Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

Tr14 gel for the treatment of acute ankle sprains: a plain language summary of the TRAUMED trial

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Summary

What is this summary about?
This is a summary of an article discussing the results of the TRAUMED trial, which was originally published in the *Journal of Clinical Medicine*. This trial studied how well Tr14 gel helped with ankle **sprains** compared with either a dummy treatment (placebo) or a common painkiller called diclofenac.

What were the results of this trial, and what do they mean?
The results of this trial showed that Tr14 was effective at reducing pain caused by an **acute** or sudden ankle sprain compared with placebo and worked just as well as diclofenac. The results also suggested that Tr14 led to faster pain relief and improved foot and ankle function compared with placebo and was at least as effective as diclofenac.

How to say (double click on the sound icon to play the sound)

Apoptosis: a-pop-TOW-sis
Diclofenac: die-KLOW-fen-NAK
Efferocytosis: ef-er-OH-sih-TOW-sis
Macrophage: MAK-krow-fayj
Neutrophil: NEW-truh-fil

Sprain: When a **ligament** is stretched beyond its limit and may be torn.

Ligament: A tough, fibrous band of connective tissue that is found in a joint and connects bones to other bones.

Acute: An illness or medical condition that starts suddenly and lasts for a short period of time (days to weeks).

Who sponsored this trial?

This trial was sponsored by Heel GmbH.

Where can readers find more information?

The original article in the *Journal of Clinical Medicine is titled* 'Topical Treatment Is Effective and Safe for Acute Ankle Sprains: The Multi-Center Double-Blind Randomized Placebo-Controlled TRAUMED Trial.' You may access and read the article for free at this link: https://doi.org/10.3390/jcm13030841

Who is this article for?

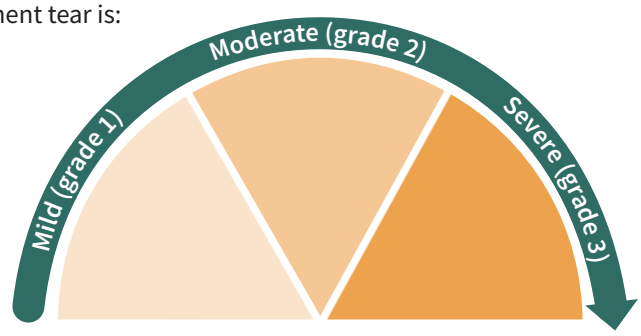
This summary may be helpful for people who have experienced an ankle sprain or who are prone to having ankle sprains. It may also be helpful for general practitioners and healthcare professionals who do not have specialist knowledge of acute ankle sprains or other people who are interested in sports medicine such as team sports physicians.

Becaris PUBLISHING

What is this trial about?

What are acute ankle sprains?

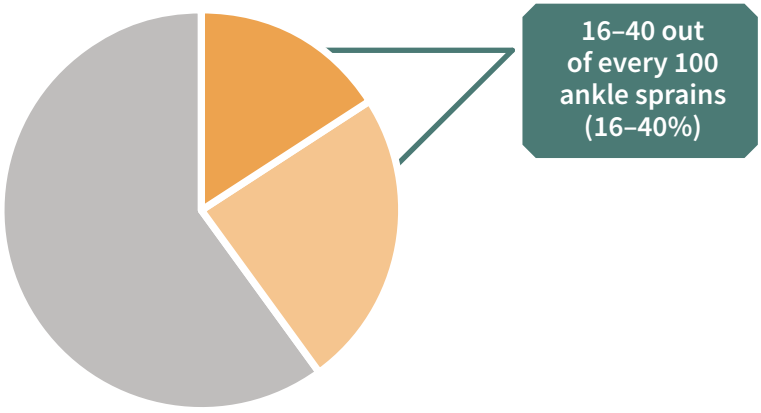
Acute ankle sprains happen when the flexible ligaments that support the ankle are stretched beyond their limit and they tear. This is often caused by inversion, when the foot rolls inwards, or by rotation, when the ankle is twisted. Acute ankle sprains can be graded based on how serious the ligament tear is:



