New Drugs in Dermatology: 2014
Marriages of Problems and Solutions

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2013

1888?
Disclosures:

- Affiliations with Bayer, Dusa, Ferndale, Galderma, Genentech, Leo, Onset, PharmaDerm, Promius, Quinnova, and Valeant

- We are Dermatologists, not Demons...
Well Ted, what are we yammering about this year?

- Old Drugs, New Twists
- Old Fungus, New Drugs
- Old Problems, New Solutions
- Just the same old s@#$!
New Twists on Old Drugs

- What do we know about what we already have (or thought we did)…in 2013
- Adapalene + BPO (Epiduo® gel)
  - Expanded age of approved use down to 9
- Desoximetasone 0.25% SPRAY (Topicort)
  - Approved for Psoriasis, and it is class I
- Acyclovir 50mg buccal (Sitavig®)
  - Finally something for inside the mouth
  - Zovirax and Zovirax-HC approved for labialis
“Why so serious?”

- We have to pay attention to the serious drugs
  - Because we are losing our skills
  - Because we are letting good medicine pass us by
  - And because we need to step up to the plate

- Apremilast
  - Oral Thalidomide analog, inhibitor of PDE4
  - currently in phase III trials for ankylosing spondylitis, psoriasis, and psoriatic arthritis
  - Published Case Reports: DLE, LP
  - Potential utilities based on MOA: Sarcoidosis
Certolizumab Pegol
Cimzia®

- Approved for PsA, 200 mg sq
  - On market for rheumatoid arthritis, Crohn’s disease, and spondyloarthropathies
  - In EU often used in combo with MTX

- RAPIDTM-PsA study
  - Phase III, multicenter, randomized, double-blind, 409 patients with adult onset PsA.
  - Loading dose of Cimzia® 400mg or placebo at baseline, week two, and week four
  - Followed by Cimzia® 200mg qowk, Cimzia® 400mg qwk x 4, or placebo qowk
Results of RAPIDTM-PsA study

- Treatment with Cimzia® resulted in improvement in skin manifestations in patients with PsA.
- Important to recognize that safety and efficacy of Cimzia® in the treatment of patients with plaque psoriasis has not been established.
The Hives have it

- Omalizumab for Chronic Urticaria: Asteria II trial
  - phase 3, multicenter, double-blind study, on anti-H1
  - 3 SQ injections, spaced 4 weeks apart
  - omalizumab doses of 75 mg, 150 mg, or 300 mg or placebo, then 16-week observation

- Week 12, the mean (±SD) change in the weekly itch-severity score
  - placebo group  $-5.1\pm5.6$
  - 75-mg group  $-5.9\pm6.5$
  - 150-mg group  $-8.1\pm6.4$
  - 300-mg group  $-9.8\pm6.0$  ($P<0.001$).
The Hives have it

- Karbinal---Carbinoxamine maleate ER suspension 4mg/5ml
  - mildly sedating antihistamine for allergic rhinitis and conjunctivitis AND urticaria
  - sustained release q12 hrs
  - mainly for symptomatic relief
Lidocaine 7% + Tetracaine 7% Cream

- Brand name = Pliaglis®
- Indication: Topical local analgesia for superficial dermatological procedures
- Use: Self-occluding; Forms pliable peel
  Applied 20-30 min for most minor and 60 min for more major procedures
- Filler injection, PDL or mild laser abrasion, tattoo removal (longer application time)
- Supplied: 30, 60 and 100gm tubes
Lidocaine 7% + Tetracaine 7% Cream

**DOSING**

<table>
<thead>
<tr>
<th>Surface Area of Treatment Site (cm²)</th>
<th>Length of PLAAGLIS for 1 mm Thickness (cm)</th>
<th>Weight of PLAAGLIS Dispensed (g)</th>
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<tr>
<td>10</td>
<td>3</td>
<td>1</td>
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<tr>
<td>20</td>
<td>6</td>
<td>3</td>
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<td>40</td>
<td>12</td>
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<td>106</td>
<td>46</td>
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<tr>
<td>400</td>
<td>121</td>
<td>53</td>
</tr>
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</table>
Acyclovir 50mg Buccal

- Brand name = Sitavig®
- Indication: Recurrent oro-labial HSV, >4/yr
- Novel Lauriad® technology which is a natural polymer derived from milk which adheres to mucosa, leading to high local drug concentration, but minimal blood level
- ONE tab, applied w/in one hour of prodrome onset reduces duration of attack by 0.5 day based on RCT involving 775 patients
Acyclovir Buccal 50mg

- Apply one tablet
- Upper gum at incisor on same side as HSV lesion
- Hold pressure for 30 seconds
- Allow to remain in place until falls off (minimum 6 hours) (study median 14 hours)
Antifungal Overload

