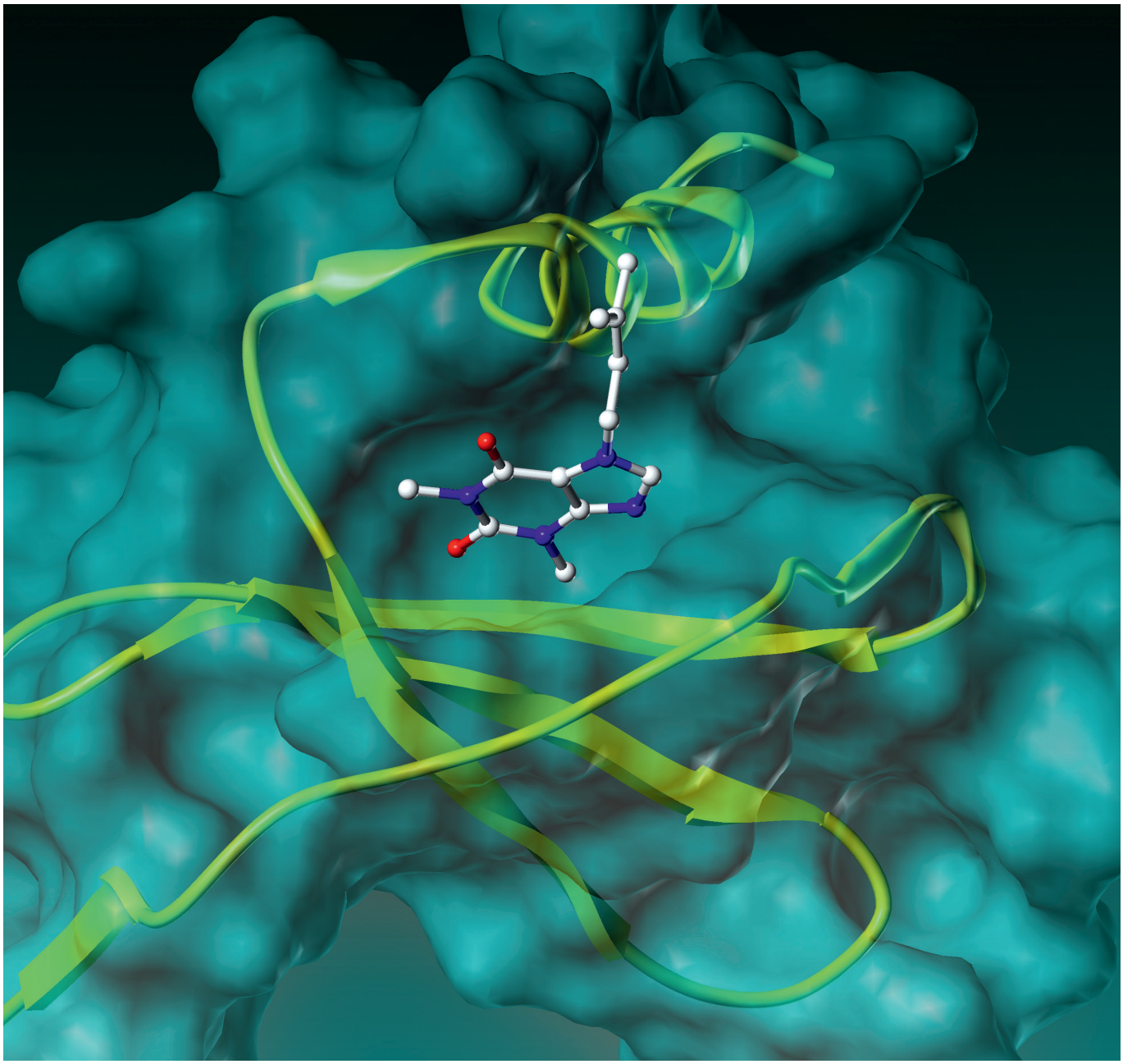
# ATOPHYLLINE®

## Bioinspired atopic skin care

**Management of atopic skin: Improves quality of life, pruritus, skin barrier function, erythema, moisturising.**



ATOPHYLLINE® has been patented - Greenpharma holds the exclusive exploitation rights.

# Scientific background

### NEUTRALIGAND: A BIO-INSPIRED STRATEGY

"In all things of Nature, there is something of the marvellous" (Aristotle). Take small animals such as ticks, what ingenuity it deploys to be under the radar of our immune defence! Evasins are one of it. They intercept chemokines that trigger inflammation in our immune system making the tick furtive: a big lesson from a small pest!