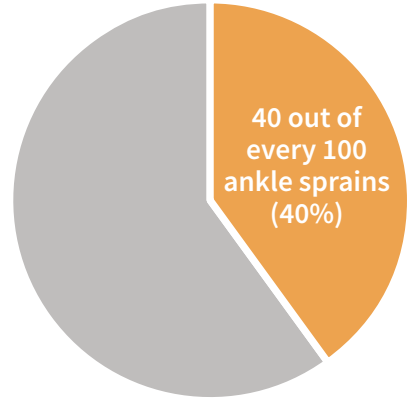
Symptoms of an acute ankle sprain include:

- Pain when putting weight on the affected ankle.
- Feeling like the ankle is unstable (instability).
- Problems with walking or moving.

Acute ankle sprains are common injuries that lead to more than 1 million medical attendances a year around the world, for example visiting the emergency room.



Caused by doing sports



At risk of becoming a **chronic** injury, when a medical condition lasts and/or worsens over a long time, with long-lasting instability

What are the treatment options for acute ankle sprains?

There are different treatments available for acute ankle sprains. For mild and moderate grade sprains, common therapies include painkillers taken by mouth or applied topically on the skin. Other treatment methods include rest, ice, compression, and elevation (together known as RICE).

Non-steroidal anti-inflammatory drugs (NSAIDs) are often recommended to treat acute ankle sprains. NSAIDs reduce **inflammation** and pain by blocking the production of **prostaglandins**, which are chemicals in the body that contribute to inflammation and pain. Diclofenac is a type of NSAID that is commonly used for ankle sprains.

However, research shows that NSAIDs can cause acute pain to be more likely to turn into **chronic** pain and may disrupt the body's natural healing process. This could put a person at risk of getting injured again.

Chronic: A long-term medical condition or event that is long lasting.

NSAID: Non-steroidal anti-inflammatory drug, a category of common painkillers that target inflammation.

Inflammation: The body's response to an injury or illness, causing heat, pain, redness, and swelling.

Prostaglandins: Natural chemicals made by the body that help control processes like inflammation, pain, fever, and blood flow.

How is Tr14 different from other treatments for acute ankle sprains?

The small molecules and proteins in the body that induce inflammation are known as **pro-inflammatory mediators**. NSAIDs such as diclofenac work by blocking the activity of these pro-inflammatory mediators. Tr14 does not block inflammation, but instead supports the body's normal process of resolving inflammation.

