# Optimal dose finding of TRPM8 agonist for antipruritic therapy: a randomized controlled trial

**Learning Objective: To determine the optimal concentration of TRPM8 agonist cream (Cryosim-1) that effectively reduces chronic pruritus while maintaining favorable skin tolerability.**

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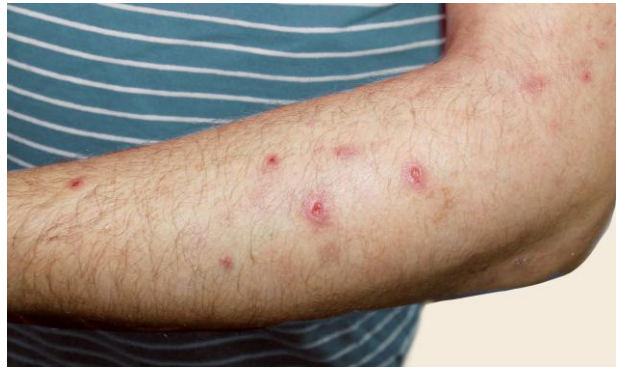
# Introduction

## Chronic Prurigo

## Prurigo Nodularis (PN)

- Persistent pruritus >6 weeks + excoriated papules, nodules, plaques from repetitive scratching
- Clinical impact: Severe itch → sleep disturbance Psychological distress, reduced quality of life
- Pathophysiology: Complex neuro–immune circuits Histamine-independent mechanisms → distinct from acute pruritus

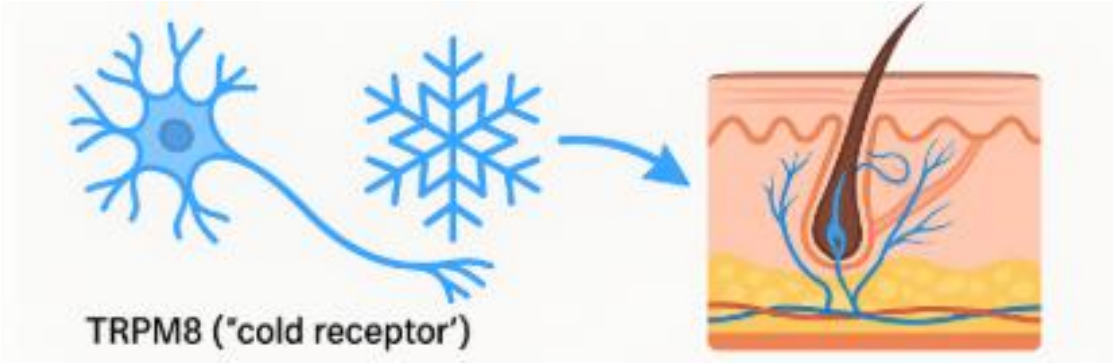


## Current Treatments and Limitations

- **Available therapies**
  - Topical: corticosteroids, calcineurin inhibitors
  - Systemic: immunosuppressants, neuromodulators, biologics
- **Recent advances**
  - FDA approval: Dupilumab, Nemolizumab → 56–60% response in trials
- **Remaining challenges**
  - Delayed onset of action
  - High cost
  - Ongoing need for topical or adjunctive options

## TRPM8 Channel and Cryosim-1

- **TRPM8 ("cold receptor")**
  - Induces cooling sensation → counteracts itch via competing neural pathways
- **Cryosim-1 features**
  - Selective TRPM8 agonist, cooling without changing skin temperature
  - 1.5% gel: demonstrated antipruritic efficacy (Lee et al.)
  - Limitation: transient irritation on sensitive skin
- **Improvement strategy**
  - Developed low-concentration creams (0.1%, 0.5%) with moisturizing base