Bioinspired by chemokine-clearing molecules to escape the host immune system (Proudfoot *et al* PNAS 2003;100:1885-90), we used this original strategy to tackle atopic skin desorders and identified a natural derivative to neutralize a specific chemokine by a direct binding to it (Galzi *et al* Pharmacol Ther 2010;126:39-55).

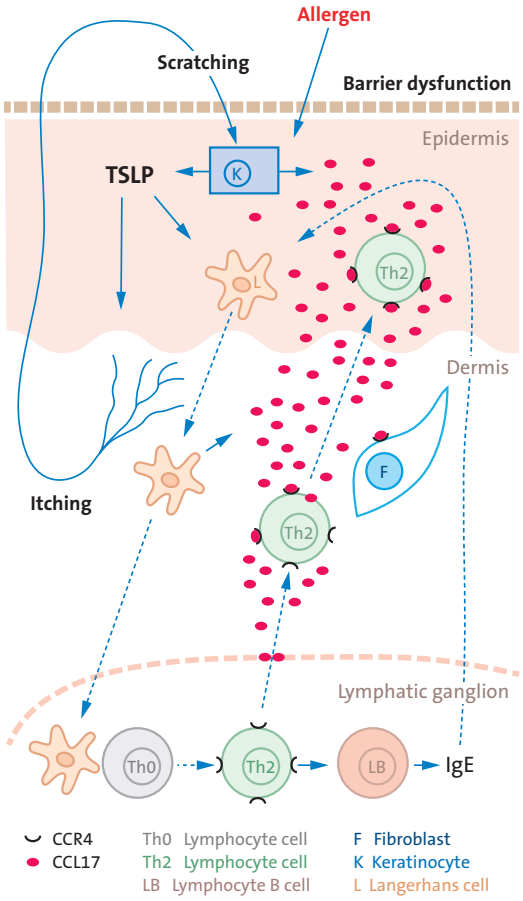
### CCL17 TARGET

CCL17 (or Thymus and Activation-Regulated Chemokine, TARC) is a bio-marker of atopic dermatitis (AD), its concentration is proportional to the severity of AD (Thijs *et al* Curr Opin Allergy Clin Immunol 2015;5:453-60).

CCL17 is a chemokine produced by dendritic cells in response to keratinocytes and inflammatory cells in skin atopic sites (Bieber NEJM 2008;358:1483-94) after contact with allergens.

CCL17 attracts Th2 cells, eosinophils and dendritic cells which possess CCR4 receptor at their surface, that amplifies and sustains the allergic response (Perros *et al* Allergy 2009;64:995-1002).

**Atophylline® was identified as a CCL17 neutraligand (Abboud *et al* Sci. Rep. 2015;5:14746).**

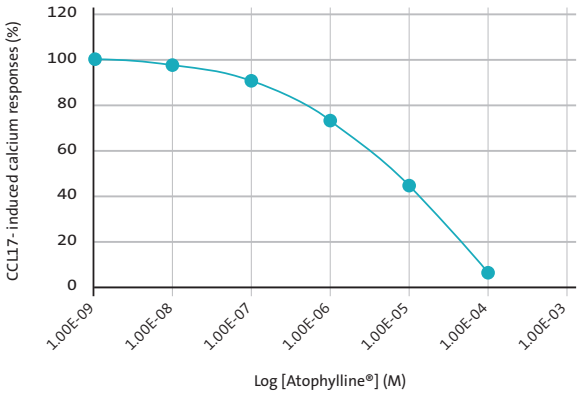



**Vicious circles of AD based on CCL17.**

## *In vitro* intracellular effect of Atophylline® on CCL17-CCR4

On HEK-293 cell line expressing CCR4.
The activation of CCR4 by CCL17 (5nM) induces intracellular calcium responses.

**Atophylline® inhibits dose-dependently the CCL17–CCR4 interaction.**



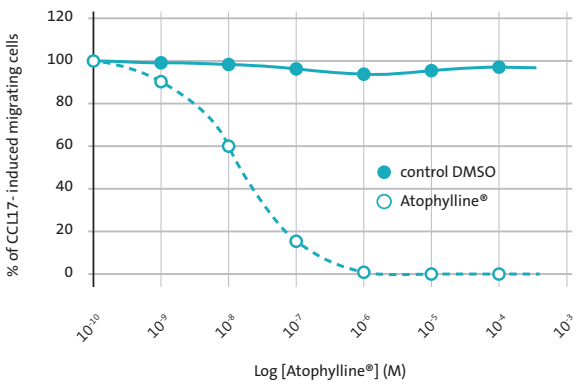

## *In vitro* intercellular effect of Atophylline® on CCL17-CCR4

On T- cell line (HUT78) expressing CCR4 and labelled with calcein AM, cell dye.