- Out of nowhere the market is flooded
- Luliconazole is approved
- Efinaconazole and Tavaborole are not
- Itraconazole 200 mg tablets with new dosing protocol
- Ketoconazole gel (Xolegel) and Itraconazole tablets (Onmel) are back
- Econazole Foam is coming
Mechanism of Action: Ergosterol Biosynthesis

An essential integrity component of fungal cell walls and not found in plants or animals

Squalene → Squalene epoxide → Lanosterol → Ergosterol

Squalene epoxidase
Lanosterol cyclase
14-α demethylase

Class generally considered fungicidal
Class generally considered fungistatic

Inhibitor: Allylamines¹,²,³ including naftifine

Inhibitor: Triazoles including itraconazole
Inhibitor: Imidazoles including Oxiconazole, econazole, luliconazole

Study Design

Tape stripping performed at each interval (Days 1, 15, 29, 43) and amount of naftifine quantified

N=12

Naftifine HCl Cream, 2%

Day 1 (Baseline)

Week 2 (End of treatment)

Week 4

Week 6

Naftifine HCl Gel, 2%

### Baseline Demographics for All Subjects Receiving Study Treatment at Least Once

<table>
<thead>
<tr>
<th></th>
<th>Cream, 2% N = 6</th>
<th>Gel, 2% N = 6</th>
<th>Total N = 12</th>
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<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (100)</td>
<td>5 (83.3)</td>
<td>11 (91.7)</td>
</tr>
<tr>
<td><strong>Age (years), Mean (SD)</strong></td>
<td>39.5 (11.7)</td>
<td>38.8 (15.9)</td>
<td>39.2 (13.3)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Body Mass Index, Mean (SD)</strong></td>
<td>29.3 (3.6)</td>
<td>24.6 (2.9)</td>
<td>26.9 (4.0)</td>
</tr>
</tbody>
</table>
### Tape Strip Results

**Total Naftifine Hydrochloride Recovered from the Tape Strip Samples (ng/cm²)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 15</th>
<th>Day 29</th>
<th>Day 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naftifine Cream, 2%</td>
<td>N = 6</td>
<td>N = 6</td>
<td>N = 6</td>
<td>N = 6</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.10 (0.21)</td>
<td>321.63 (245.90)</td>
<td>66.60 (157.38)</td>
<td>2.87 (3.39)</td>
</tr>
<tr>
<td>Median</td>
<td>0.01</td>
<td>349.00</td>
<td>1.65</td>
<td>2.07</td>
</tr>
<tr>
<td>Naftifine Gel, 2%</td>
<td>N = 6</td>
<td>N = 5*</td>
<td>N = 5*</td>
<td>N = 5*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.01 (0.01)</td>
<td>199.97 (172.83)</td>
<td>5.45 (5.08)</td>
<td>20.30 (28.98)</td>
</tr>
<tr>
<td>Median</td>
<td>0.01</td>
<td>108.82</td>
<td>3.06</td>
<td>9.65</td>
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</tbody>
</table>

*One subject in the naftifine gel, 2% group was discontinued from the study prior to dosing completion (Day 13). This subject was not included in the final pharmacokinetic analysis.*
# Quantity of Naftifine Hydrochloride Recovered from Sequential Tape Strip Sets

<table>
<thead>
<tr>
<th>Tape Strip Sets</th>
<th>Naftifine Cream, 2% N = 6</th>
<th>Naftifine Gel, 2% N = 5*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 15</td>
<td>Day 29</td>
</tr>
<tr>
<td>Tape Strips 1-5</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>189.9 (142.3)</td>
<td>45.0 (106.9)</td>
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<tr>
<td>Median</td>
<td>224.1</td>
<td>0.86</td>
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<tr>
<td>Tape Strips 6-10</td>
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<tr>
<td>Mean (SD)</td>
<td>58.6 (54.2)</td>
<td>9.1 (21.2)</td>
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<tr>
<td>Median</td>
<td>79.6</td>
<td>0.29</td>
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<tr>
<td>Tap Strips 11-15</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>30.4 (32.5)</td>
<td>6.1 (14.4)</td>
</tr>
<tr>
<td>Median</td>
<td>20.7</td>
<td>0.10</td>
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<tr>
<td>Tap Strips 16-20</td>
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<tr>
<td>Mean (SD)</td>
<td>21.9 (24.1)</td>
<td>4.2 (9.8)</td>
</tr>
<tr>
<td>Median</td>
<td>18.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Tap Strips 21-25</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>20.9 (17.6)</td>
<td>2.2 (5.1)</td>
</tr>
<tr>
<td>Median</td>
<td>21.3</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Values are in (ng/cm²)*

*One subject in the naftifine Gel, 2% group was discontinued from the study prior to dosing completion (day 13). This subject was not included in the final pharmacokinetic analysis.

