilitative Sports Medicine, Technical University Munich, Munich, Germany
[4]DEYRE Clinic, Madrid, Spain

Correspondence to:
Dr Carlos González de Vega, Medical Director
MEDYR Clinic, Sports Medicine & Rehabilitation Hernani 54, 28020, Madrid, Spain
Tel.: + 34 91 5360029
Fax: + 34 91 5530414
Email: cgdv@telefonica.net

Disclosures
JG and CGV received financial support for the study; CS, BW and CGV had financial support for the submitted work from Biologische Heilmittel Heel GmbH; CGV, BW and CS are advisory board members for Traumeel for Biologische Heilmittel Heel GmbH; CS and CGV have received consultancy fees from Biologische Heilmittel Heel GmbH; BW has received consultancy fees from Biologische Heilmittel Heel GmbH and Johnson & Johnson; BW has received payment for lectures, including as a speaker on speaker bureaus, from Biologische Heilmittel Heel GmbH, Astra Zeneca, Berlin Chemie, Bristol-Myers Squibb; CGV has received payment for developing and delivering educational presentations for Biologische Heilmittel Heel GmbH; BW has received payment for developing and delivering educational presentations for Johnson & Johnson; there are no other relationships or activities that could appear to have influenced the submitted work.
Trial registration
NCT01066520

Introduction

Acute ankle sprains, particularly those involving the lateral ligament complex, are frequently reported to be the most common musculoskeletal injury (1–3). Without adequate care, acute ankle trauma can lead to chronic problems, such as pain, joint instability, restriction and loss of function (2,4).

Topical diclofenac has been consistently demonstrated to be an effective agent in reducing pain and inflammation in acute ankle sprain and other musculoskeletal disorders (5–7), with improvements in patients' functional capacity, mobility and global assessment (6,8). Topical diclofenac is usually better tolerated than oral non-steroidal anti-inflammatory drugs (NSAIDs) (6,7,9), and is a useful benchmark for pharmacological intervention in musculoskeletal injuries.

Traumeel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany) is a fixed combination of plant and mineral extracts used for treating inflammation and pain caused by musculoskeletal injuries (10). Effectiveness and tolerability of Traumeel for musculoskeletal injuries have been reported in randomised controlled trials, which demonstrate reductions in pain and swelling, and improvements in the mobility of joints such as ankle and knee (11–14). Traumeel has also demonstrated efficacy equivalent to conventional management (15), NSAIDs (16) and diclofenac (17) in pain relief and improving joint mobility. Traumeel is well tolerated, with very few adverse effects (12,13,15–21).

The objective of this large multicentre, randomised and controlled study was to compare the effectiveness and tolerability of a homeopathic medication, Traumeel, with a conventional therapy, diclofenac, both administered topically in the reduction of pain and restoration of function in individuals with mild-to-moderate acute ankle sprain. Diclofenac was

selected as the comparator because of its broad study database and because it is the most widely used NSAID (5,22,23). Diclofenac sodium gel (D-G) at a concentration of 1% was selected because it is widely available. Topical preparations of Traumeel and D-G were chosen as they are convenient, easy to use, and are available on prescription and over the counter (OTC).

Methods

Participant selection

Participants were physically active adults including athletes, (physician's opinion from patient's case history) aged 18–40 years, who had experienced an acute unilateral ankle sprain of the lateral ligaments within the past 24 h. They were also required to have moderate (100-point Visual Analogue Scale [VAS] score, 30–60 mm) to severe (>60 mm) pain on weight bearing according to the participant's assessment of ankle pain, and be unable to perform their usual training/sports activities. Grade of ankle sprain was evaluated at baseline by physician's assessment and x-ray to eliminate fracture, and on day 7 by using a stress-test [pronation stress of the ankle with predefined power].

Individuals were excluded if they had sustained a similar injury of the same joint within the last 6 months, bilateral ankle injury, complete rupture of the ankle ligaments in need of surgical intervention (i.e. Grade 3 ankle sprain), confirmed fracture or injury concurrent with knee injury, or required bed rest, hospitalisation, casting or surgery. They were also excluded if they had clinically important laboratory test abnormalities or debilitating acute/chronic illness, or had used corticosteroids in the previous 8 weeks; long-acting NSAIDs, cyclooxygenase (COX)-2 inhibitors or tramadol in the previous 24 h; any other analgesics in the previous 6 h; or were sensitive to any component of the study drugs; or were abusing medical substances or alcohol. Participants provided written informed consent to participate.

Study design

The Traumeel Acute Ankle Sprain Study (TAASS) was a multicentre, prospective, randomised, blinded and active-controlled study comparing Traumeel ointment (T-O) and Traumeel gel (T-G) (Biologische Heilmittel Heel GmbH) with D-G 1% (Heumann Pharma GmbH & Co) in the treatment of acute unilateral ankle sprain. The study was conducted at 15 outpatient centres in Spain in accordance with the Declaration of Helsinki, Seoul 2008, International Congress for Harmonization, Good Clinical Practice (ICH-GCP) and the appropriate regulatory policy of participating institutions, and approved by the Spanish Institutional Review Board/Ethics Committee and the Research Ethics Committee of each investigator's site. Investigators were consultant musculoskeletal specialists.

This non-inferiority study was performed with a two-stage adaptive design (24), with a planned interim analysis after study completion by 240 evaluable subjects (Stage I). The intention was to either stop the study according to the predefined stopping rules (definite success or failure), or, with both T-O and T-G eligible for continuation, continue to Stage II with the option of including only two (i.e. T-O or T-G vs. D-G) or all three treatment arms.

After initial screening, eligible individuals entering Stage I were randomised 1:1:1 to receive T-O, T-G or D-G for 14 days, according to a randomisation schedule generated by IDV Data Analysis & Study Planning (Krailling, Germany). Computerised randomisation to treatment was achieved centrally; investigators received random blocks of six treatment kits along with the envelopes, and assigned patients to treatment on the basis of the order of kit receipt. Randomisation was double blind for T-G and D-G, and single (investigator) blind for T-O (the consistency of gel and ointment was different), although participants did not know which drug was in which preparation (medication was packed in identical containers). For all study medication, 2 g (approximately 6 cm squeezed onto a measured dosing card) was applied topically, 3 times daily over the injured area. The treated skin was left uncovered by clothing for at least 15 min after application, and showering or bathing were not permitted for at least 1 h after application. Participants were assessed at baseline (day 0), on days 4, 7 and 14 of treatment, and at follow up on day 42.