In a two compartment Transwell system.

The activation of CCR4 by CCL17 (3nM) induces cell migration responses.

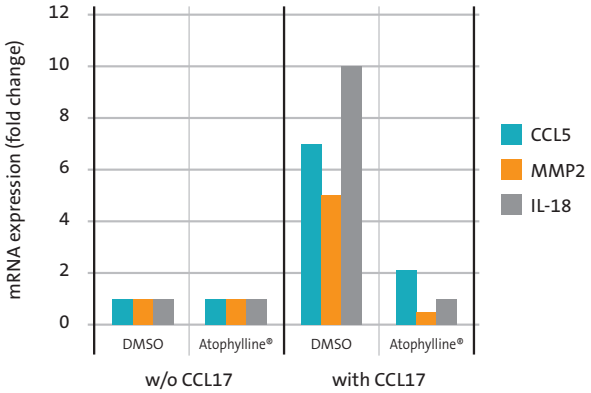
**Atophylline® inhibits dose-dependently the migration of T cells.**



# *In vitro* effect on CCL17 induced genes

On keratinocytes HaCat cell line.
Induction: 100 ng/ml CCL17.
10 µM Atophylline®.
Expression MMP-2, IL-18 and CCL5 measured by RT-PCR.

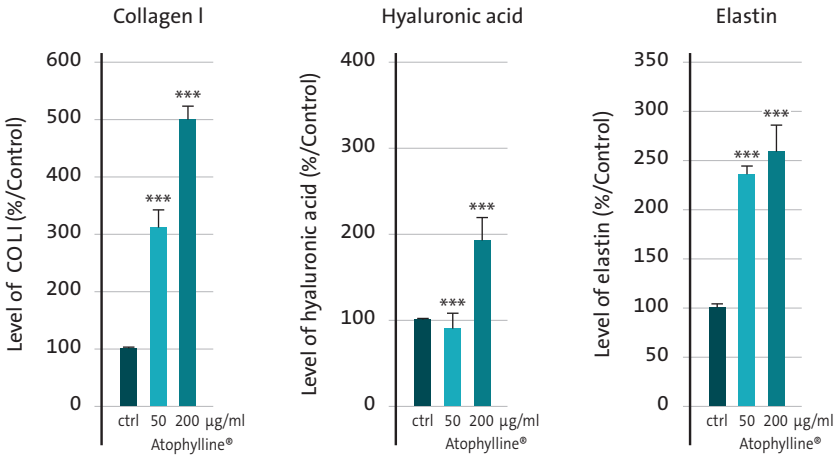
CCL5 is a chemo-attractant for T cells, eosinophils, and basophils into inflammatory sites.
MMP2 is a protease involved in the breakdown of extracellular matrix.
IL-18 is a mediator of the Th2 response and contributes to the development of atopic dermatitis skin lesion (Konishi *et al* PNAS 2002;99(17):11340-5).




## Atophylline® inhibits the expression of atopic dermatitis contribution genes.

# *In vitro* effect on the main component of extracellular matrix

On human normal fibroblasts.
Atophylline® at 50 µg/ml (0.005%) and 200 µg/ml (0.02%).
48h of treatment.
Collagen I, hyaluronic acid and elastin were measured by ELISA and normalised by the quantity of protein.




***p<0.001 versus Control

## Atophylline® significantly stimulates the synthesis of collagen, elastin and hyaluronic acid for the extracellular matrix regeneration.

# Safety studies

Skin irritation: non irritating, "Dermatologically tested".

Skin sensitization (Marzulli-Maibach): non irritating, hypoallergenic.

Occular irritation (Het Cam test): practically non irritant.

Genotoxicity (Ames test): No mutagenicity.

Phototoxicity (3T3 NRU PT): does not show a predictive phototoxic potential.

**Formulation:**
Add Atophylline® in premix with glycol or propanediol at the beginning of the process in one of the phase before emulsifying or during cooling process.
Atophylline® can be heated for a short time at 80°C.

