CLINICAL TRIAL RESULTS SUMMARY

A Study to Evaluate the Safety, Tolerability and Efficacy of GR1014 cutaneous gel as a topical radioprotector in the prevention of the radiodermatitis occurring with adjuvant radiotherapy for localised breast cancer after lumpectomy

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Medicine(s) Studied: GR1014 cutaneous gel (GR1014-CG)

Protocol Number: GRA.05.SPR.0001

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Dates of Trial: 26 JUL 2024 until 1 DEC 2025*

*This study was stopped earlier than planned. This is the date that the study sites were notified of the early termination.

Graegis Pharmaceuticals Ltd, the Sponsor would like to thank you for your participation in this clinical study. All the participants helped researchers learn more about GR1014 cutaneous gel (GR1014-CG) when applied to the skin. GR1014-CG was developed as a topical treatment to help protect against radiation-induced skin reactions (radiodermatitis). Radiodermatitis can occur in patients who have had breast-conserving surgery to remove cancer tissue (known as lumpectomy) and who receive radiation therapy (known as adjuvant radiotherapy (RT) after breast-conserving surgery to remove cancer tissue (known as lumpectomy). Graegis Pharmaceuticals Ltd reviewed the results of the study and prepared a report. This document is a summary of that report.
If you participated in this study and have any questions about the results, please contact the doctor or staff at your study site.

This summary presents the results of a single clinical study. The information provided here is for informational purposes only.

WHY WAS THIS STUDY CONDUCTED?

What is the medical condition targeted by GR1014 Cutaneous Gel?

Breast cancer is the most common cancer among women. It is often treated by surgically removing the tumour followed by RT to reduce the risk that the cancer comes back and improve survival. However, RT, can also cause side effects that affect the healthy tissues, the most frequent being radiodermatitis. The symptoms of radiodermatitis include skin redness, swelling, dry or moist peeling of the skin and pain. These skin reactions usually begin 1 to 4 weeks after RT starts and may persist or worsen during treatment. In most cases, the skin improves and heals in about 2 to 4 weeks after the end of RT. There are currently no approved treatments for radiodermatitis. Patients usually apply pain-relieving and calming creams on the skin to reduce discomfort. However, these treatments have not always been shown to work well or they work only for a short time.

What is GR1014 Cutaneous Gel?

GR1014 Cutaneous Gel (GR1014-CG) is a medicine developed by Graegis Pharmaceuticals Ltd designed to be applied directly to the skin before each RT session. The active ingredient of GR1014-CG is amifostine thiol, a well-known radioprotective agent. Based on the mechanism of action of amifostine thiol, GR1014-CG may help lower the risk and reduce the severity of radiodermatitis. GR1014-CG is a liquid when kept cold or at room temperature. It turns into a gel when in contact with the warmer surface of the skin.

What was the purpose of this study?

This study was carried out to find out whether GR1014-CG is safe and effective to help prevent radiodermatitis. The study involved patients with localised, non-metastatic breast cancer and who had previously undergone breast-conserving surgery (lumpectomy). Participants received RT after surgery and were treated either with GR1014-CG or with a placebo gel that did not contain the active ingredient. Two different strengths of GR1014-CG were studied: 4.7% and 2.4%.

WHO COULD TAKE PART IN THIS STUDY?

Patients were evaluated to ensure that they met the criteria for participation in the study. Patients could take part if they:

- ☑ Were female aged 18 years or older.
- ☑ Had primary cancer restricted to the breast (localised breast cancer) without metastases and also had lumpectomy and required RT.
- ☑ Had recovered from their most recent surgery and, if applicable, from post-surgery chemotherapy.
- ☑ Had no signs of skin irritation or inflammation in the area of the breast to be irradiated.

WHAT HAPPENED DURING THIS STUDY?

How was this study performed?

This study was a randomised, placebo-controlled parallel-group Phase 2 study. This means that participants were assigned by chance to receive either placebo gel or one of two strengths of GR1014-CG and were studied in parallel. Neither the doctors nor the participants knew which treatment each participant received. This is known as a double-blind study and helps ensure fair and reliable results).

First, a study doctor checked each participant to make sure they were suitable to join the study. This is known as the screening period. The participants were, then, assigned by chance at the beginning of the treatment period to one of the three treatment groups to receive:

- **Placebo (Vehicle group)**
- **2.4% GR1014-CG**
- **4.7% GR1014-CG**

A total of 273 participants were planned to be included in the study.

The study was planned to take place in two 2 periods:

- A Safety Run-In phase with 30 participants (8-10 participants in each treatment group). After this phase an independent Scientific Committee was to review the safety results. Based on these findings, the Committee would then decide to continue the study (main phase) as in the Run-In phase or stop one of the two doses or stop the entire study.
- A main phase: If the Scientific Committee approved to continue the study, additional participants would be enrolled to reach the planned total of 273 participants.

The RT scheme that the participants followed in this study included fewer treatment sessions at a higher radiation dose (ultra-hypofractionated RT). A maximum of 5 RT sessions was planned for each participant. GR1014-CG or the placebo gel was applied to the skin at least 15 minutes before each RT session.

After finishing RT, participants returned to the study centers for evaluation visits:

- Once a week for 4 weeks after the last RT session
- Then again 6 weeks and 8 weeks after the last RT session.

During these visits, the doctors examined the participants for radiodermatitis in addition to other skin changes or side-effects. During the Safety Run-In, the doctors also took blood:

- At the last RT session to measure how quickly amifostine thiol is absorbed from GR1014-CG through the skin to the blood, how long it stays in the blood, and how fast the body removes it.