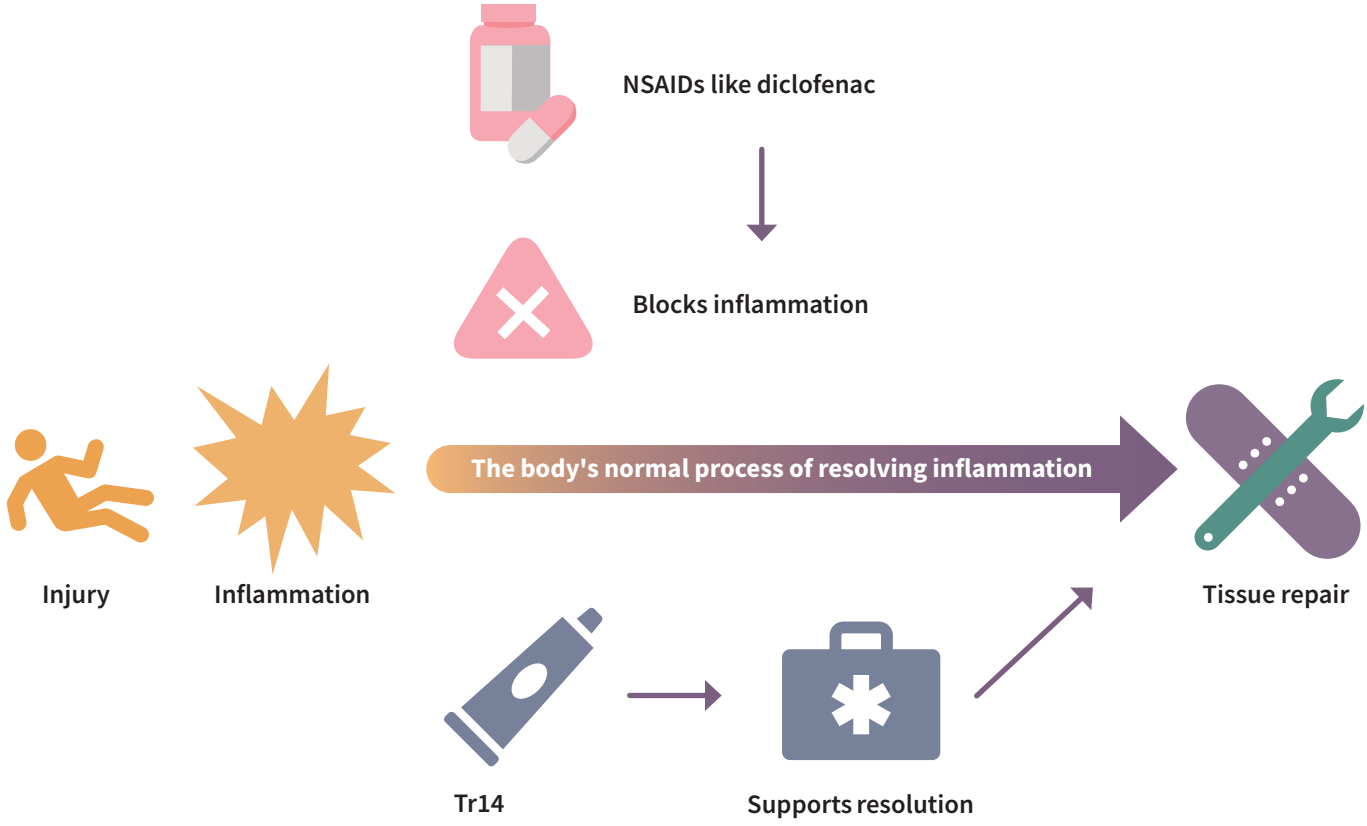
Research shows that resolving inflammation is an active process, rather than a passive process, as researchers previously thought. This process of resolving inflammation is driven by other small molecules and proteins in the body called **specialized pro-resolving mediators**.

Pro-inflammatory mediators: Small molecules and proteins in the body that cause an inflammatory reaction.

Specialized pro-resolving mediators: Natural chemicals made by the body that help to resolve inflammation and stimulate tissue repair.

The processes of acute inflammation and resolving inflammation share some common molecules that change their behaviour as time progresses. For example, diclofenac can block the pro-inflammatory activity of prostaglandins, which may reduce pain and inflammation in the short-term. But blocking prostaglandins also blocks the production of specialized pro-resolving mediators. This delays the body's normal process of resolving inflammation and increases the risk of pain becoming chronic.

Tr14 is a non-prescription topical gel that helps pro-resolution processes without blocking the effects of prostaglandins.



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Why was the TRAUMED trial needed?

A previous clinical trial showed that Tr14 worked just as well as diclofenac for managing pain and improving joint function in people with a mild to moderate ankle sprain. However, this earlier trial mostly included young, active people and it did not have a **placebo** group.

Placebo: A fake treatment that looks like the treatment being studied but doesn't contain any active medicine.

The current trial, called the TRAUMED trial, was designed to learn more about how well Tr14 works and how safe it is for a broader, more diverse group of people. This trial also compared Tr14 with both a placebo and diclofenac.

What were the aims of the TRAUMED trial?

The main questions the researchers wanted to answer in this trial were:

- Did Tr14 reduce the participants' ankle pain during passive movement compared with the placebo, and did it work as well as diclofenac?
- Did Tr14 reduce the time it took to reach 50% improvement in pain during passive movement compared with placebo, and did it work as well as diclofenac?
- Did Tr14 improve the participants' foot and ankle joint function compared with placebo, and did it work as well as diclofenac?
- What **adverse events** did the participants experience during the trial?