All subjects received the same advice; the use of rest, ice, compression, elevation (RICE) was restricted to immediately after the event, and before starting study treatment. No patient reported using RICE after the start of study treatment. Systemic corticosteroids and analgesics were prohibited during the study. Rescue medication for pain control (paracetamol 500 mg tablets, up to four daily) was permitted but not in the 24 h before study visits.

Compliance with application of study drugs was ensured by study personnel administering the test drugs and by a patient diary. Patients also recorded use of RICE, rescue medications and concomitant medications in the patient diary.

Interim analysis of Stage I suggested that the study should continue to Stage II with all three treatment arms (i.e. no definite success or failure). Using the same procedures as for Stage I, additional

participants were enrolled, assessed and treated in Stage II. Stage I was carried out from August 2009 (first participant enrolled) to January 2011 (last participant completed), inclusive; Stage II was carried out from March to September 2011, inclusive. Data from Stages I and II for the T-O and T-G groups were combined for analyses; the combined results are presented here.

Primary efficacy variables

The primary efficacy measures were the percentage change from baseline to day 7 for the participant's assessment of ankle pain (maximum), as measured by a 100 mm VAS (0 = no pain; 100 = worst imaginable pain), and the change from baseline to day 7 of the Foot and Ankle Ability Measure (FAAM) (25) Activity of Daily Living subscale (ADL). The FAAM is a validated self-reported questionnaire (25) that assesses physical function of individuals with musculoskeletal disorders of the leg, foot and ankle. The FAAM ADL subscale comprises 21 single items assessing activities of daily living such as standing, walking and going up and down stairs. The final score of the ADL subscale was standardised to a 0–100 scale where 0 = worst level of physical function, 100 = highest level of physical function.

Secondary efficacy variables

Secondary variables were measured on days 4, 7, 14 and 42. They included percentage change from baseline of ankle pain (maximum), self-assessed using a 100 mm VAS (as described above); change from baseline of the FAAM ADL subscale (as described above) (25); and change from baseline of the FAAM sports subscale (25) that comprises 8 single items assessing various sports activities such as running and jumping. As with the FAAM ADL subscale, the final score of the FAAM sports subscale was standardised to a 0–100 scale where 0 = worst level of physical function, 100 = highest level of physical function. Swelling was measured by the 'figure-of-eight' method (26) (mean of three repeated measurements) with the ankle in a neutral position for eversion and inversion while flexed to 90 degrees. Normal function/activity was measured on a 5-point scale (0 = normal, 4 = severely restricted because of pain) and change from baseline was calculated. Time to normal function, that being during training and during sports activities, was self-reported by patients. A global assessment of treatment efficacy was assessed using a 5-point rating scale (1 = very good, 5 = worsening of symptoms) on day 14, and rescue medication use was determined by counting the number of tablets taken during the treatment and follow-up periods.

Safety variables and vital signs

Local tolerability of study treatments were evaluated by the physician after application and treatment-emergent adverse event data were collected at each visit. Adverse events (AEs) were categorised by primary system organ class and MedDRA preferred terms. Medical history and previous medications were detailed at screening. Physical examinations, vital signs, body weight and height were recorded at study visits.

Data analysis

Primary efficacy analyses

For the primary efficacy analysis, equality of effects of test and reference treatments was investigated using a test for non-inferiority. Effect size analyses were made by applying the Wilcoxon–Mann–Whitney (WMW) test that provides the Mann–Whitney (MW) estimator (27,28). The relevant benchmarks for the MW estimator were: 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 and 0.71 = large superiority (27). Statistical significance was determined by the confidence interval approach, whereby non-inferiority was shown if the lower bound of the confidence interval (LB-CI) was lying above the predefined non-inferiority margin of 0.4.

The study-wise alpha level was specified at 0.025 (one-sided) and both primary efficacy criteria could be tested with the full alpha if the first test was statistically significant (28). All patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations were evaluated as the full analysis set (29,30). Missing data were handled by the 'Last Observation Carried Forward' method. Primary analyses were based on the Intent-To-Treat sample. For the primary efficacy criteria, the one-sided test for non-inferiority with alpha 2.5% and 97.5% CI was employed (WMW procedure).

Multiple testing in an adaptive design

Two treatment comparisons were made within the two-stage adaptive study design. The procedure is a combination of two principles of a multiple level alpha control: the closure principle (for multiple comparisons; intersection hypothesis) (31) and the two-stage adaptive design. The operating characteristics of the two-stage Bauer–Koehne procedure (24) were: $P1 < 0.0102$ (one-sided), stop after Stage I because of success; $P1 \geq 0.5$, stop after Stage I because of futility; and $0.0102 \leq P1 < 0.5$, continue to Stage II with c-alpha for combined stages = 0.0038, for combined two stages P1* P2. If the intersection hypothesis (24) H_0 was not rejected

at $alpha_1 = 0.0102$, then Stage II was planned with both treatments; if $p > alpha_0$, then the study is stopped because of futility; if $p < alpha_1$, then the two single hypotheses can be tested. If one (or both) of the latter is significant, then the study can be stopped for that (or both) treatment. Likewise, if one (or both) test is not significant, then Stage II may be performed with that (or both) treatment.

The intersection hypothesis is tested using the Fligner–Wolfe test, which is a generalised Wilcoxon–Mann–Whitney test, based on a comparison of the two test treatments combined and the reference treatment (32). The two single comparisons are performed using the standard WMW test. As the comparator is an active reference treatment, the test is a (one-sided) test for non-inferiority with the null hypothesis: H_0:MW < 0.40, the one-sided bound of the CI should be >0.4 to reject the null hypothesis.

Sample size calculation

For sample size estimation, the following stipulations were made: alpha = 0.025 (one-sided), beta = 0.1 (power = 0.9, winning chance of sponsor 9:1), and MW = 0.4, non-inferiority bound. Within the two-stage Bauer–Koehne procedure (operating characteristics as above) (24), Stage I was based on a sample size of $N = 240$ (80/group) after which an interim analysis was performed for the primary criteria. There was no definite success or failure so the study proceeded to Stage II in an adaptive manner, i.e. with all unblinded data results.

