# CUPS. New contribution to plaque psoriasis treatment

ASAC pharma

Barcelona, 14 de marzo de 2012

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## 1. The Company

# ASAC Pharma

## Alicante (Spain)

## Company Profile

| | |
|---|---|
| Area | Human Health. Mainly Prescription Only Medicines |
| Products | POM´s (Dermatology, Traumatology, Otolaringology, General Medicine)<br>- Allergy Taylor Made Vaccines. Allergy Diagnostics, Allergen extracts. Bacterial vaccines.<br>- Cosmetics.<br>- Medicinal Plant Extracts. |
| Group | 5 national companies.<br>6 international companies (Brazil, Mexico, Guatemala, Morocco, Algeria, Senegal) |
| Staff | 245 employees worldwide. Over 25% graduate. |

## Company Profile

| | |
|---|---|
| Turnover group | 26 millions €. |
| R&D | - Development of medicaments, allergy vaccines, cosmetic products.<br>- Investment 5% of the sales. |
| Public subvention | - CDTI (Centre for the Development of Industrial Technology).<br>- IMPIVA<br>- Spanish Ministry of Industry . |

# The Product.

Target Indications:

New therapeutic concept for the treatment of Psoriasis and other inflammatory hiperproliferative diseases.

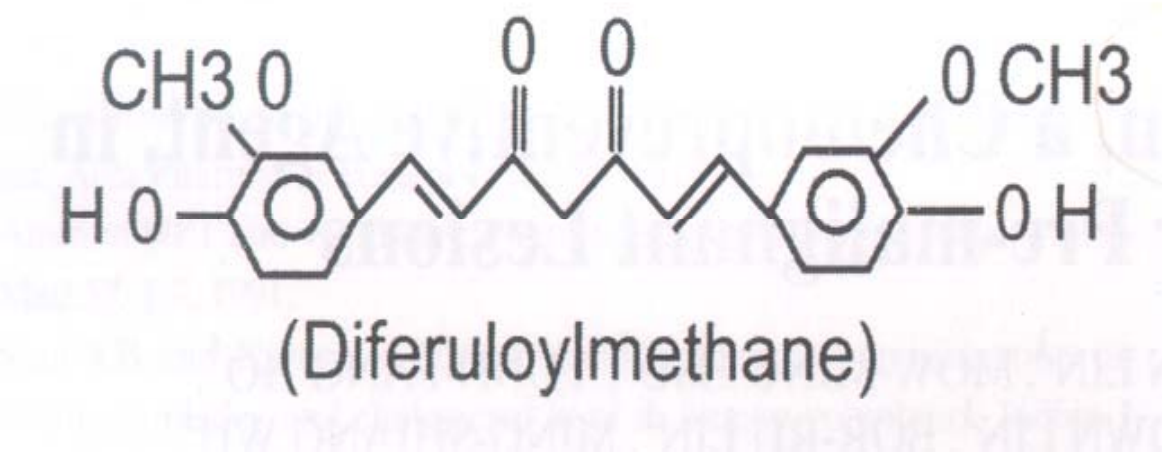
# The Product.

## Target Indications: PSORIASIS

Psoriasis is a chronic, inflammatory and proliferative disease of the skin, affecting 1.5-3.0% of the global population.
The most prevalent form , plaque psoriasis (*psoriasis vulgaris*), is marked by the appearance of skin lesions in the form of scaly, red plaques. Psoriasis is caused by the overproduction and immature migration of keratinocytes to the surface to the skin.

# The Product.

## Curcumin



## **The Product.** Innovative mechanisms of action:

**Low Concentration of Curcumin Induce Growth Arrest and Apoptosis in Skin Keratinocytes Only in Combination with UVA or Visible Ligth.**
Dujic J, Kippenberger S, Hoffmann S, Ramirez-Bosca A, Díaz-Alperi J, Bereiter-Hann J, Kaufmann R and Bernd A.
*Journal of Investigative Dermatology (2007)* ***127****, 1992-2000*
*J.W. Goethe University,Frankfurt – ASAC Pharma*

**Curcumin in combination with visible light inhibits tumor growth in a xenograf tumor model.**
Dujic J, Kippenberger S, Hoffmann S, Ramirez-Bosca A, Díaz-Alperi J, Bereiter-Hann J, Kaufmann R and Bernd A and Hofmann Mathias.
*International Journal of Cancer:* ***124****, 1422-1428 (2009)*
*J.W. Goethe University, Frankfurt – ASAC Pharma*

# **The Product.** Innovative mechanisms of action.

**Test model:** HaCaT-Keratinocytes

- **Cellular Uptake of Curcumin:** Rapid penetration, maximum after 45 min.

- **Intracellular distribution**: Perinuclear distribution in the cytoplasm. Curcumin do not enter the nucleus.

- **Curcumin combined with UVA or visible light inhibits cell proliferation:** HaCaT keratinocytes, primary fibroblast, melanocytes, melanoma cells (MMLI, G-361), and epithelial carcinoma A-431cells.

- **Curcumin combined with UVA did not induce toxic membrane damages.** Cell membrane integrity was not changed by curcumin alone and with UVA.

# **The Product.** Innovative mechanisms of action.

**Test model:** HaCaT-Keratinocytes

**- Curcumin combined with UVA induced apoptotic bodies.**

We found apoptotic nuclei in cells 24 hours after treatment with curcumin(1mcg/ml)+ UVA.