Adverse event: Any unwanted or unexpected health problem that happens to someone during a clinical trial, whether or not it was caused by the treatment being studied.

The researchers also looked at other results during the trial, such as how much pain participants felt when resting. You can find a full list of the questions they studied on the websites at the end of this summary.

What happened during the trial?

Who took part in the TRAUMED trial?

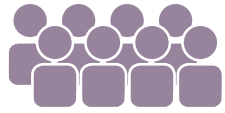
The TRAUMED trial occurred from February 2018 to November 2022. It included 625 participants in Germany who were aged 18 to 78 years and had painful acute ankle sprains. People could not join this trial if they had an acute sprain in both ankles, if their ankle injury was severe, or if they had previously injured the same ankle in the 6 months before joining the study.

What happened during the TRAUMED trial?

This was a **double-blind trial**. This means that the participants, researchers and trial doctors did not know which treatment each participant was receiving.

Double-blind: A clinical trial design where neither the participants nor the researchers know who is getting the treatment being studied and who is getting the placebo or comparison treatment.

Randomization: When a computer program is used to assign participants to different treatment groups by chance, not by choice.



625 participants randomized

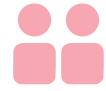
Eligible participants were randomized to one of three treatment groups. This means that a computer program was used to randomly choose which trial treatment the participants applied. Clinical trials use **randomization** to make sure treatments are allocated fairly. Participants in this trial received either Tr14, placebo, or diclofenac starting on Day 1

318 participants applied Tr14

This was about 2 in 4 participants

155 participants applied the placebo

This was about 1 in 4 participants



152 participants applied diclofenac

This was about 1 in 4 participants

Treatment period

7 days

During the treatment period, the participants applied the treatment they had been allocated as a gel directly to their affected ankle, 3 times each day for 7 days

Follow-up period

7 days

2 participants excluded from the final results

participant excluded from the final results **1**

316 participants in the Tr14 final results

155 participants in the placebo final results

151 participants in the diclofenac final results

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The final results of this trial included 622 participants. The safety results included all 625 participants who received at least one dose of trial treatment. The characteristics of these 622 participants at the start of the trial are listed in this table.

	Tr14 gel (out of 316 participants)	Placebo gel (out of 155 participants)	Diclofenac gel (out of 151 participants)
Average age	35.2 years	36.0 years	34.7 years
Percentage of female participants	49.4% (156)	43.9% (68)	42.4% (64)
Percentage of male participants	50.6% (160)	56.1% (87)	57.6% (87)
Percentage of Caucasian participants	96.5% (304)	98.1% (152)	98.7% (149)
Percentage of Black participants	1.0% (3)	1.3% (2)	0.0% (0)
Percentage of Asian participants	0.3% (1)	0.0% (0)	0.0% (0)
Percentage of participants of another ethnic origin	2.2% (7)	0.6% (1)	1.3% (2)
Percentage of participants with a mild ankle sprain	68.4% (216)	66.5% (103)	72.2% (109)
Percentage of participants with a moderate ankle sprain	31.6% (100)	33.5% (52)	27.8% (42)
Average **Visual Analogue Scale (VAS)** score for pain during passive movement	74.9	75.5	74.9
Average **Foot and Ankle Ability Measure Activities of Daily Living (FAAM-ADL)** score	51.4	49.7	50.6

Visual Analogue Scale (VAS): A line from 0 to 100 millimetres that participants use to measure their pain. A score of 0 represents no pain and, a score of 100 represents the worst pain imaginable.

Foot and Ankle Ability Measure Activities of Daily Living (FAAM-ADL): A questionnaire used to assess how well someone can do daily activities such as walking or climbing stairs. It is scored out of a total of 84 points, and the higher the score the easier it is for someone to carry out their daily activities.

