# TAR-0520 GEL, A NOVEL TREATMENT FOR THE PREVENTION OF CHEMOTHERAPY- INDUCED SKIN TOXICITIES

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## Introduction

**Cooling systems have demonstrated effectiveness** in mitigating chemotherapy-induced skin toxicities[1-3]. By promoting vasoconstriction (**VC**) and reducing local blood flow, these systems lower the concentration of chemotherapeutic agents in the skin to levels below the threshold for toxicity.

**Tarian Pharma offers an innovative alternative:** pharmacologically induced vasoconstriction via topical delivery.

**TAR-0520 gel** is a patent-protected topical formulation designed for **24-hour sustained release of brimonidine tartrate**, a selective alpha-2 adrenergic receptor agonist.

TAR-0520 induces localized and reversible VC of superficial cutaneous vessels

## Methods

**Two Phase 1, monocentric, investigator-blinded, randomized trials were conducted to evaluate the safety, pharmacodynamics (PD), and pharmacokinetics (PK) of TAR-0520 gel in healthy volunteers.**

**Local tolerance -** standard 21-day model in healthy volunteer:

- **Study 1:**
  - 20 participants received escalating concentrations of TAR-0520 gel (0.5% to 1.5% brimonidine tartrate), placebo, and a marketed comparator.
  - Applications: daily to six predefined mini-zones on the chest.
- **Study 2:**
  - 26 women received daily applications of either 2 or 4 mg/cm² of TAR-0520 gel (1% or 1.5%) on both the face and chest.

Local tolerance assessed daily using a standardized irritation scoring scale, with key endpoints including:

- mean cumulative irritation index (CII) and
- maximum irritation score observed during the study.

**PD effects**

- Subgroup of 12 participants in study 1 underwent objective skin color measurements on Days 1, 7, and 15 using a chromameter.
- a* value (red color component), indicative of superficial capillary vasoconstriction, measured over a 24-hour period post-application.
- Intensity and duration of skin blanching used to assess PD potency.

**PK of TAR-0520 gel** (1%)

- Maximal exposure conditions in a separate cohort of 8 participants.
- Each received 2 grams of gel applied over 1,000 cm² (upper chest, back, and face) daily for five days.
- Full PK profiles were obtained on Days 1 and 5. Blood samples were collected pre-dose and at 40 min, 75 min, 2.5 h, 4 h, 6 h, 12 h, and 24 h post-application.
- Quantification was performed using a validated analytical method with a lower limit of quantification (LLOQ) of 11.68 pg/mL

## Results

### GENERAL SAFETY

- No adverse reactions or SAEs were reported
- Vital signs were not modified by treatment.
- Standard laboratory tests did not show any signals.
- ECG remained within clinical norms

### LOCAL TOLERANCE

- Study 1, CII was <1 for all 6 formulations, thus classified as non-irritant
- Study 2, all 4 treatment regimens were well tolerated, with no irritation reported.

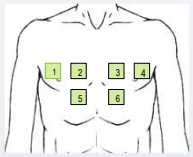


Fig 1: Product application in study 1

| STUDY 1 (Chest) 11 women, 9 men; mean age: 45 | TAR-0520 gel 0,5% | TAR-0520 gel 0,75% | TAR-0520 gel 1% | TAR-0520 gel 1,5% | Reference 0,5% | TAR-0520 gel vehicle |
|---|---|---|---|---|---|---|
| **CII** | 0,05 | 0 | 0,1 | 0 | 0,1 | 0,05 |
| **Worst score** | | | | | | |
| n (%) | 20 (100%) | 20 (100%) | 20 (100%) | 20 (100%) | 20 (100%) | 20 (100%) |
| No irritation (%) | 19 (95%) | 20 (100%) | 19 (95%) | 20 (100%) | 19 (95%) | 19 (95%) |
| Minimal barely perceptible erythema | 1 (5%) | 0 | 1 (5%) | 0 | 1 (5%) | 1 (5%) |
| Mild irritation or worse | 0 | 0 | 0 | 0 | 0 | 0 |