# Objective

## Aims

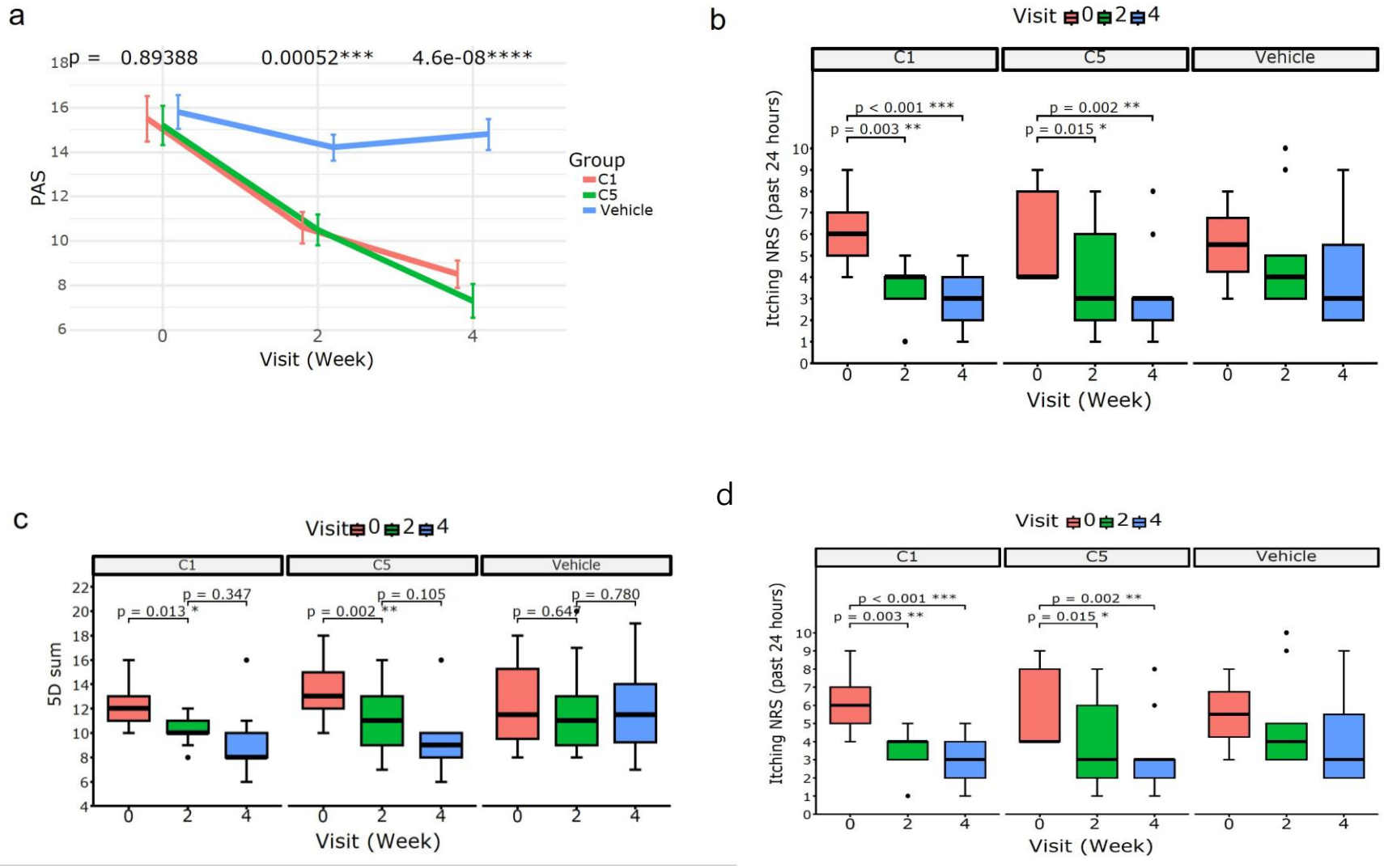
- Evaluate **efficacy and safety** of low-dose Cryosim-1 cream (0.1%, 0.5%) vs. vehicle control
- Identify **optimal concentration** for daily long-term use