**- Curcumin combined with UVA or visible light induced cytochrome *c* release.**

**- Curcumin combined with UVA activated caspases 9 and 8.**

**- Curcumin combined with UVA or visible light inhibited NFkB.**

# The Product. Innovative mechanisms of action. Pilot Clinical Trial 1

**EFFICACY PILOT CLINICAL TRIAL, PHASE IV,NON-CONTROLLED, OF 600 MG/DAY OF TURMERIC EXTRACT STANDARDIZED TO 12% (72 MG CURCUMIN) IN CURCUMINE + PHOTOTHERAPY UVA ON THE TREATMENT OF PATIENTS WITH CHRONIC MODERATE TO SEVERE PLAQUE PSORIASIS.**

**EudraCT 2006-003395-35**

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

Treatment was administered up to 8 weeks or until the Psoriasis Area and Severity Index (PASI) reduction >90% from baseline was achieved. The study was conducted in 22 patients of both sexes.

Patients were seen at a screening visit and then at baseline and weeks 0, 1, 2, 3, 4, 5, 6, 7, 8, and 10 for safety and efficacy evaluations.

Maximum of 2 phototherapy UVA sessions per week.

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

## Efficacy endpoints:

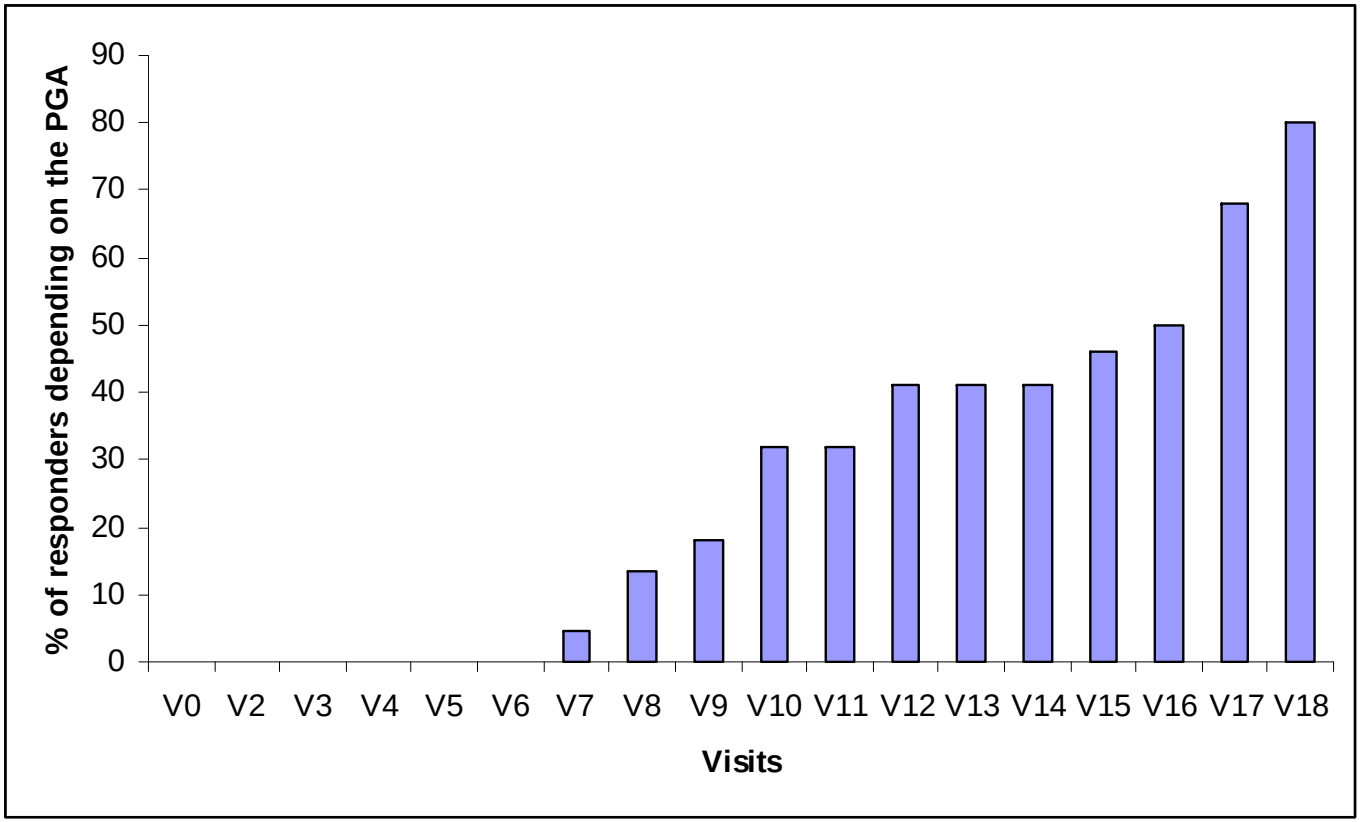
Two primary assessment variables were used in order to establish the percentage of responders, following the EMEA criteria (EMEA 2004):

a) Physician's global assessment (PGA), qualifying patients with a degree of "almost clear" or "clear" as responders.

b) Number of patients whose Psoriasis Area and Severity Index (PASI) improved more than 75% from baseline (PASI > 75%) at each visit. The time course of response was calculated as the time to achieve a PASI reduction > 75%.