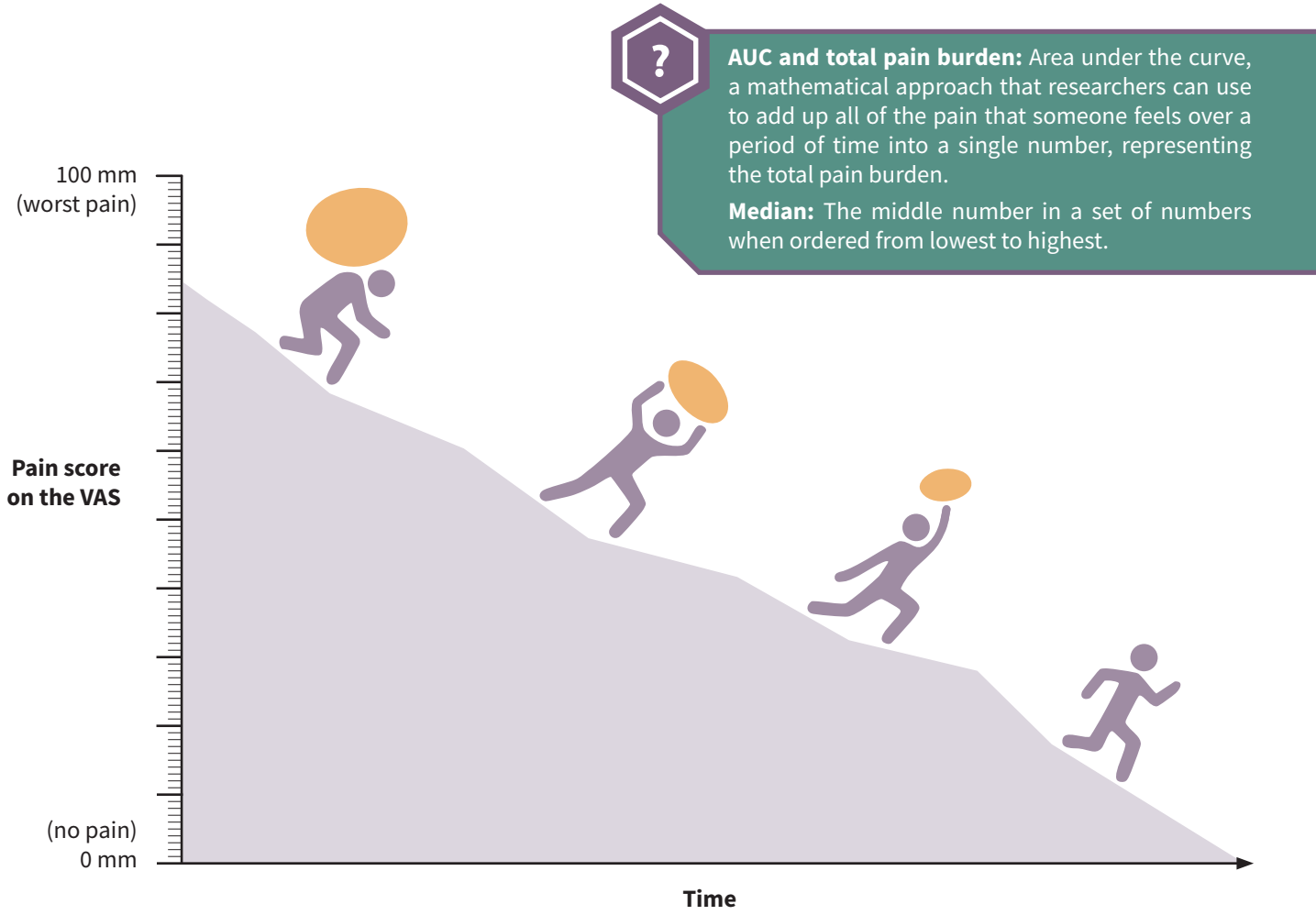
How did the researchers assess the participants' ankle pain?

