Topical Solution of Cyclosporine for mild to moderate atopic dermatitis and psoriasis (Cyclatop)

spherium biomed®

Madrid, 15 de noviembre de 2016

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1. The Institution: Spherium Biomed

- Portfolio, clinical stage Biopharmaceutical company that sources its pipeline from academic research
- Lean, virtual business model
- No therapeutic focus, projects as stand alones
- Staff of 13, mostly PhDs with 10+ years industry experience
- Privately owned, major shareholder: Ferrer

Pipeline as of Nov. 2016

Therapeutics	Preclinical POC	Clinical POC
SP13004 Prevention and treatment of mucositis induced by cancer chemoradiotherapy		●
SP12006 OTC combination for moderate muscular pain.		●
SP14019 Topical treatment for psoriasis and atopic dermatitis		●
SP15016 Nephroprotector to prevent drug-induced Acute Kidney Injury		●
SP12054 Topical treatment for actinic keratosis	●	
SP12008 Biological for the treatment of Lupus and other auto-immune diseases.	●	
SP14037 Biological for the treatment of Amyotrophic Lateral Sclerosis (ALS).	●	
SP14040 New small molecule for cognitive impairment in Alzheimer's disease and Schizophrenia	●	
SP15028 Muscle atrophy and degeneration	●	

2. The product concept: topical formulation of cyclosporine for atopic dermatitis / psoriasis

Systemic Cyclosporine (calcineurine inhibitor as tacrolimus and pimecrolimus) approved for the temporary treatment of severe dermatological indications:

- **Atopic dermatitis (AD)**
- **Psoriasis**

Its use is limited for safety reasons (mainly nephrotoxicity)

KOL dermatologists state that a topical Cyclosporine formulation could be very useful to:

- **Reduce systemic exposure and related adverse effects.**
- **Increase therapeutic arsenal in atopic dermatitis and Psoriasis**
- **Reduce the use of topical corticosteroids**

The product: innovative aspects

Spherium has developed a **unique, proprietary topical** cyclosporine formulation:

- Proprietary formula IP protected.
- Established manufacturing method currently in **GMP pilot scale** with internationally recognized CMO.
- Analytical methods developed and specifications defined.
- **Stable** at least 12 months.
- COGS: Less than 10-15% of ex-factory prospective price.
- Topical solution (oil microemulsion), **administered with a spray** (no propellant gas)
- Differentiation aspects from other calcineurin inhibitors (burning, ease of use, onset) to be determined during clinical trials

Market outlook in Atopic Dermatitis

Disease

- Chronic or chronically relapsing inflammatory skin disease arising from a complex interrelationship of environmental, immunologic, genetic, and pharmacologic factors.

Prevalence

- 10–20% of children
- 1–3% of adults in developed countries
- In the United States has nearly tripled in the past thirty to forty years

Current treatment

- Basic therapy: emolients/moisturizers
- Induction therapy: topical corticosteroids (low acceptance in children) or topical calcineurin inhibitors (reported skin burning).
- Maintenance therapy: topical calcineurin inhibitors or systemic immunmodulators (only in adults).
- Need: drugs that effectively controls patients' pruritus.

Market size

- Topical segment global sales is about $1.300 M.
- Systemic Cyclosporine worldwide sales are around $300M.

Market outlook in psoriasis – Topical products

Disease

- Psoriasis is an incurable genetic, systemic, inflammatory, and chronic skin disorder Psoriasis is a chronic, immune-mediated inflammatory skin disease. Due to its remitting and relapsing nature, psoriasis presents a global public health concern.

Prevalence

- With an overall prevalence of 2–3% worldwide (Perera et al., 2012).
- The highest number of cases was in the mild category followed by moderate in all the markets.

Current treatment

Market size

- For mild or moderate disease, patients may start with topical therapies, which may be over-the-counter (OTC) or prescription products. The use of corticosteroids, vitamin D analogues, keratinolytics, tazarotene, anthracyclines, and coal tar are included in this group.
- Current sales of topical products are around $ 1.500 M, ($1.200 M in the US)

Development status preclinical

***Ex vivo* data**

- Distribution to different skin layers in a 24hs Franz cell penetration test using healthy human skin and radioactive CsA shows cyclosporine levels to reach at least 200X the expected IC50 concentration.

***In vivo* data**

- Proven dose dependent efficacy in animal model for atopic dermatitis. Effect comparable to current gold standard topical treatment.

Safety data

- Drug already approved in the indication for systemic administration.
- Minimal systemic exposure due to topical administration
- Good tolerance in 4 Week dermal tolerance study in minipigs
- No dermal sensitization (Buehler test in guinea pig).