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

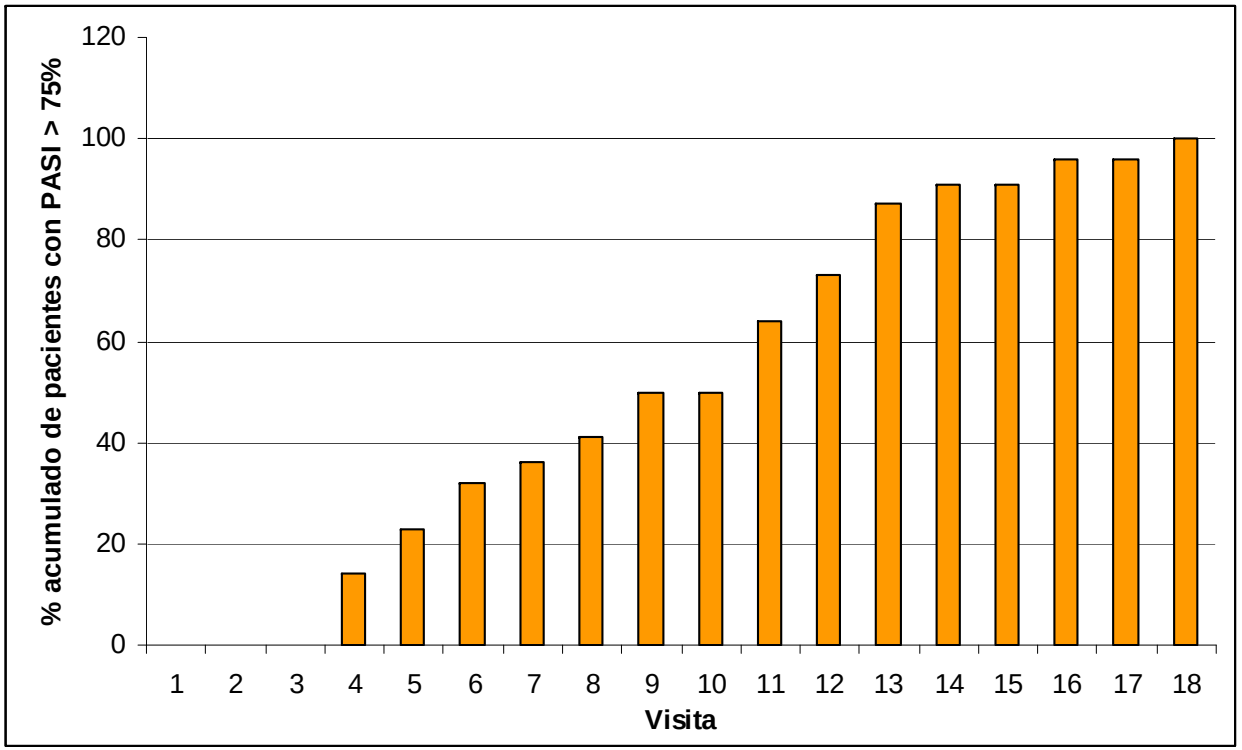
## RESULTS PGA




Cumulative percentage of patients (80%) achieving a PGA value of “almost clear” or “clear” at each visit (visit 18 = week 10)

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

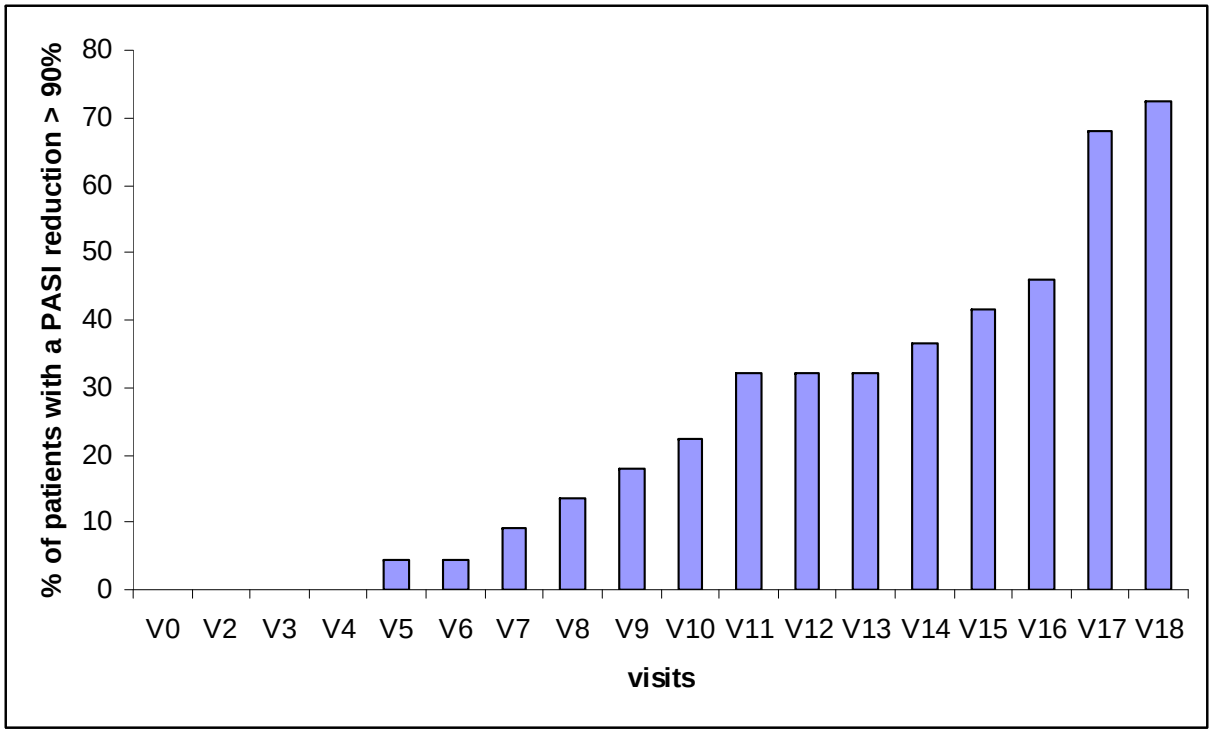
## RESULTS PASI > 75




Cumulative percentage of patients (100%) achieving a reduction > 75% from baseline PASI (PASI > 75%) in the successive visits of the study (visit 18= week 10)