The researchers used the VAS to measure the participants' ankle pain. The VAS is a line that is 100 millimetres (mm) long with 0 at one end and 100 at the other end. On the scale, 0 is defined as no pain and 100 is defined as the worst pain imaginable.

The trial doctors moved the injured ankle, and the participants used the VAS to record the level of pain they experienced. This is called pain during passive movement. The participants recorded their pain during passive movement using the VAS at the start of the trial, after 2, 4, and 7 days of applying their trial treatment, and again after 14 days, which was at the end of the follow-up period.

The researchers used a mathematical approach called the '**area under the curve**' (**AUC**) to analyse the participants' VAS scores. This approach is commonly used in clinical trials that measure pain. AUC allows researchers to measure the participants' pain over time.

AUC is calculated on a graph that shows time on the horizontal axis (left and right) and VAS scores to represent pain on the vertical axis (up and down). This creates a curve on the graph, and the AUC represents the total amount of pain that a participant experienced over a period of time. This is known as the **total pain burden** and is shown by the shaded area in the graph below.



The researchers used all of the participants' AUC scores to calculate a **median**. The median is the middle number in a set of numbers when ordered from lowest to highest. In this trial, the researchers measured median AUC for pain during passive movement at Day 4 and Day 7 as the main result.

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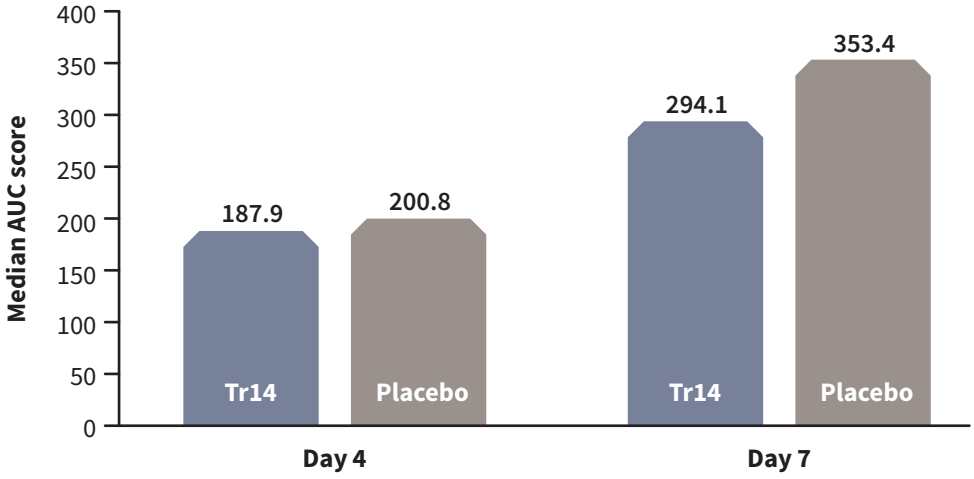
What were the results of the TRAUMED trial?

Did Tr14 reduce the participants' ankle pain during passive movement compared with the placebo, and did it work as well as diclofenac?

The researchers found that Tr14 was significantly more effective at reducing pain during passive movement in participants with an acute ankle sprain at Day 4 and Day 7 compared with placebo.