Other analyses

Secondary efficacy criteria were evaluated using the same statistical tests and confidence intervals as for the primary efficacy criteria (WMW procedure). Time to normal function was analysed using the log-rank test and Kaplan–Meier curves. The safety population comprised all patients who had at least one dose of medication and one contact with the investigator after this first dose. AEs were presented by descriptive statistics and Fisher's exact test.

Sample size calculation was performed using Nnpar 1.0, and data were entered with Report 6.4.19 or higher as database, and analysed with Report 6.4.19 or higher for descriptive statistics and TESTIMATE 6.1.03 or higher for inferential statistics (all software from IDV Data Analysis & Study Planning, Krailling, Germany).

Results

Participant disposition

Of the 449 individuals enrolled into the study (i.e. 299 participants in Stage I and 150 in Stage II), all were randomised to treatment (Figure 1). Two participants in the T-G group did not receive treatment; they withdrew their consent for participation in the trial after randomisation and before receiving the first medication dose. Stages I and II participants in each treatment group were combined for the analyses.

Participant characteristics

Demographic and other participant characteristics are shown in Table 1; there were no significant differences between the treatment groups. On day 7, ankle sprains were classified according to sprain grade (33): Grade 1 (mild, ligaments over-stretched), and Grade 2 (moderate, partial rupture) or Grade 3 (severe, complete rupture of the lateral ankle ligament complex; study exclusion criterion) (Table 1). The three participants (one from each of the three groups) with Grade 3 sprain, which were included in the study at baseline before final grading and in the analysis, were considered unlikely to statistically significantly affect the outcomes.

Compliance to study medication

From participant diaries, overall compliance to study medication was very good and indicated that 75% of participants had a total compliance above 90%. No significant difference was seen between the three treatment groups. Compliance below 80% (i.e. non-compliance) was reported for 12 participants (8.4%) in the T-O group, 5 participants (3.6%) in the T-G group and 5 participants (3.6%) in the D-G group ($p = 0.1139$, R by 2 analysis).

Concomitant medications

Concomitant medications were taken by 23 participants and were mainly analgesics and antipyretics, for headache, infections and pain. A total of 11/31 participants with AEs required concomitant medication. There was no significant difference in the proportions of participants in each group requiring concomitant medication: T-O, 3/9 participants (33.3%); T-G, 5/14 participants (35.7%); D-G, 3/8 participants (37.5%).

Evaluation of efficacy

Primary outcome measures

There were no statistically significant between-group differences in baseline pain VAS scores and in baseline FAAM ADL subscale scores. At all visits in the main treatment period, the confidence intervals were above the predefined lower equivalence margin (0.40), demonstrating non-inferiority of T-O and T-G vs. D-G for the treatment of pain and for the improvement of ankle function.