Preclinical efficacy in Atopic Dermatitis

Challenge
10% DNFB (100µl)
ears & groins

Day 1

Challenge
2% DNFB (100µl)
ears

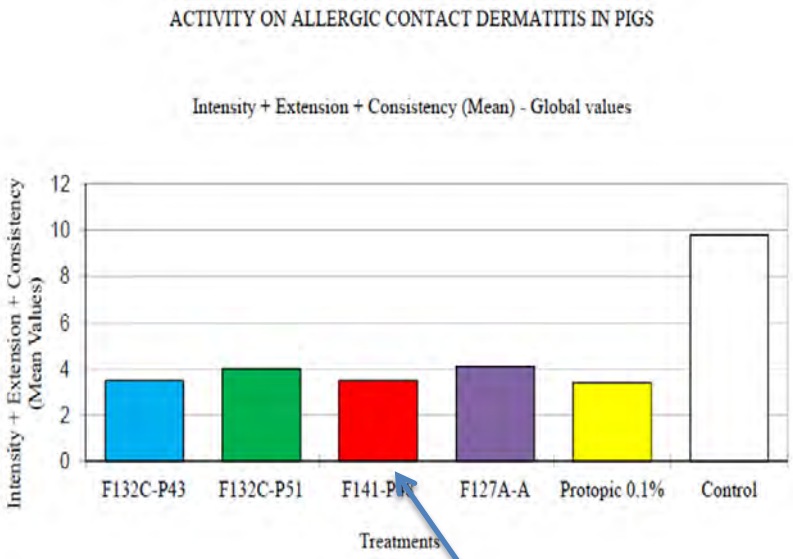
Day 4

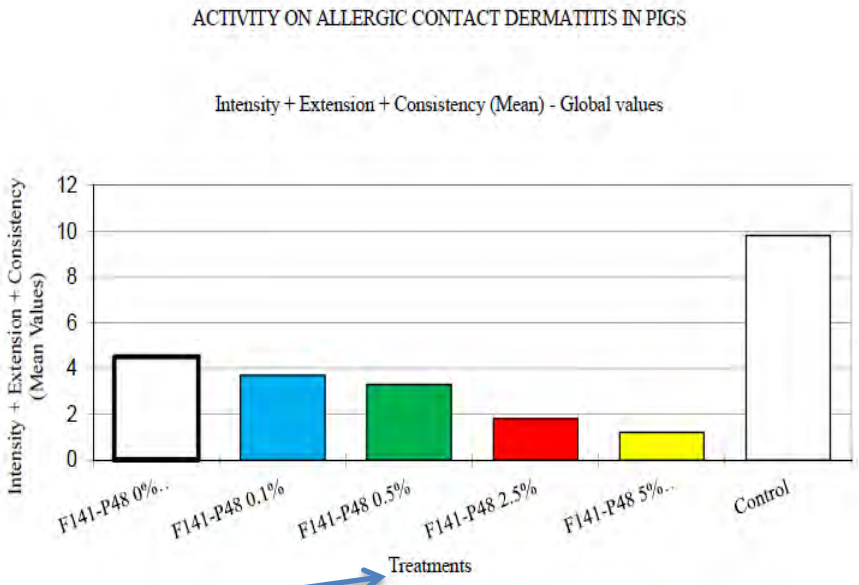
Challenge
1% DNFB (20µl)
6 sites on each back
+
Treatment
630mg
0.5 and 6h

Day 12

Evaluation of the treated areas

Day 13





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Development status clinical: phase IIa

- POC clinical trial in Atopic Dermatitis patients started in October 2016 in 8 Spanish clinical centers. **EudraCT: 2016-000467-16.** *5 adult patients under treatment as of November 15th*
- The study is designed as randomized, double-blind and vehicle-controlled study with intra-individual (left-right) comparison of treatments.
- Mild to moderate atopic dermatitis.
- 36 patients in three age cohorts of patients: 2 to 12 years , 12 to 18 years and 18 to 75 years old.
- Duration 28 days. BID application (twice a day).
- End points:
  - Absolute change from baseline of Eczema Area and Severity Index (EASI)
  - IGA and ADSI scores of the treated body area (CsA vs Vehicle control placebo)

Further development of topical cyclosporine

- Preclinical testing to confirm topical safety:
  - ✓ Phototoxicity (both in EU and USA)
  - ✓ Additional FDA studies: Chronic study minipig, ADME after dermal administration, possible additional: carcinogenesis in rat (to be confirmed).

- Clinical testing (per indication):
  - ✓ Safety studies
  - ✓ 1 Dose finding trial
  - ✓ 2 Phase III Efficacy trials

  Expected cost: about $20 to $30M (less for the second indication)

- Total investment to NDA filing about $30 to $40 M (including CMC development)

- Time to market: 5-6 years (no less than 4 years assuming full speed, parallel development strategy)

Intellectual Property

- The project is protected by 2 patent filings:

  - IP filing claiming the general formulation system:

    “NANOPARTICLES COMPRISING ESTERS OF POLY (METHYL VINYL ETHER-CO-MALEIC ANHYDRIDE) AND USES THEREOF“ nº WO 2012/140252 A1

    Priority April 15^{h} 2011

    National extensions: Argentina, Australia (**granted**), Canada, China, Europe, Hong Kong, India, Japan (**granted**), Mexico, USA (**granted**).

  - **New IP filing claiming the specific Cyclosporine formulation:**

    ***"CYCLOSPORINE A TOPICAL COMPOSITIONS“* nº EP16382001.2**

    Priority January 4th 2016

Risks and Pitfalls

- Technical risk below standard (known molecule, already approved for the indication)
- Commercial risk main concern:
  - Competitors in the space (protopic and elidel), going generic
  - Oral products coming in

  But...

  - Very positive perception of CsA by dermatologists
  - Pediatric target not prone to corticoids, or systemic products
  - Unsatisfied, long term patient base. Recognized need for more topical alternatives in terms of products and administration

3. Partnering

Open to discuss Licensing / Codevelopment / Option schemes in exchange of development, manufacturing or territorial commercial rights.

Top line results from current POC clinical trial expected 2Q 2017

Contact information

Contact person:

Name: Mª Isabel Berges, Managing partner & CBDO

Telephone: *0034 – 637057432*

e-Mail: *mberges@spheriumbiomed.com*

Spheriumbiomed S.L.

Address: Carrer Joan XXIII, 10
E-08950 – Esplugues de Llobregat
Barcelona, Spain

Web: www.spheriumbiomed.com