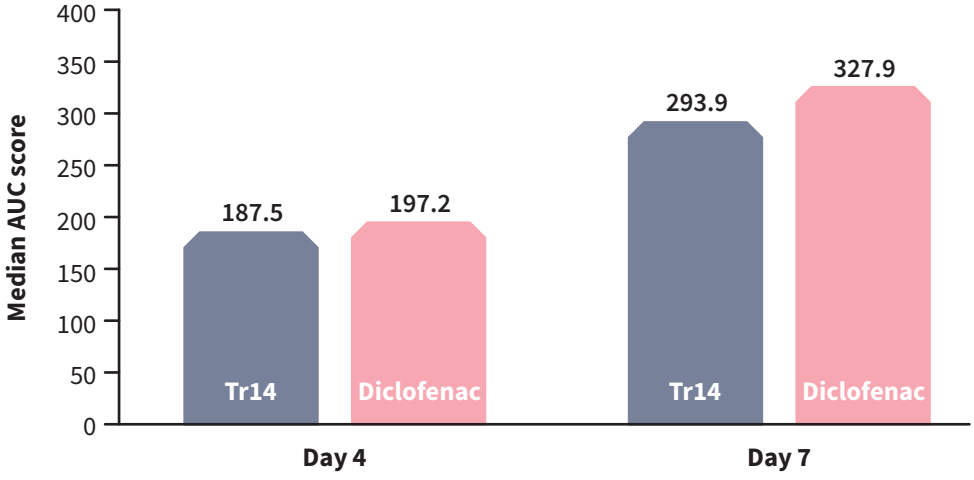
To test this, the researchers compared AUC for the Tr14 group with AUC for the placebo group at Day 4 and Day 7. A lower AUC means that the participants experienced less pain. The median AUC scores at Day 4 and Day 7 for the Tr14 group and the placebo group are shown in the graph below.



Tr14 was significantly more effective at reducing pain than placebo

The researchers also compared AUC for the Tr14 group with AUC for the diclofenac group at Day 4 and Day 7. They wanted to find out if Tr14 was no worse than diclofenac at reducing pain. This is also known as a non-inferiority comparison.

The researchers found that Tr14 was non-inferior to diclofenac at reducing pain in participants with an acute ankle sprain at Day 4 and Day 7. The median AUC scores at Day 4 and Day 7 for the Tr14 group and the diclofenac group are shown in the graph below.



Tr14 was non-inferior to diclofenac at reducing pain

Non-inferiority comparison: A type of comparison between two treatments to find out if the new treatment is no worse than the existing treatment.

Did Tr14 reduce the time it took to reach 50% improvement in pain during passive movement compared with placebo, and did it work as well as diclofenac?

In this trial, the researchers also wanted to measure how long it took for the participants to achieve a 50% improvement in the pain they experienced during passive movement.

To test this, the researchers recorded the number of days it took for the participants to achieve a 50% improvement in pain during passive movement and calculated a median for each group. The researchers then compared the median number of days for the Tr14 group with the median number of days for the placebo group and the diclofenac group.

The researchers found that there was a significant 1-day reduction in the Tr14 group compared with the placebo group and the diclofenac group. The median number of days to achieve a 50% improvement in pain during passive movement for each of the groups is shown in this table.

	Tr14 gel (out of 316 participants)	Placebo gel (out of 155 participants)	Diclofenac gel (out of 151 participants)
Median number of days to achieve a 50% improvement in pain during passive movement	6.0 days	7.1 days	7.0 days

Did Tr14 improve the participants' foot and ankle joint function compared with placebo, and did it work as well as diclofenac?

In this trial, the researchers also wanted to measure how well the participants' feet and ankles functioned after taking their trial treatment.

To do this, the researchers used a questionnaire called the FAAM-ADL subscale. This is used to understand how well a person can perform daily activities, such as walking and climbing stairs.

The participants were asked to complete the FAAM-ADL at the start of the trial and then at different points during the trial. The participants' answers were used to generate a score for the questionnaire. A lower score means an improved level of physical function.

The researchers found that participants in the Tr14 group had significantly improved joint function compared with the participants in the placebo group at all visits. The median FAAM-ADL scores for the participants in the Tr14 group and the placebo group are shown in this table.

	Tr14 gel (out of 316 participants)	Placebo gel (out of 155 participants)
Median FAAM-ADL score at Day 2	47.4	46.4
Median FAAM-ADL score at Day 4	31.0	35.7
Median FAAM-ADL score at Day 7	17.1	26.2
Median FAAM-ADL score at Day 14	4.8	9.5

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The researchers also compared the median FAAM-ADL scores for the participants in the Tr14 group with the participants in the diclofenac group. The researchers wanted to find out if Tr14 was non-inferior to diclofenac in improving the participants' foot and ankle joint function.

The researchers found that Tr14 was non-inferior to diclofenac in improving the participants' joint function. The median FAAM-ADL scores for the participants in the Tr14 group and the diclofenac group are shown in this table.