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

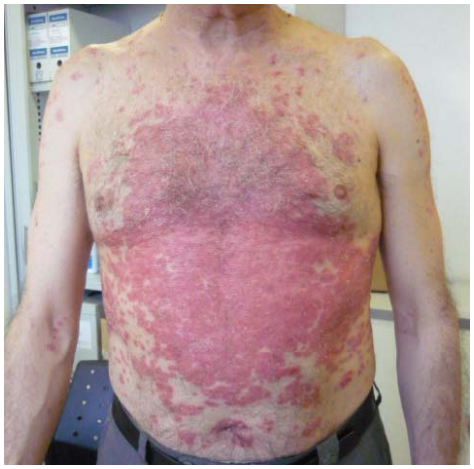
## RESULTS PASI > 90



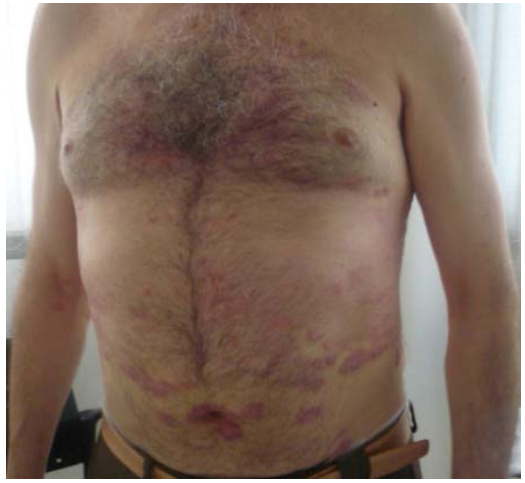

Cumulative percentage of patients (75%) achieving a reduction > 90% from baseline PASI (PASI > 90%) in the successive visits of the study (visit 18= week 10)

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

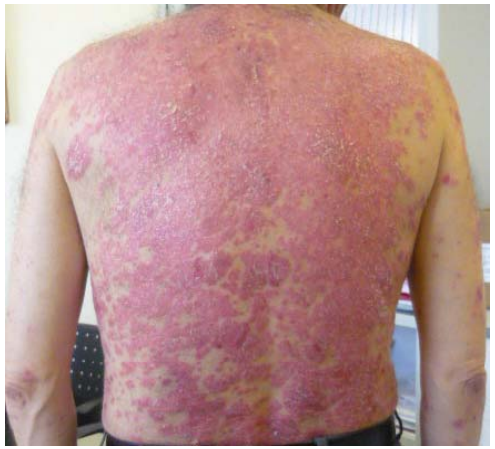
## Example of Psoriasis Improvement in a Patient

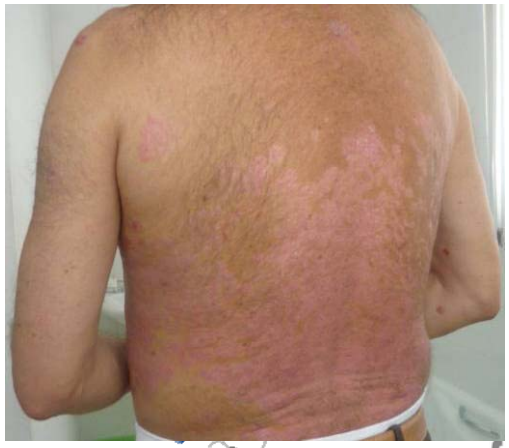


WEEK 0



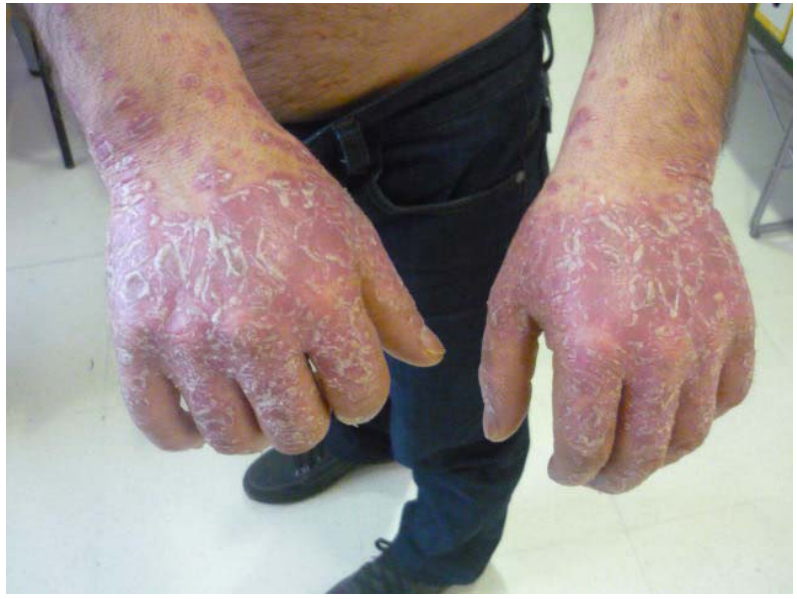
WEEK 10



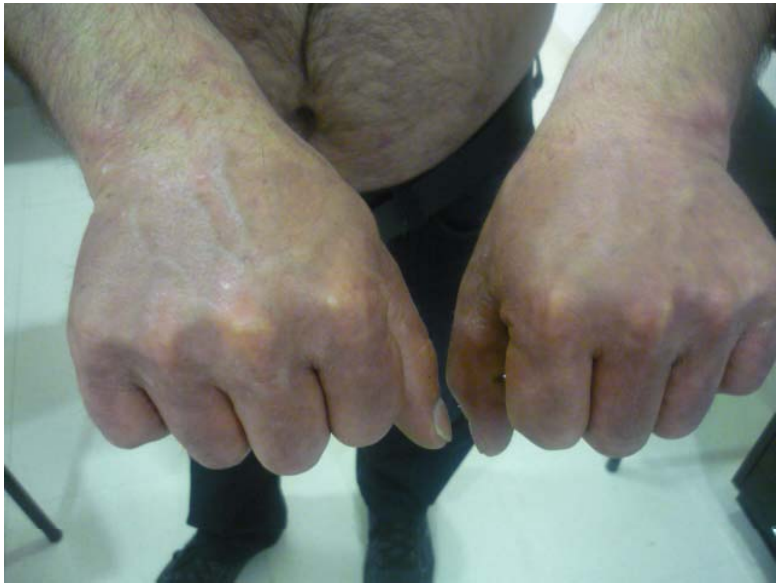


# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

## Example of Psoriasis Improvement in a Patient



WEEK 0



WEEK 10

# The Product. Innovative mechanisms of action. Pilot Clinical Trial I

## ADVERSE EVENTS.

The digestive adverse events, meteorism and gastric acidity, attributable to the treatment, could be related according to the investigators to the great amount of ingested tablets (2 tablets 3 times to the day).