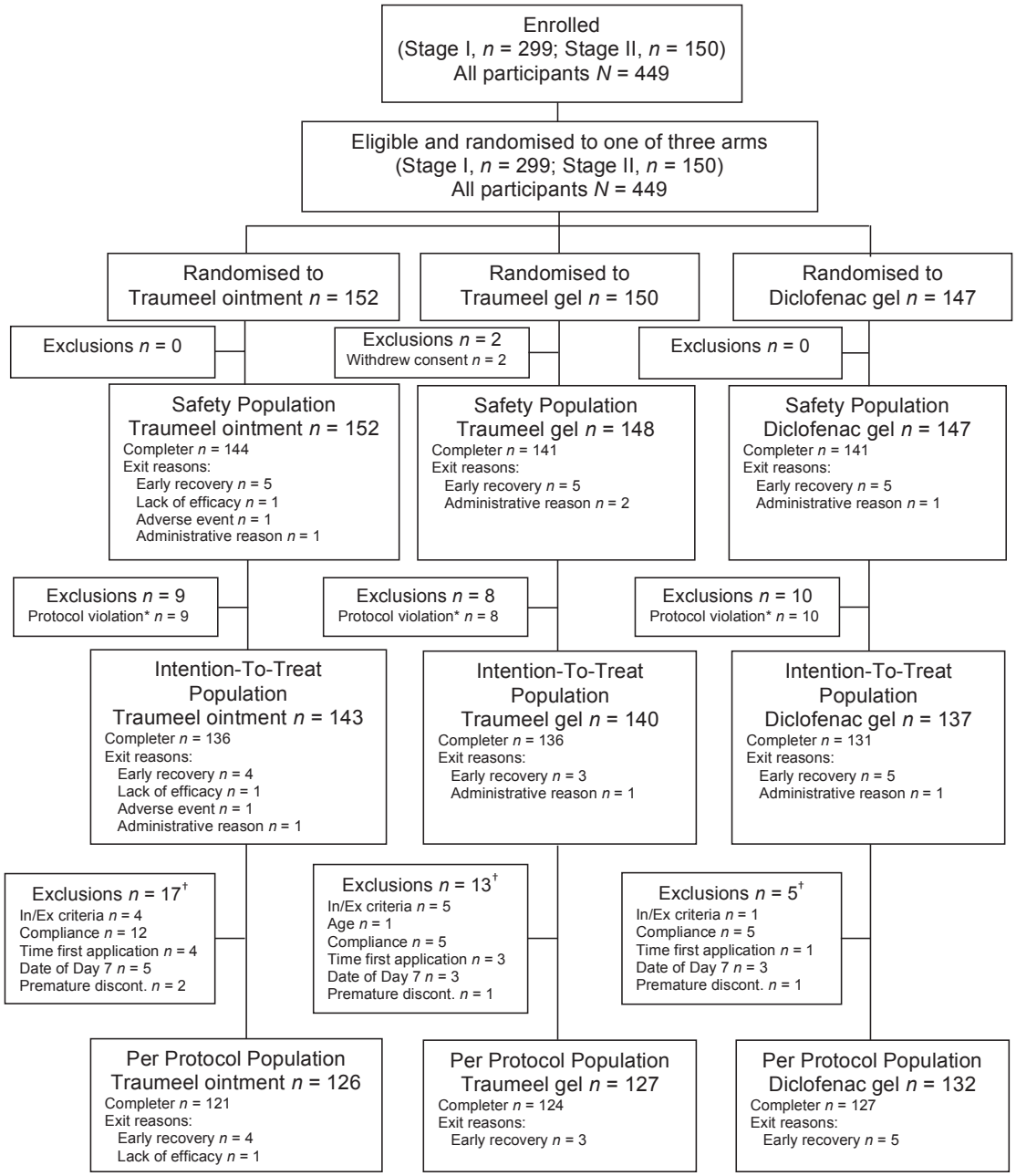

Figure 1 TAASS trial flowchart of study population with ankle sprain randomised and followed up in study monitoring efficacy. Exclusions, all circumstances leading to exclusion from Safety or Intent-To-Treat or Per Protocol populations; In/Ex criteria, inclusion/exclusion criteria; time first application, first time of first application of study drug; date of day 7, date of Visit 3 (day 7); premature discont., premature discontinuation (not efficacy related); administrative reasons including 'lost to follow up'; * 'severe' violation of the VAS pain inclusion criterion (VAS <30 mm); † a participant may have had more than one reason for exclusion; ‡ includes the participant in the Traumeel ointment group who discontinued the study prematurely on day 8 because of worsening of the injury.

On day 7, median percentage reductions in pain VAS scores from baseline were 60.6% for the T-O group, 71.1% for the T-G group and 68.9% for the D-G group (Figure 2A). Total pain relief was reported by 12 (8.5%), 7 (5.0%) and 8 (5.9%) participants in each of the groups, respectively. For both Traumeel preparations vs. D-G, pain VAS effect sizes show less than 'small' group differences on day 7, with effect sizes varying between benchmarks for equality (0.5) and small inferiority (0.44) (Figure 2B,C).

At day 7, median improvements in FAAM ADL subscale scores from baseline were 26.2 points for the

Table 1 Demographics and baseline characteristics of participants (Intent-To-Treat population) in the TAASS study

Baseline characteristic	Traumeel ointment N = 143	Traumeel gel N = 140	Diclofenac gel N = 137
Grade of ankle sprain, n (%)			
Grade 1	80 (56.7%)	87 (62.1%)	74 (54.4%)
Grade 2	60 (42.6%)	52 (37.1%)	61 (44.9%)
Grade 3	1 (0.71%)	1 (0.71)	1 (0.74)
Age, years, mean (SD; range)	28.3 (6.58; 17–45)	27.7 (6.62; 17–48)	27.1 (6.05;18–40)
Effect size*	0.5500 (p = 0.1480)	0.5208 (p = 0.5489)	–
Gender, n (%)			
Male	104 (72.7)	101 (72.1)	103 (75.2)
Female	39 (27.3)	39 (27.9)	34 (24.8)
Effect size*	0.5123 (p = 0.6840)	0.5152 (p = 0.5877)	–
Ethnicity, n (%)			
Caucasian	138 (96.5)	133 (95.0)	132 (96.4)
Asian	0 (0)	0 (0)	0 (0)
African	2 (1.4)	1 (0.7)	1 (0.7)
Latin American	3 (2.1)	6 (4.3)	4 (2.9)
Other	0 (0)	0 (0)	0 (0)
Effect size*	n/a	n/a	–
BMI kg/m^2, mean (SD; range)	24.1 (3.0;16.6–34.0)	23.6 (2.9; 16.5–31.3)	23.5 (2.8;16.9–35.2)
Effect size*	0.5665 (p = 0.0546)	0.5150 (p = 0.6662)	–
Smoker, n (%)			
Yes	35 (24.5)	22 (15.7)	18 (13.1)
No	108 (75.5)	118 (84.3)	119 (86.9)
Effect size*	0.4433 (p = 0.0215)	0.4871 (p = 0.6095)	–
Location, n (%)			
Left	64 (44.8)	66 (47.1)	66 (48.2)
Right	79 (55.2)	74 (52.9)	71 (51.8)
Effect size*	0.5171 (p = 0.6318)	0.5052 (p = 0.9045)	–
Previous episode, n (%)			
Yes	35 (24.5)	28 (20.0)	42 (30.7)
No	108 (75.5)	112 (80.0)	95 (69.3)
Effect size*	0.5309 (p = 0.2847)	0.5533 (p = 0.0526)	–

BMI, body mass index; SD, standard deviation; n/a, not applicable. Previous episode, previous sprain in same ankle.
*Effect size (Mann–Whitney estimator) vs. diclofenac gel; benchmarks for group difference inferiority/superiority: 0.5 = equal, 0.44/0.56 = small, 0.36/0.64 = medium, 0.29/0.71 = large; p-value (Wilcoxon–Mann–Whitney test).

T-O group, 26.2 points for the T-G group and 25.0 points for the D-G group (Figure 3A). For both Traumeel preparations vs. D-G, FAAM ADL subscale effect sizes show less than 'small' group differences on day 7 (and at all other time points) (Figure 3B,C).

Secondary outcome measures

T-O and T-G were non-inferior to D-G on all secondary outcome variables (Table 2). Approximately 90% or more patients had returned to normal function/activity and over 90% of participants in all groups assessed their treatment as 'very good'/'good'. Median reductions in ankle swelling were demonstrated by all groups on days 4, 7 and 14 (Table 2). Swelling was reduced mostly during the first week of treatment (day 7: −0.50 cm, −0.50 cm and −0.485 cm for the T-O, T-G and D-G, respectively). Following injury (start of treatment) participants resumed usual training and sports activities after approximately median 14 days and 19 days, respectively (p > 0.1). Notably, for both Traumeel preparations vs. D-G, there were no significant differences in either the percentage of participants taking/not taking rescue medication and the total amount of rescue medication taken (CI above the predefined lower equivalence margin of 0.40).