# Technical data

INCI name: Isopentenyltheophylline
CAS No: 374708-38-0
Use concentration: 0.1% - 0.5%
Aspect : white powder

| Solubility in glycols and propanediol | 3% | 1% |
|---|---|---|
| Glycerin | Insoluble | Insoluble |
| Caprylic / Capric Triglyceride | insoluble | partially soluble |
| Propanediol | partially soluble | soluble |
| Butylene Glycol | partially soluble | soluble |
| Pentylene Glycol | soluble | soluble |

# Clinical trial on the restoration of atopic skin

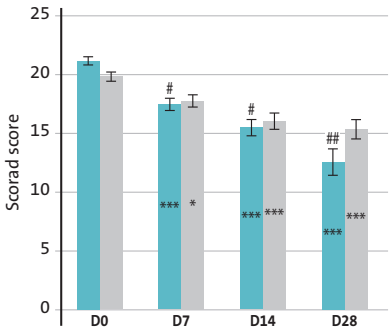
On 2 groups of 22 volunteers with mild-to-moderate atopic dermatitis treated with Atophylline® vs. Placebo.

Twice daily application on skin during 28 days.

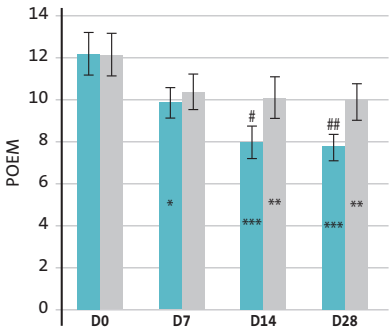
Active product:
Atophylline® **0.44% -** Glycerin **4.56%**.

Placebo: Glycerin **4.56%**.

SCORAD

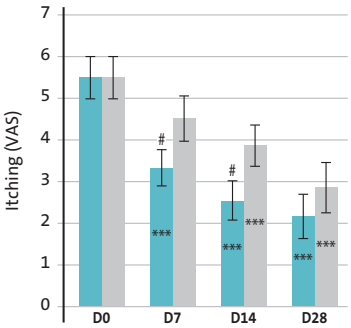



POEM

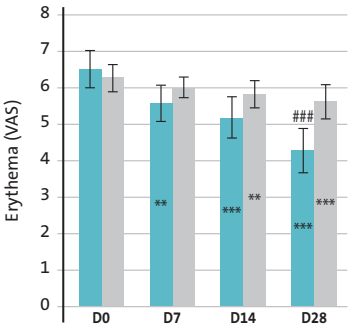



## Atophylline® significantly improves atopic skin symptoms and quality of life.

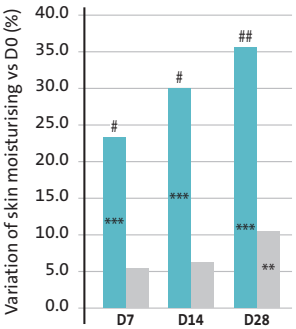
Itching



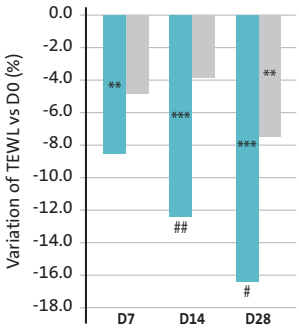

Skin inflammation




Corneometry




Skin barrier function




ATOPHYLLINE® PLACEBO

*p<0.05 **p<0.01 ***p<0.001 vs. D0

#p<0.05 ##p<0.01 ###p<0.001 vs. placebo

## Atophylline® significantly reduces the pruritus from D7 and the skin inflammation. Atophylline® significantly improves the skin hydration and the skin barrier function.

# Self evaluation of efficacy

| | Positive answers |
|---|---|
| The skin is more hydrated: | 86% |
| The skin is less dry and desquamated: | 90% |
| The skin is less reddened: | 90% |
| The skin is smoother: | 90% |
| The skin is softer: | 86% |
| The skin is more tonic and elastic: | 81% |
| The product soothes the skin: | 95% |
| The product provides comfort and relief to the skin: | 95% |

| | Positive answers |
|---|---|
| The product improves pinching/itching sensations: | 86% |
| The product avoids the sensation of tightness after use: | 95% |
| The sensation of roughness on the skin is decreased after use: | 86% |
| I perceived the repairing effect of the product: | 90% |
| The atopic dermatitis affected area is reduced by the use of the product: | 81% |
| Does the skin appear healthier ? | 86% |
| Globally, do you feel better in regards of the related effects of the atopic dermatitis ? | 81% |

## Atophylline® is highly approved by the users.

**GREENPHARMA SAS** 3, allée du titane - 45100 Orléans, FRANCE - Tel : +33 238 259 980 - Fax : +33 238 259 965
Société par Actions simplifiée au capital de 37 000€ - 433 756 269 000 26 RCS ORLEANS, APE 7211 Z (ORLEANS 2002 B 369) - TVA FR 45 433 756 269
info@greenpharma.com - www.greenpharma.com - linkedin.com/company/greenpharma