# The Product. Innovative mechanisms of action. Pilot Clinical Trial 2

***A PHASE IV, UNICENTER, DOUBLE-BLIND, CONTROLLED, PILOT CLINICAL TRIAL ON THE EFFECTS OF TURMERIC EXTRACT CENTRUM® STANDARDIZED AT 12% IN CURCUMIN + LOCAL PHOTOTHERAPY WITH BLUE LIGHT (REAL OR SIMULATED) AND UVA PHOTOTHERAPY IN THE REST OF THE BODY , IN ADULTS WITH AT LEAST A 6 MONTHS HISTORY OF MODERATE TO SEVERE PLAQUE PSORIASIS***

***EudraCT 2008-006420-65***

# The Product. Innovative mechanisms of action. Pilot Clinical Trial II

**Primary Objectives:**

a) **To determine the percentage of responders to curcumin + local phototherapy with blue light versus the absence of blue light in the area (PGA).**

b) **Percentage of responders to curcumin + UVA phototherapy (PASI >75).**

# The Product. Innovative mechanisms of action.

## Pilot Clinical Trial II

### BLUE LIGHT LAMP

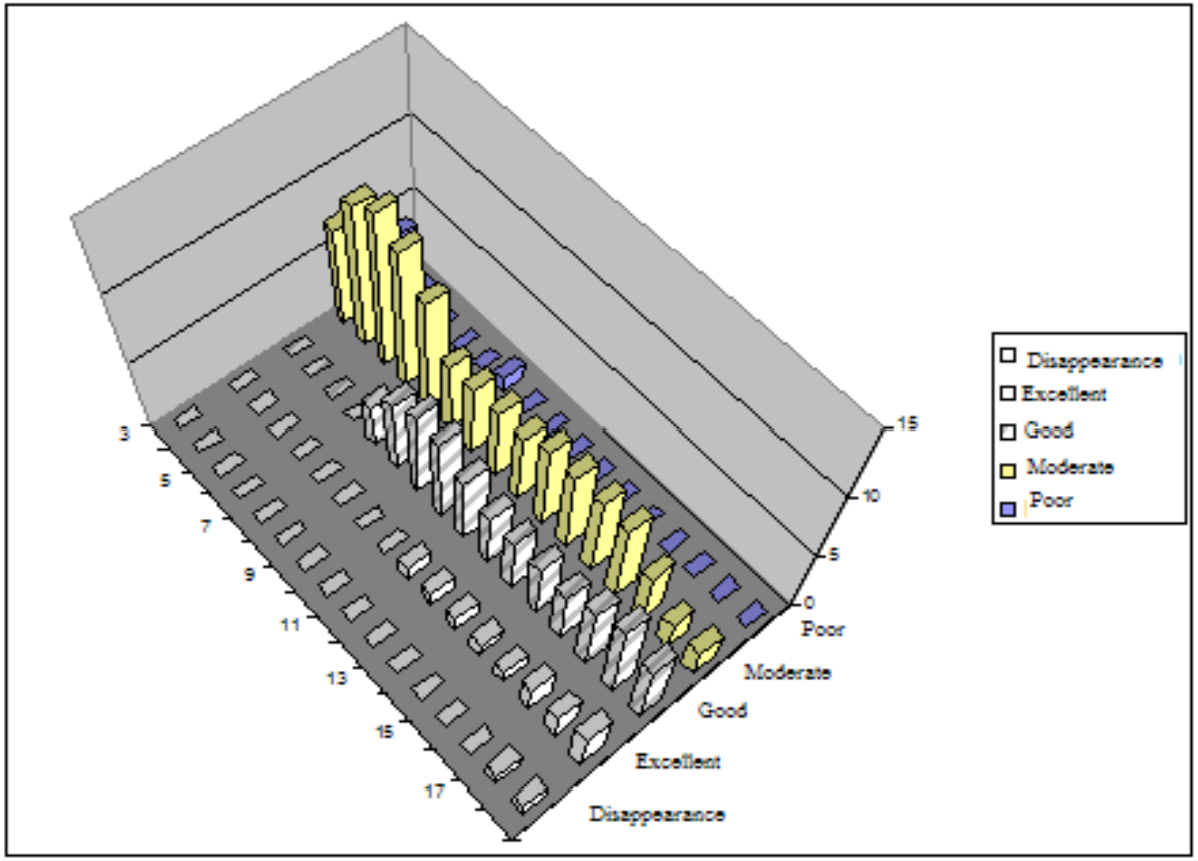
# The Product. Innovative mechanisms of action.