### Subject population characteristics

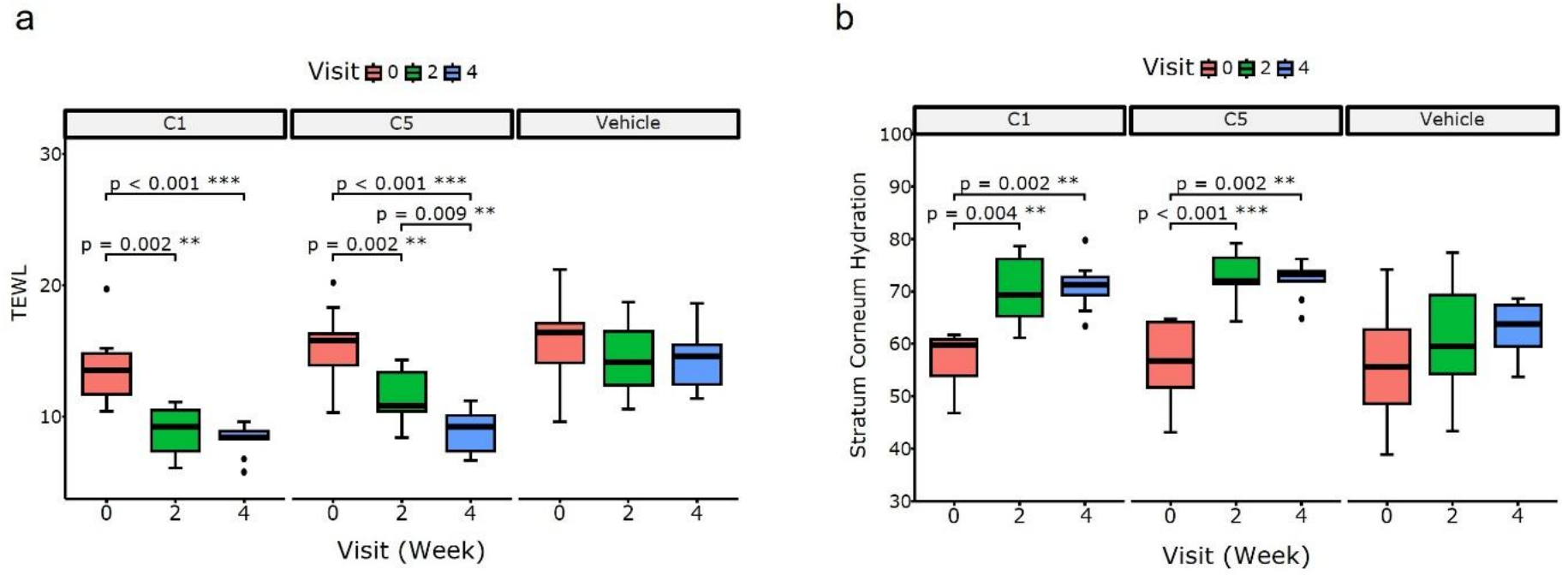
| Characteristic | Vehicle (n=10) | 0.1% Cryosim-1 (n=10) | 0.5% Cryosim-1 (n=10) | p-value |
|---|---|---|---|---|
| Age (years) | 48.5±14.2 | 46.9±13.6 | 48.0±14.3 | 0.952 |
| Sex (M/F) | 4/6 | 4/6 | 4/6 | 1.000 |
| 24-hour itch NRS | 6.1±1.5 | 6.2±1.5 | 5.7±1.6 | 0.789 |
| TEWL (g/m²/hr) | 15.5±2.9 | 14.3±3.1 | 15.8±3.0 | 0.701 |
| SCH (A.U.) | 55.7±7.3 | 58.1±7.0 | 57.3±7.1 | 0.854 |
| DLQI | 9.1±7.2 | 7.8±3.2 | 9.3±4.8 | 0.723 |
| 5D Itch Scale | 12.0±2.5 | 12.2±2.5 | 13.6±2.7 | 0.587 |
| PAS | 15.5±3.0 | 15.8±3.2 | 15.2±3.1 | 0.812 |