Evaluation of safety

Of the 447 participants in the safety population, one participant (0.2%) in the T-O group discontinued

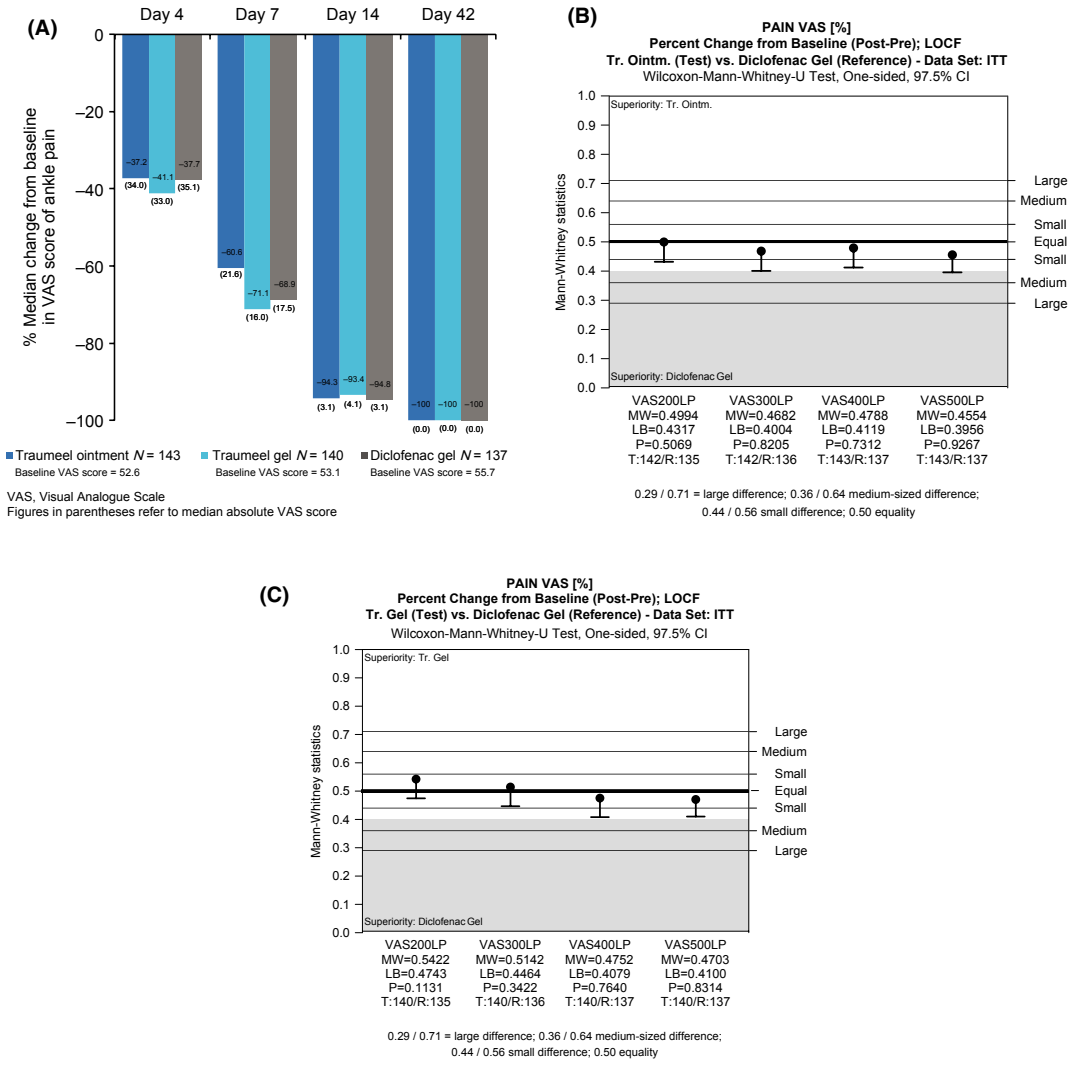

Figure 2 Pain Visual Analogue Scale score (percentage change from baseline; LOCF, Intent-To-Treat population). (A) VAS pain: percentage change from baseline (ITT population). (B) Traumeel ointment vs. diclofenac gel: effect sizes (Mann–Whitney) and one-sided 97.5% CI. (C) Traumeel gel vs. diclofenac gel: effect sizes (Mann–Whitney) and one-sided 97.5% CI. ITT, Intent-To-Treat; LB, Lower bound of the one-sided confidence interval; LOCF, Last Observation Carried Forward; MW, Mann–Whitney estimator; P, p-value of one-sided Wilcoxon–Mann–Whitney test; T/R, valid number of participants in Traumeel (test) group/valid number of participants in diclofenac gel (reference) group; Tr, Traumeel; VAS, Visual Analogue Scale; VAS200LP, day 4; VAS300LP, day 7; VAS400LP, day 14; VAS500LP, day 42.

the study prematurely on day 8 because of worsening of the injury.

A total of 43 AEs were reported for the 447 participants receiving treatment: 9/152 participants (5.9%) in the T-O group, 14/148 participants (9.5%) in the T-G group and 8/147 participants (5.4%) in the D-G group (p = 0.3310). Possibly or probably related AEs were reported by 5/152 participants (3.3%), 3/148 participants (2.0%) and 3/147 participants (2.0%) in the groups, respectively (Table 3). The majority were mild or moderate in severity and none was serious. All AEs resolved by day 42 with the exception of 'ankle pain' that was 'ongoing' in one T-O-treated participant, and 'new ankle sprain' that was 'improved, not resolved' in one D-G-treated participant.

AEs included headache, nasopharyngitis, oropharyngeal pain, back pain, swelling, erythema and pruritus. Events were generally reported by one or two participants only and evenly distributed among the treatment groups, with no differences in frequency reaching statistical significance.

There were no notable changes from baseline in vital signs. All three treatments were well tolerated locally, as assessed by redness, swelling and itching at the site of injury, with over 97% of participants without symptoms.