## Pilot Clinical Trial II
## RESULTS

20% of 10 patients that received simulated therapy were considered as *responders*, compared to 100% of the 11 patients treated with real therapy (0%). ***This difference is statistically significant (p = 0.001; two-sided Fisher's exact test).***

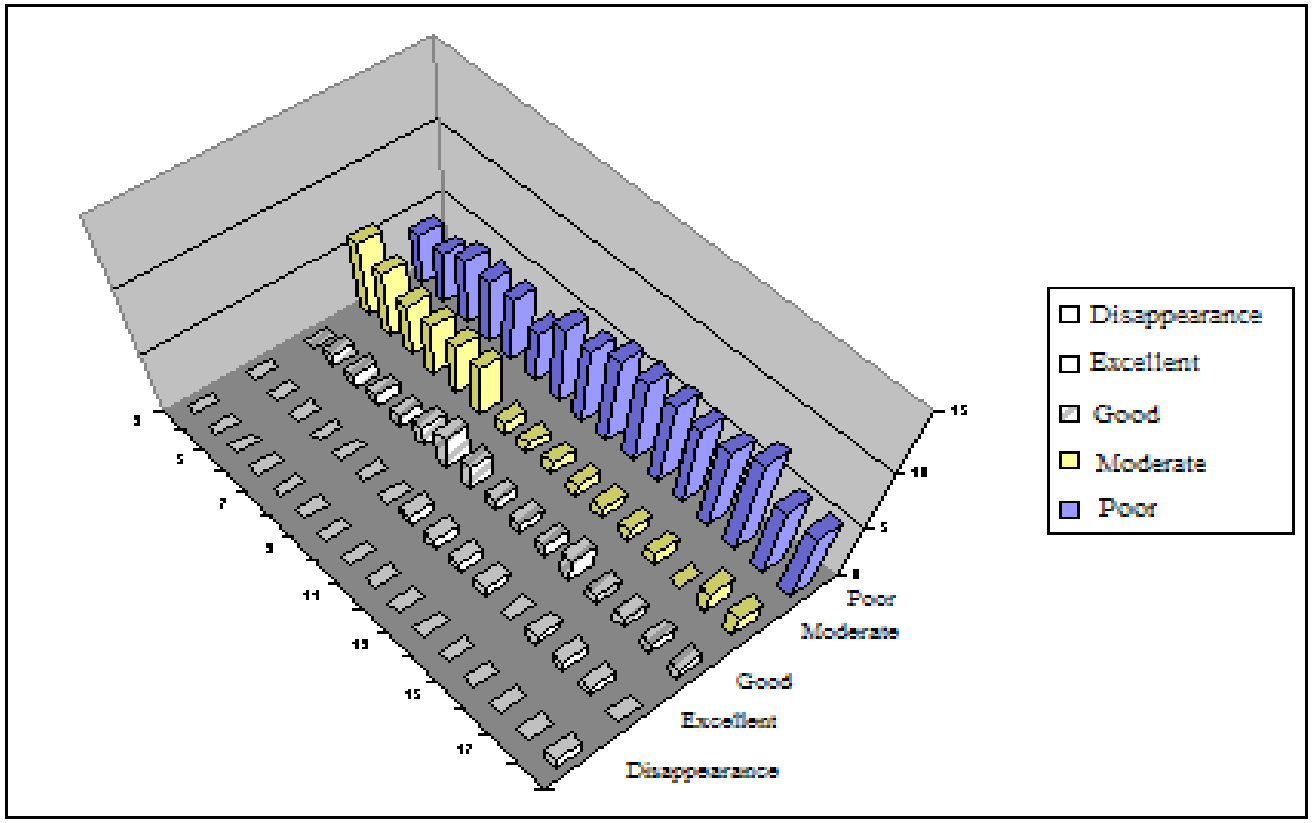
# The Product. Innovative mechanisms of action. Pilot Clinical Trial II

## RESULTS:Time distribution (per visit) of the response to real phototherapy with blue light in the target area by the PGA.



# The Product. Innovative mechanisms of action. Pilot Clinical Trial II

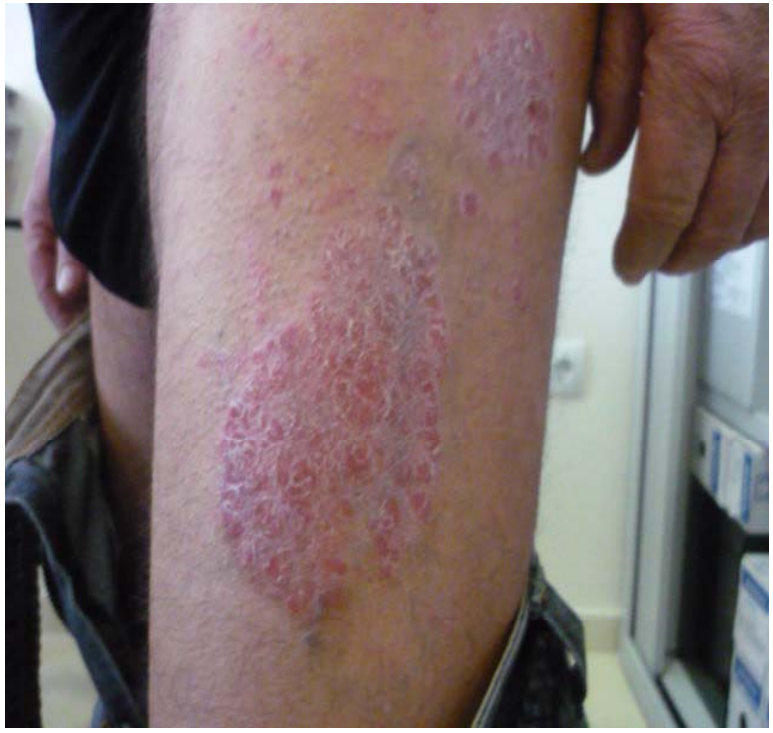
## RESULTS: Time distribution (per visit) of the response to simulated phototherapy with blue light in the target area by the PGA.