## Results

# Figure 1. Effects of Cryosim-1 on Itch Severity: Evidence from PAS, 24-Hour NRS, and 5D Itch Scale



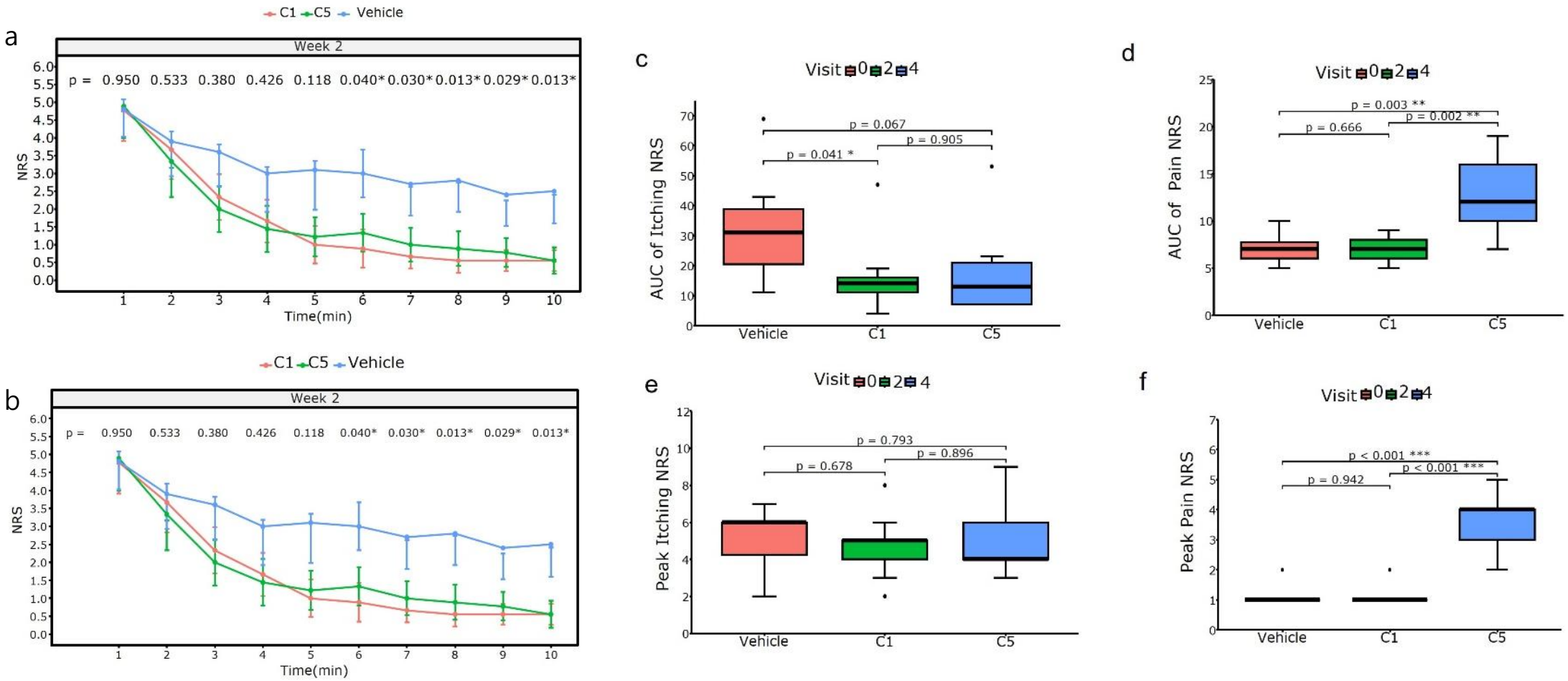
## Figure 2. Improvement in skin barrier function assessed by TEWL and stratum corneum hydration.




(a) TEWL (Transepidermal Water Loss) decreased significantly in both C1 and C5 groups from baseline to Week 4, indicating improved barrier integrity. No significant changes were noted in the vehicle group.

(b) Stratum Corneum Hydration (SCH) increased significantly in both active treatment groups, while no meaningful changes were observed in the vehicle group. *Error bars indicate variability; *p-values denote statistical significance.

# Figure 3. Immediate sensory response following a single application at Week 2.

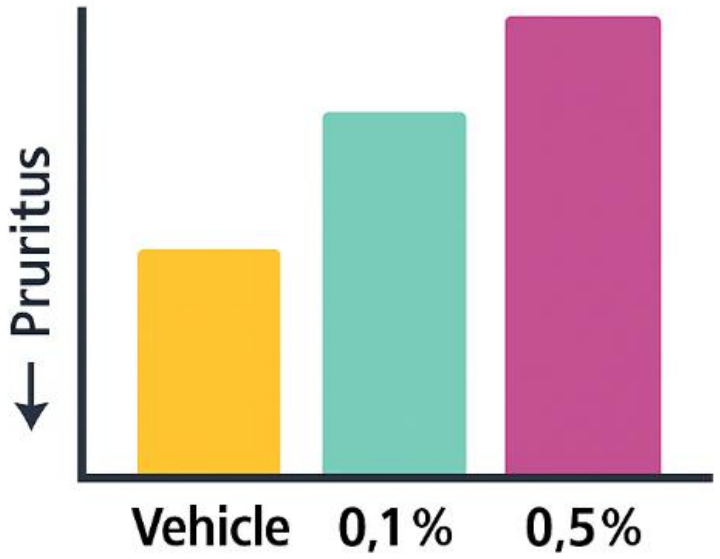



(a–b) Time-course of itch and pain scores over 10 minutes. (c–d) Area under the curve (AUC) of itch and pain.

(e–f) Peak NRS values. Cryosim-1 significantly reduced itch burden but 0.5% group showed increased stinging sensation.

## Conclusion

- Cryosim-1 creams at 0.1% and 0.5% effectively relieved pruritus and improved skin barrier function.
- Due to comparable efficacy and fewer adverse effects, the 0.1% concentration is considered the optimal and safer option.






**Conflict of Interest:** The authors declare no conflicts of interest.