	Tr14 gel (out of 314 participants)	Diclofenac gel (out of 146 participants)
Median FAAM-ADL score at Day 2	47.2	46.4
Median FAAM-ADL score at Day 4	31.0	32.1
Median FAAM-ADL score at Day 7	16.9	21.2
Median FAAM-ADL score at Day 14	4.8	7.1

What adverse events happened during the trial?

An adverse event is an unwanted or unexpected health problem that happens to a participant during a trial. Adverse events may or may not be caused by the study treatment. Doctors keep track of all adverse events that happen in a trial. An adverse event is considered serious when it is life-threatening, causes prolonged problems or requires hospital treatment.

How many participants experienced adverse events, and what adverse events happened during the trial?

The adverse events that occurred in 2 or more participants are shown in this table. There were other adverse events that happened in fewer participants.

	Tr14 gel (out of 318 participants)	Placebo gel (out of 155 participants)	Diclofenac gel (out of 152 participants)
How many participants experienced adverse events?	2.8% (9)	3.9% (6)	1.3% (2)
 Headache	0.9% (3)	0.0% (0)	0.0% (0)
 Common cold	0.3% (1)	0.6% (1)	0.0% (0)
 Dry skin on the treated area	0.3% (1)	0.0% (0)	1.3% (2)

How many participants experienced serious adverse events, and what serious adverse events happened during the trial?

There were 0.2% of participants who experienced serious adverse events during the trial. This was 1 out of 625 participants.

- There was 1 participant in the diclofenac group who experienced a serious adverse event. This was an arm bone fracture that was unrelated to trial treatment.
- None of the participants in the Tr14 group or the placebo group experienced serious adverse events.

None of the participants died during the trial.

Were there any medical problems that the trial doctors reported as possibly related to the trial treatment?

An **adverse drug reaction** is an adverse event that the trial doctors reported as possibly related to the trial treatment. The results from several trials are needed to decide if a treatment causes an adverse drug reaction.

Adverse drug reaction: A harmful or unwanted effect that is linked to the drug being studied.

The only adverse drug reaction in the trial was dry skin. This is shown this table.

	Tr14 gel (out of 318 participants)	Placebo gel (out of 155 participants)	Diclofenac gel (out of 152 participants)
How many participants experienced adverse drug reactions?	0.3% (1)	0.6% (1)	1.3% (2)
Dry skin	0.3% (1)	0.6% (1)	1.3% (2)

What do the findings of the TRAUMED trial tell us?

The results of this trial demonstrated that Tr14 was effective at reducing pain from an acute ankle sprain compared to placebo and worked just as well as diclofenac. The results also showed that Tr14 provided faster pain relief and improved foot and ankle function compared to placebo and was at least as effective as diclofenac.

However, this study was short and only looked at treatment use over 14 days. This means the researchers could not know if participants developed further ankle problems after they left the trial. Future studies of Tr14 should consider how this timeframe affects clinical trial results.

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Where can readers find more information about this trial?

The full title of the original publication is 'Topical Treatment Is Effective and Safe for Acute Ankle Sprains: The Multi-Center Double-Blind Randomized Placebo-Controlled TRAUMED Trial'. It was published in the *Journal of Clinical Medicine*. The full publication can be found here: https://doi.org/10.3390/jcm13030841

You can read more about the trial at the following websites:

- https://clinicaltrials.gov/study/NCT06192420?term=2016-004792-50&rank=1
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004792-50/results

Financial disclosure

The TRAUMED trial was sponsored by Heel GmbH.

Competing interests disclosure

Ludger Gerdesmeyer and Gino Kerkhoffs received consultancy fees to participate in Advisory Board meetings during the conception, conduct and analysis of this clinical trial. Konstantin Cesnulevicius, Myron Schultz and Alta Smit are employees of Heel GmbH. Helmut Pabst has no competing interests to report. The authors of this summary have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the summary apart from those disclosed.

Writing disclosure

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