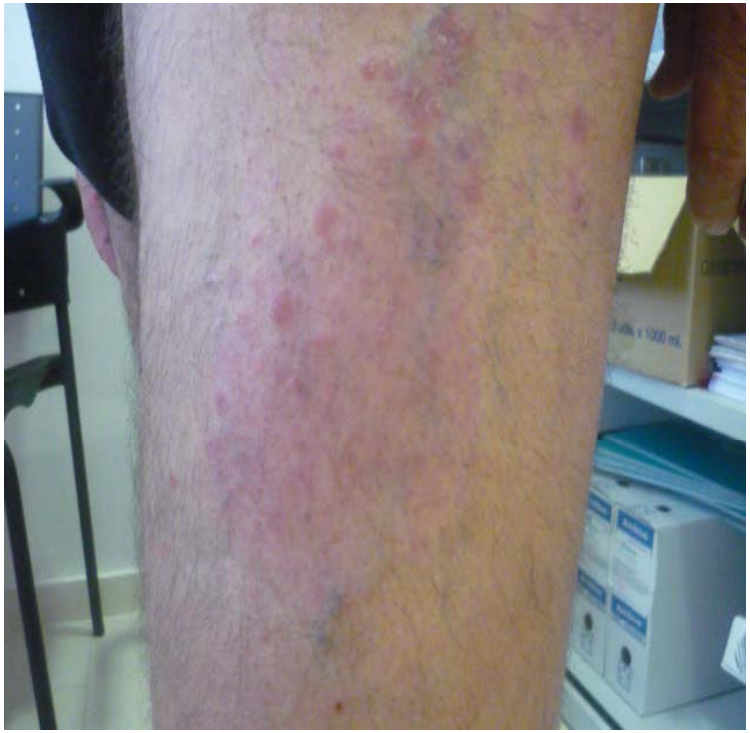
# The Product. Innovative mechanisms of action. Pilot Clinical Trial II

## RESULTS

Example of Psoriasis Improvement in a Patient treated (curcumin+blue light)



WEEK 0

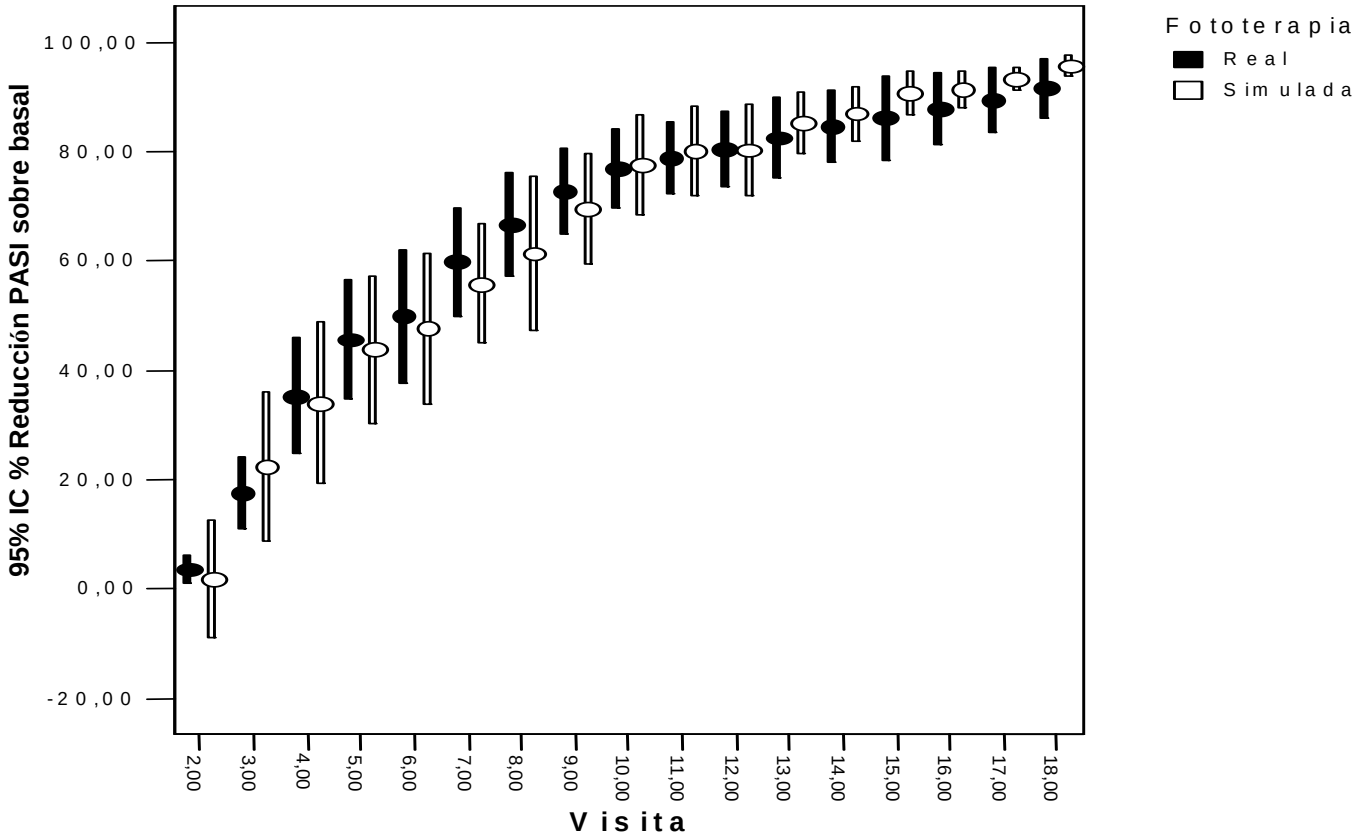


WEEK 10

# The Product. Innovative mechanisms of action. Pilot Clinical Trial II

## RESULTS

**Evolution over time of the percentage of PASI reduction compared to the score at the start of the study (95%CI) in both groups. The rest the body treated with curcumin+UVA**