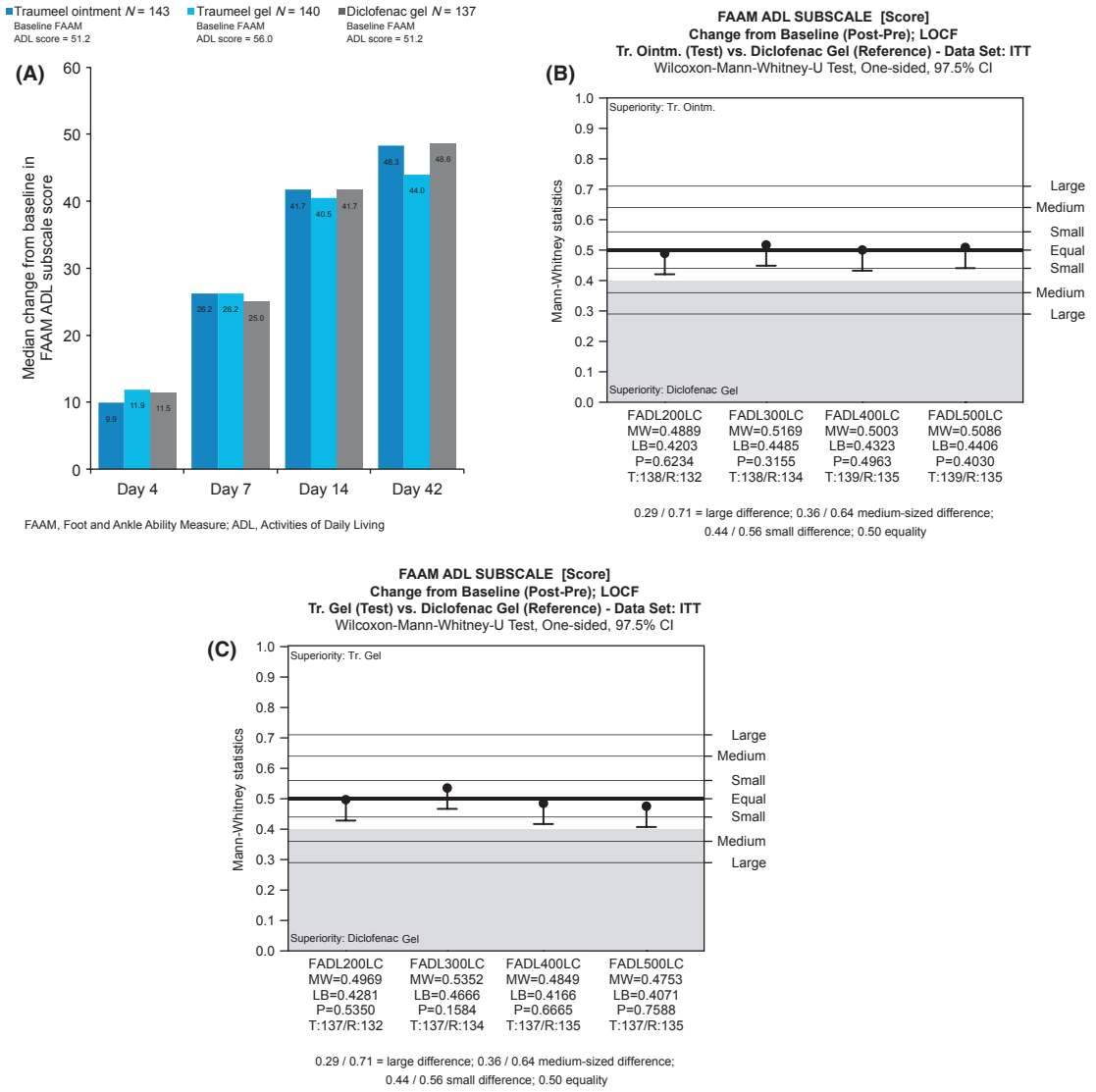

Figure 3 Foot and Ankle Ability Measure Activities of Daily Living subscale (changes from baseline; LOCF, Intent-To-Treat population). (A) FAAM ADL subscale: changes from baseline (ITT population). (B) Traumeel ointment vs. diclofenac gel: effect sizes (Mann–Whitney) and one-sided 97.5% CI. (C) Traumeel gel vs. diclofenac gel: effect sizes (Mann–Whitney) and one-sided 97.5% CI. FAAM ADL, Foot and Ankle Ability Measure Activities of Daily Living subscale; FADL200LC, day 4; FADL300LC, day 7; FADL400LC, day 14; FADL500LC, day 42; ITT, Intent-To-Treat; LB, Lower bound of the one-sided confidence interval; LOCF, Last Observation Carried Forward; MW, Mann–Whitney estimator; P, p-value of one-sided Wilcoxon–Mann–Whitney test; T/R, valid number of participants in Traumeel (test) group/valid number of participants in diclofenac gel (reference) group; Tr, Traumeel.

Discussion

This randomised, controlled and blinded study confirmed that T-O and T-G were non-inferior to the widely used NSAID, D-G 1%, in the reduction of pain and restoration of function in individuals with mild-to-moderate acute ankle sprain. This finding confirms the efficacy of Traumeel and might broaden the therapy options for patients and healthcare professionals who would prefer to avoid the use of topical NSAIDs in Grade 1 and 2 ankle sprains.

This study did not include a placebo-control arm, which may have had some relevance to the assessment of an injury that usually resolves without treatment. However, Traumeel has been shown to be more effective than placebo in the treatment of musculoskeletal disorders in previous randomised controlled trials (11–14). Specifically in ankle injuries, treatment with T-O resulted in more rapid and more frequent improvement in upper ankle mobility and significant reductions in swelling and pain compared with placebo at 2 weeks (11,12).

Table 2 Secondary efficacy variables (Intent-To-Treat population)

	Traumeel ointment N = 143	Traumeel gel N = 140	Diclofenac gel N = 137
Ankle pain (VAS) score, median			
Change from baseline (day 14),%	−94.3	−93.4	−94.8
Baseline	52.6	53.1	55.7
Absolute score (day 14)	3.1	4.1	3.1
FAAM ADL subscale score, median points			
Change from baseline (day 14)	41.7	40.5	41.7
Baseline	51.2	56.0	51.2
FAAM Sports subscale score, median points			
Change from baseline (day 14)	50.0	50.0	50.0
Baseline	18.8	25.0	18.8
Ankle swelling, 'figure of eight', median, cm			
Change from baseline (day 14)	−0.67	−0.67	−0.57
Baseline	55.13	54.07	54.00
Normal function/activity, participants reporting scores of 0 or 1 n (%)			
Day 14	128 (89.5%)	133 (95.0%)	131 (95.6%)
Baseline	29 (20.3%)	23 (16.4%)	27 (19.7%)
Global assessment of treatment efficacy:[a]			
Day 14, mean	1.6	1.6	1.5
No. (%) participants reporting treatment as 'very good'/'good'	131 (92.3%)	128 (92.1%)	127 (92.7%)
Rescue medication (paracetamol)			
No. (%) participants (treatment/follow-up periods)	28 (19.7%)	29 (20.7%)	20 (14.6%)
Tablets per participant, mean	1.5	1.6	1.0

Negative figures indicate a reduction.
[a]Participant assessed on a 5-point rating scale (1 = very good, 2 = good, 3 = satisfactory, 4 = no improvement, 5 = worsening of symptoms).