- Before the 1st RT session and after the last RT session to measure calcium levels, as low calcium in the blood is a known side effect of amifostine when it is administered through a vein.

Where did this study take place?

This study took place at 4 different research sites in France and the UK.

How long did this study last?

The study began on 26 July 2024

The study Sponsor decided to stop the study earlier than planned -after completion of the Safety Run-In phase- because of enrolment challenges, which made unlikely that the planned total number participants (273) for the entire study could be reached in a reasonable timeframe.

The study was ended on 1st December 2025 when the sites were notified about the early discontinuation.

The last participant completed the study (Safety Run-In phase) on 11 June 2025.

Who participated in this study?

In total, 29 adult women were randomised in the Safety Run-In phase of the study. Of these, 28 received the study treatment (placebo or GR1014-CG):

- 8 women aged between 56 and 64.5 years received placebo gel and constituted the **Placebo Group**
- 12 women between the age of 57.5 and 75.5 years received the lower strength of GR1014-CG and constituted the **GR1014-CG 2.4% group**.
- 8 women between the age of 58 and 71 years received the higher strength of GR1014-CG and constituted the **GR1014-CG 4.7% group**.

WHAT MEDICAL PROBLEMS PARTICIPANTS HAD DURING THIS STUDY AND WHAT WERE THE MAIN RESULTS?

During the study, the researchers recorded all medical problems experienced by the participants. Some medical problems may occur for reasons not related to the study treatment (for instance caused by an underlying disease, RT, or by chance). Other medical problems may be possibly related to the study treatments (GR1014-CG or placebo). By comparing medical problems across treatment groups, researchers aimed to better understand the side effects that might be specifically caused by GR1014-CG.

Medical problems that occur during a clinical study are called adverse events. An adverse event that is life-threatening, needs hospital care, causes death, or is considered by the study doctor as medically important is called a "serious adverse event".

Adverse events for which a link to GR1014-CG cannot be ruled out are called "related adverse events" to GR1014-CG.

In this study, researchers found that:

- Overall, GR1014-CG was well-tolerated at both tested strengths (2.4% and 4.7%) and no major safety concerns were identified in this study.
    - There were no serious adverse events.
    - No participants stopped treatment because of adverse events.
    - 27 out of 28 participants had at least one adverse event during the study: All 8 participants from the Placebo group, and 19 of the 20 participants who received

GR1014-CG (11 of 12 participants from GR1014-CG 2.4% group and all 8 participants from GR1014-CG 4.7% group).

  - One participant who received GR1014-CG 2.4% experienced 5 adverse events on the skin that were considered possibly related to GR1014-CG. This included skin irritation radiation-related skin injury, itching, a red rash with small raised bumps, and small visible blood vessels on the skin.

- The active ingredient in GR1014-CG, amifostine thiol, is known to cause certain side-effects such as sudden drop in blood pressure when standing up, skin rash, feeling of sickness (nausea), and vomiting when given through a vein. Although GR1014-CG was applied to the skin, the researchers specifically monitored for these effects. Some of these events were reported in 4 of 27 participants (14.8%): nausea in 2 participants who received GR1014-CG, breast swelling (oedema) in 1 participant in the Placebo group, and skin rash in 1 participant in the Placebo group. After careful evaluation, none of these events were considered related to GR1014-CG.
  - Only a small number of participants had detectable levels of the active ingredient amifostine thiol in their blood at any time during the study. This was seen in 1 out of 8 participants from GR1014-CG 2.4% group and 3 out of 11 participants from GR1014-CG 4.7% group.
- Most participants who received GR1014-CG, regardless of the strength, (19 of 28 participants, 67.9%), had mild (Grade 1) radiodermatitis, few had moderate (Grade 2) radiodermatitis (3 of 28 participants, 10.7%), and 6 of 28 participants did not have radiodermatitis. In the Placebo group (8 participants), 5 (62.5%) had mild radiodermatitis and 3 had no radiodermatitis.
- Because the study was stopped early and included only a small number of participants, it was not possible to assess whether GR1014-CG helps in reducing or preventing radiodermatitis.

HOW HAS THIS STUDY HELPED PARTICIPANTS AND RESEARCHERS?

This study helped researchers to learn more about the safety profile of GR1014-CG.

Overall, the results of this study suggest that GR1014-CG was safe and well-tolerated at both tested strengths (2.4% and 4.7%). Non-serious adverse events assessed as related to GR1014-CG 2.4% treatment were reported in a single participant.

The results also showed that after GR1014-CG was applied to the skin, very little or none of the active ingredient amifostine thiol entered the bloodstream. This may help explain why side effects that are known to occur when this drug is given through a vein were not seen in this study.

Because the study was stopped early and only a small number of participants received treatment, it did not offer the researchers the ability to conclude on the protective effect of GR1014-CG.

Therefore, further studies involving more participants would be needed to better understand whether GR1014-CG can help prevent or reduce skin side effects associated with RT.

ARE THERE PLANS FOR FURTHER STUDIES?

At the time of this summary, no other study is planned.

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

If you have questions about the results of your study, please speak with the doctor or staff at your study site. For more details on this study protocol, please visit:

www.clinicaltrials.gov	Use the study identifier NCT07192588
or	
https://www.isrctn.com	Use the study identifier 61697120

Once again, if you participated in this study, **thank you** for volunteering. Our research aims to identify the best ways to support participants, and your contribution was essential to this work.