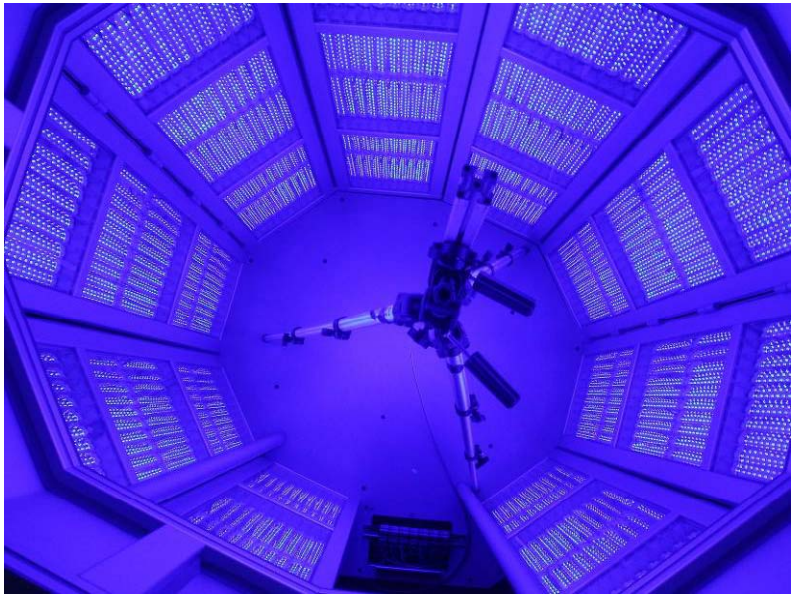


# The Product. Differential features facing the market.

| SYSTEMIC TREATMENTS TO MODERATE - SEVERE PLAQUE PSORIASIS | | | | | |
|---|---|---|---|---|---|
| | BIOLOGICS | | PUVA | CUPS + UVA | CUPS + BLUE LIGHT |
| Mechanism | TNF-α | IL-12, IL-23 | DNA aducts | Apoptosis | Apoptosis |
| Results: PASI 75% at 12 weeks | (347) 56,8% | (347) 73,8 % | (30) 80% | (43) 100% | (24) On going |
| Results:PASI 90% at 12 weeks | (347) 23,1% | (347) 44,7% | (30) ?????? | (43) 70% | (24) On going |
| Time until a new relapse. Severity | 1,8 months Severeplaque Psoriasis | 4,5 months Severeplaque Psoriasis | 7 months ModeratePlaque Psoriasis | 12 months Mild Plaque Psoriasis | |
| Cost | 8.976,78 € | 8.934,4 € | 1.800,0 € | 2.500,0 € | |
| Visits to Dr. | 6 | 4 | 36 | 18 | |

# The Product. Current status of development

## BLUE LIGHT CABINE PROTOTYPE



# The Product. Current status of development.

A PHASE IV, UNICENTER, OPEN, WITH BLINDED EVALUATION, PILOT CLINICAL TRIAL ON THE EFFECTS OF TURMERIC EXTRACT CENTRUM® STANDARDIZED AT 12% IN CURCUMIN + PHOTOTHERAPY WITH BLUE LIGHT VS. OXORALEN + PHOTOTHERAPY WITH UVA (PUVA) IN ADULTS WITH AT LEAST A 6-MONTHS HISTORY OF MODERATE TO SEVERE PLAQUE PSORIASIS.

EudraCT **2010-024158-13**

# The Product. Current status of development.

- Synthesis process of ASAC Curcumin. Medalchemy - Alicante University

- Drafting of the Drug Master File of API

## Next steeps:

- Pharmacotoxicological Profile of ASAC Curcumin.

- Galenic development.

- Phase I, Phase II and Phase III.

# The Product. IPR protection.

**Application International Number:** PCT/ES2008000787_

**International Publication Number:** WO2009080850

**Title:**
*Method for Increasing the Therapeutic Efficacy of Curcuminoids and Analogues.*

**Status:** The Patent is in Regional Phase.

**PCT Selected Countries:** European Unión, USA, Canada, Australia, Russia, Mexico, Brazil, Korea, Japan, China, South Africa, Morocco.

**Countries no PCT**: Argentina

# The Product. Pitfalls & Risks to be considered

**GLOBAL BUSINESS INTELLIGENCE – GBI *Research.***

**The Future of Dermatology Therapeutics, Analysis and Market Forecasts to 2016.**
**Publication Date: March 2010.**

- **Global Psoriasis Therapeutics Market:**

**- "For moderate to severe patients, any emerging drug with new targets, better efficacy and safety and a lower price will also cause an impact".**

**- "A product with disease modifying mechanisms providing a better safety profile and good efficacy is sure to achieve blockbuster drug status. Thus, there is a strong opportunity for any drug that offers better efficacy and safety than is provided by the current players.**

# **The Product.** Pitfalls & Risks to be considered

**GBI *Research.* The Future of Dermatology Therapeutics, Analysis and Market Forecasts to 2016.**

Products for psoriasis in the development pipeline are strong, 125 molecules in various phases of development.

**- 7 molecules in Phase III**
3 are biologics products and have identical mechanisms of action that current biological drugs.

**- 61 molecules in Phase II**
19 are biologics drugs, 7 of them have different mechanisms of action that current biological drugs.

- **31 molecules in Phase I.**

**- 26 molecules in Preclinical Phase.**

# **The Product.** Pitfalls & Risks to be considered

## CUPS.

- **Pharmacotoxicology profile**. Low risk.

- **Phase I.** Low risk.

- **Phase II.** Important step to confirm the high % of responder patients and minor adverse events found at the pilot clinical studies performed.

-**Two ways:**

Curcumin + Phototherapy UVA

Curcumin + Phototherapy Blue Light (better safety profile)

# Partnering Opportunities.

ASAC Pharma is open to consider all potential collaborations with the pharmaceutical industry.