Table 3 Adverse events (AE) considered 'possibly' or 'probably' related to study treatment

	Traumeel ointment N = 152		Traumeel gel N = 148		Diclofenac gel N = 147	
	AE n	Participants n (%)	AE n	Participants n (%)	AE n	Participants n (%)
Pain	2	1 (0.7)	–	–	–	–
Swelling	–	–	–	–	3	2 (1.4)
Joint injury	1	1 (0.7)	–	–	–	–
Joint sprain	1	1 (0.7)	1	1 (0.7)	–	–
Hypoaesthesia	1	1 (0.7)	–	–	–	–
Dry skin	–	–	1	1 (0.7)	–	–
Erythema	3	2 (1.3)	–	–	–	–
Pruritus	1	1 (0.7)	1	1 (0.7)	1	1 (0.7)

A participant could report an adverse event on more than one occasion.

Reviews of diclofenac, incorporating ankle sprain studies, also demonstrate its superiority in reducing pain and inflammation over placebo (5,6,8). With their known efficacy and the possibility of joint instability and decreased range of motion without treatment (2,4), it was considered unreasonable to withhold treatment in this study population that want to quickly return to normal function. In this study, Traumeel and diclofenac administered topically were both well tolerated, with few treatment-related AEs and high rates of treatment adherence.

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 (34). Mechanistic studies suggest Traumeel stimulates production of the inhibitory cytokine, transforming growth factor-beta, thereby indirectly preventing pro-inflammatory lymphocytes from perpetuating the inflammatory reaction (35), and accelerates wound healing (34).

To our knowledge, there is no previous randomised controlled trial of T-O and T-G vs. D-G in ankle sprain. One previous randomised controlled study compared T-O with diclofenac ointment in elite athletes with non-traumatic tendon pain (14). Reductions in peri-tendinous diameter/oedema and pain, and time to return to activity were significantly better for Traumeel-treated participants (14). This improved efficacy of Traumeel vs. diclofenac may have been a result of the differing indication and participant population compared with those in our study. Additionally, in observational studies, Traumeel has demonstrated an efficacy (pain and mobility) equivalent to diclofenac with similar or better tolerability in individuals with tendinopathies (T-O and D-G) (17) and epicondylitis (Traumeel and diclofenac injections) (16).

This study was not without limitations. Individuals enrolled into randomised controlled trials may not be representative of the broad range of individuals treated in clinical practice (36). These participants were physically active people rather than people incurring ankle sprains through general activities of daily living. However, as efficacy was self-evaluated, it could reasonably be assumed that this study population might have been more critical of a treatment that did not work than the general population.

A potential study limitation was single (investigator) blind randomisation of the T-O group. While the containers were identical, the consistency of gel and ointment differ and therefore it was difficult to have all treatments blinded from both investigators and patients. However, participants did not know which drug (Traumeel or diclofenac) was in which preparation.

T-O and T-G were as effective as D-G 1% for the symptomatic treatment of pain and restoration of function in individuals with mild-to-moderate ankle sprain. Traumeel and other complementary and alternative medicine interventions have the potential to increase achieved community effectiveness (37). Specifically, musculoskeletal problems are reported to be areas of clinical practice in which conventional treatments are not fully effective (37). Traumeel may therefore be considered a viable treatment option and an alternative to topical diclofenac.

Acknowledgements

This study was sponsored by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany. Study management, data analysis and editorial support were funded by Biologische Heilmittel Heel GmbH.

We would like to acknowledge the TAASS principal investigators: Jose Antonio Lekue Galiano, Servicios Médicos del Athletic de Bilbao, Bilbao; Ana de la Torre Combarros, Servicios Médicos del Getafe Club Deportivo, Madrid; Tomás Fernández Jaén, Cesar Flores Lozano, Clínica CEMTRO, Madrid; Carlos Melero Romero, Encarnación Tenza Marmolejo, Centro Andaluz de Medicina del Deporte (CAMD), Malaga; Francisco Esparza Ros, Centro Médico Juan XXIII, Murcia; Juan de Dios Beas Jiménez, Centro Andaluz de Medicina del Deporte, Seville; Antonio David Sánchez González, Clínica Mediper, Seville; Fernando Jiménez Díaz, Centro de Medicina y Deporte, Toledo; Belén Esparza Beltrán, Centro International de Rehabilitación de Deportistas (CIRD), Valencia; Rafael Plaza Delgado, Servicios Médicos del Levante Union, Valencia; José Nebot Rodrigo, Clínica Nebot, Valencia; Rafael Ramos Galera, Servicios Médicos del Real Vallodalid, Valladolid; Antonio F Laclériga Giménez, Hospital Viamed Montecal, Zaragoza.

We are grateful to Chiltern (Madrid, Spain) and Biologische Heilmittel Heel GmbH for study planning and coordination, regulatory activities and investigator recruitment; to Chiltern for study monitoring, data management and data query resolution; and to IDV Data Analysis & Study Planning (Krailling, Germany) and Johannes C Vester for statistical planning data analysis, statistical analyses and for writing the clinical study report. Data analysis and Stage II decisions were the responsibility of the external biometricians at IDV Data Analysis & Study Planning (Krailling, Germany) and were independent of the sponsor of the study (Biologische Heilmittel Heel GmbH). The authors would like to thank Dr Susan Libretto for preparation of the manuscript and Aspen Medical Media for editorial assistance.

Author contributions

CGV and JG were principal investigators during the study. CGV, CS, BW and JG were involved in editing, critically reviewing the manuscript for intellectual content and approving of the article.

References

1 Woods C, Hawkins R, Hulse M, Hodson A. The football association medical research programme: an audit of injuries in professional football: an analysis of ankle sprains. *Br J Sports Med* 2003; **37**: 233–8.

2 Ivins D. Acute ankle sprain: an update. *Am Fam Physician* 2006; **74**: 1714–20.

3 Fong DTP, Hong Y, Chan LK, Shu-Hang Yung P, Chan KM. A systematic review on ankle injury and ankle sprain in sports. *Sports Med* 2007; **37**: 73–94.

4 Wolfe MW, Uhl TL, Mattacola CG, McClusket LC. Management of ankle sprains. *Am Fam Physician* 2001; **63**: 93–104.

5 Banning M. Topical diclofenac: clinical effectiveness and current uses in osteoarthritis of the knee and soft tissue injuries. *Expert Opin Pharmacother* 2008; **9**: 2921–9.