Table 1: Tolerance results in study 1

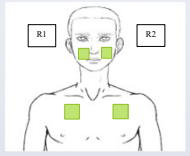


Fig 2: Product application in study 2

| STUDY 2 (Face & Chest) 26 women mean age: 37 | TAR-0520 gel 1% at 2 mg/cm2 | TAR-0520 gel 1% at 4 mg/cm2 | TAR-0520 gel 1,5% at 2 mg/cm2 | TAR-0520 gel 1,5% at 4 mg/cm2 |
|---|---|---|---|---|
| **CII** | 0 | 0 | 0 | 0 |
| **Worst score** | | | | |
| n (%) | 13 (100%) | 13 (100%) | 13 (100%) | 13 (100%) |
| no irritation (%) | 13 (100%) | 13 (100%) | 13 (100%) | 13 (100%) |
| minimal barely perceptible erythema | 0 | 0 | 0 | 0 |
| mild irritation or worse | 0 | 0 | 0 | 0 |

Table 2: Tolerance results in study 2

### PHARMACODYNAMICS

- Maximum VC effects achieved between 4- and 6-hours post-application, persisting up to 24 hours for TAR-0520 1% and 1.5%.
- TAR-0520 gel demonstrated greater vasoconstrictive potency compared to the marketed reference product
- Dose-dependent response with higher concentrations producing more pronounced and sustained vasoconstriction.
- Stronger vasoconstrictive effects were observed on the face compared to the chest.

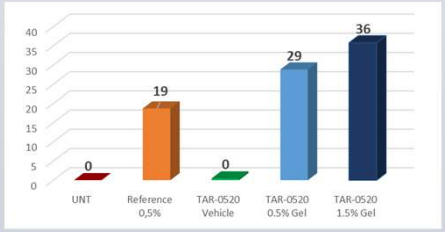


Fig 3: Vasoconstriction potency, $AUC_{0\text{-}24h}$ of chromametric a* parameter

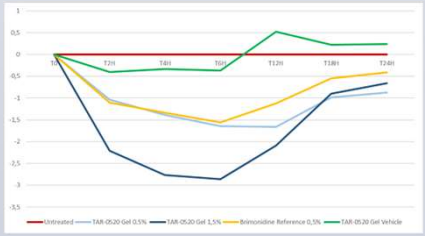

Fig 4: Evolution of chromametric a* parameter over 24 hours

### PHARMACOKINETICS

- Minimal systemic exposure, with the majority of plasma samples remaining below the LLOQ.
- No evidence of systemic accumulation, as indicated by the $AUC_{0-24}$h ratio between Day 5 and Day 1, which was 1.74 ± 0.5
- Systemic exposure was comparable to two commercially available brimonidine tartrate formulations at lower concentrations (0.2% and 0.5%).

## Discussion

TAR-0520 gel demonstrated excellent local tolerability, without irritation when applied to the face, chest, upper back, or hands, even at concentrations up to 1.5%.

Despite the application of a high daily dose (2 g) and the use of a sensitive quantification method, plasma concentrations of brimonidine remained consistently low and often below LLOQ.

These findings confirm the gel's sustained release profile, resulting in systemic exposures comparable to those of marketed brimonidine products formulated at lower concentrations.

PD assessments revealed a clear dose-dependent vasoconstrictive response, with higher concentrations producing sustained effects lasting up to 24 hours, underscoring the product's potential for once-daily application.

## Conclusions

TAR-0520 gel exhibited a favorable safety profile:

- ✓ no local irritation
- ✓ minimal systemic exposure

Sustained vasoconstriction, induced by TAR-050 gel, for up to 24 hours supports a convenient once-daily application regimen.

TAR-0520 gel emulates the mechanism of action of cooling systems by inducing local vasoconstriction, with the added advantages of being painless and easily integrated into diverse chemotherapy protocols.

Target indications in the TAR-0520 development program include:

- ✓ EGFR inhibitor–associated folliculitis,
- ✓ Hand-foot syndrome,
- ✓ Chemotherapy-induced peripheral neuropathy and
- ✓ Chemotherapy-induced alopecia.

The first Phase 2 clinical studies in cancer patients began in 2024 and are ongoing.

## References

1. Lambert KA, et all. Scalp hypothermia to reduce chemotherapy-induced alopecia: A systematic review and meta-analysis. Gynecol Oncol. 2024 Sep;188:71-80.
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3. Lacouture ME, et all; ESMO Guidelines Committee. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. Ann Oncol. 2021 Feb;32(2):157-170.