6 Zacher J, Altman R, Bellamy N et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Curr Med Res Opin* 2008; **24**: 925–50.

7 Massey T, Derry S, Moore RA, McQuay HJ. Topical NSAIDs for acute pain in adults. *Cochrane Database Syst Rev* 2010; **6**: CD007402.

8 Simon LS, Grierson LM, Naseer Z, Bookman AAM, Shainhouse JZ. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain* 2009; **143**: 238–45.

9 Taylor RS, Fotopoulos G, Maibach H. Safety profile of topical diclofenac: a meta-analysis of blinded, randomized, controlled trials in musculoskeletal conditions. *Curr Med Res Opin* 2011; **27**: 605–22.

10 Schneider C. Traumeel – an emerging option to nonsteroidal anti-inflammatory drugs in the management of acute musculoskeletal injuries. *Int J Gen Med* 2011; **4**: 225–34.

11 Zell J, Connert WD, Mau J, Feuerstake G. Behandlung von akuten Sprunggelenksdistorsionen: Doppelblindstudie zum Wirksamkeitsnachweis eines homöopathischen Salbenpräparats [Treatment of acute sprains of the ankle: controlled double-blind trial to test the effectiveness of a homeopathic preparation]. *Fortschr Med* 1988; **106**: 96–100. English translation available in: *Biol Ther* 1989;VII (1):1–6.

12 Böhmer D, Ambrus P. Treatment of sports injuries with Traumeel® ointment: a controlled double blind study. *Biomed Ther* 1992; **10**: 290–300.

13 Thiel W. The treatment of recent traumatic blood effusions of the knee joint. *Biol Ther* 1994; **XII**: 242–8.

14 Orizola AJ, Vargas F. The efficacy of Traumeel versus diclofenac and placebo ointment in tendinous pain in elite athletes: a randomized controlled trial. *Med Sci Sports Exerc* 2007; **39**(No 5, Supplement): S78 (Abstract 858).

15 Schneider C, Schneider B, Hanisch J, van Haselen R. The role of a homoeopathic preparation compared with conventional therapy in the treatment of injuries: an observational cohort study. *Complement Ther Med* 2008; **16**: 22–7.

16 Birnesser H, Oberbaum M, Klein P, Weiser M. The homeopathic preparation Traumeel compared with NSAIDs for symptomatic treatment of epicondylitis. *J Musculoskel Res* 2004; **8**: 119–28.

17 Schneider C, Klein P, Stolt P, Oberbaum M. A homeopathic ointment preparation compared with 1% diclofenac gel for acute symptomatic treatment of tendinopathy. *Explore* 2005; **1**: 446–52.

18 Zenner S, Weiser M. Oral treatment of traumatic, inflammatory, and degenerative conditions with a homeopathic remedy. *Biomed Ther* 1997; **XV**: 22–6.

19 Zenner S, Metelmann H. Application possibilities of Traumeel S injection solution: results of multicentric drug monitoring trial conducted on 3,241 patients. *Biol Ther* 1992; **X**: 301–10.

20 Zenner S, Metelmann H. Therapy experience with a homeopathic ointment: results of drug surveillance conducted on 3,422 patients. *Biol Ther* 1994; **XII**: 204–11.

21 Arora S, Harris T, Scherer C. Clinical safety of a homeopathic preparation. *Biomed Ther* 2000; **XVIII**: 222–5.

22 MeReC rapid review. 2011.http://www.npc.nhs.uk/rapidreview/?p = 2451 (accessed September 2012).

23 United States National Library of Medicine. Diclofenac. http://livertox.nih.gov/Diclofenac.htm (accessed January 2013).

24 Bauer P, Köhne K. Evaluation of experiments with adaptive interim analyses. *Biometrics* 1994; **50**: 1929–41.

25 Martin R, Irrgang J, Burdett R, Conti SF, van Swearingen JM. Evidence of validity for the Foot and Ankle Ability Measure (FAAM). *Foot Ankle Int* 2005; **26**: 968–83.

26 Esterson PS. Measurement of ankle joint swelling using a figure of 8. *J Orthop Sports Phys Ther* 1979; **1**: 51–2.

27 Colditz GA, Miller JN, Mosteller F. Measuring gain in the evaluation of medical technology. The probability of a better outcome. *Int J Technol Assess Health Care* 1988; **4**: 637–42.

28 Maurer W, Hothorn LA, Lehmacher W. In Vollmar J, ed. *Biometrie in der chemisch-pharmazeutischen Industrie*. Stuttgart, Germany: Gustav Fischer, 1995: 3–18.

29 European Medicines Agency September 1998 CPMP/ICH/363/96. ICH Topic E 9 Statistical principles for clinical trials. Step 5. Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96). http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf. (accessed January 2013).

30 Gillings O, Koch G. The application of the principle of intention-to-treat to the analysis of clinical trials. *Drug Inform J* 1991; **25**: 411–24.

31 Bretz F, Schmidli H, Koenig F et al. Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: general concepts. *Biometrical J* 2006; **48**: 623–34.

32 Fligner MA, Wolfe DA. Distribution-free tests for comparing several treatments with a control. *Stat Neerl* 1982; **36**: 119–27.

33 Wexler RK. The injured ankle. *Am Fam Physician* 1998; **57**: 474–80.

34 Lussignoli S, Bertani S, Metelmann H, Bellavite P, Conforti A. Effect of Traumeel S®, a homeopathic formulation, on blood-induced inflammation in rats. *Complement Ther Med* 1999; **7**: 225–30.

35 Heine H, Andrä F. The antiinflammatory action mechanism of an antihomotoxic composite remedy. *Ärztezeitschrift für Naturheilverfahren* 2002; **43**: 96–104.

36 Rabeneck L, Viscoli CM, Horwitz RI. Problems in the conduct and analysis of randomized clinical trials: are we getting the right answers to the wrong questions? *Arch Intern Med* 1992; **152**: 507–12.

37 Fisher P, van Haselen R, Hardy K, Berkovitz S, McCarney R. Effectiveness gaps: a new concept for evaluating health service and research needs applied to complementary and alternative medicine. *J Altern Complement Med* 2004; **10**: 627–32.

Paper received March 2013, accepted May 2013