Luliconazole for the Treatment of Interdigital Tinea Pedis: A Double-blind, Vehicle-Controlled Study

Michael Jamati, MD; Terry Jones, MD; Steven Kamperis, MD; Phoebe Rich, MD; Katy Morton; Nori Kanamura, MD; Amir Tavakoli, PhD; DiplACT.

Tinea pedis (TP) typically occurs in the interdigital areas of the foot, manifesting with pruritus, erythema, hyperkeratosis, and sometimes vesicles. It is likely to be more severe in immunocompromised patients and can potentially lead to secondary bacterial infections and cellulitis in individuals with diabetes mellitus.

The fungal pathogens most frequently associated with TP are Trichophyton rubrum, Trichophyton mentagrophytes, and occasionally Epidermophyton floccosum. Topical antifungal preparations are a mainstay of treatment of TP; however, 1 to 4 weeks of therapy generally are required and recurrences are common. After successful topical or systemic therapy, recurrence occurs in up to 70% of patients.

Luliconazole is a novel imidazole drug with in vitro antifungal activity against dermatophytes and Candida albicans. The effectiveness of luliconazole is equal to or exceeds that of other antifungal agents, including bifonazole and terbinafine, based on its minimum inhibitory concentration. It is an animal model of dermatophytosis, luliconazole was as effective as terbinafine and superior to laniconazole.

Complete clearance was 26.8% and 45.7% subjects in the 2-week and 4-week treatment group, two weeks post-treatment.

Antifungal effect persisted several weeks post-treatment resulting in increased rates of mycologic and clinical cure.

Four weeks post-treatment complete clearance rates were 53.7% and 62.9% respectively.
Luliconazole Cream 1%: Phase 3 Studies
Complete Clearance Rates

**Patients achieving complete clearance (%)**

- **Interdigital Tinea Pedis (Pooled MITT population)**
  - N=43
  - Luliconazole Cream: 20.2%
  - Vehicle: 2.4%

- **Tinea Cruris**
  - N=35
  - Luliconazole Cream: 21.2%
  - Vehicle: 4.4%

*N=43 (Pooled MITT population)*

\(^1\)Integrated summary of efficacy (ISE)
Luliconazole Cream 1%, Terbinafine Cream 1% and Sertaconazole Cream 2%

Pilot Study in Tinea Corporis and Tinea Cruris

- Multicenter randomized, open label study in 83 patients
  - Luliconazole once daily for 2 weeks
  - Sertaconazole twice daily for 4 weeks
  - Terbinafine once daily for 2 weeks
  - 2-week follow-up relapse assessment

Sertaconazole more effective than terbinafine or luliconazole in relieving signs and symptoms of dermatophytoses, especially pruritus.

Mycologic cure was similar for all three treatments at the end of treatment and at follow-up.
Luliconazole exhibited strong antifungal activity against *Trichophyton* spp with MIC 1-4 times lower than lanoconazole or terbinafine

- 7-day topical therapy (0.5% solution) more effective than lanoconazole or terbinafine (0.5%)
- Only luliconazole achieved complete mycologic cure with 3-day therapy

Efinaconazole Mechanism of Action

- Triazole antifungal agent
- Inhibits fungal lanosterol 14α-demethylase involved in ergosterol biosynthesis at concentrations below minimum inhibitory concentrations (MICs) 4.8 times more potent than itraconazole in inhibiting ergosterol biosynthesis in T. mentagrophytes
- 7.3 times more potent than clotrimazole in C. albicans
Efinaconazole Comparative Fungal Growth Inhibition

**T. mentagrophytes**

- **Efinaconazole**
  - MIC: 0.0039
  - IC₅₀: 0.0070

- **Itraconazole**
  - MIC: 0.016
  - IC₅₀: 0.0338

**C. albicans**

- **Efinaconazole**
  - MIC: 0.001
  - IC₅₀: 0.0004

- **Clotrimazole**
  - MIC: 0.008
  - IC₅₀: 0.0029

Representative Patient Examples
Efinaconazole 10% Solution

Baseline

Week 36

Week 24

Tavaborole Properties

- MW = 152 amu
- Water solubility = 0.8 mg/mL
- logP = 1.24
Boron has a Unique Bonding Orbital Configuration: An Empty P-Orbital

- Boron has an empty P-orbital & can form a new bond under specific conditions
- The new bond forms a tetrahedral structure
- Exploitation of P-Orbital Expands Drug Design Possibilities
Tavaborole represents a new class of anti-fungals

AN2690-A76 Adduct in Editing Site

Leucine in Synthetic Site

\[ \text{tRNA}^{\text{Leu}} \]
Tavaborole has broad spectrum anti-fungal activity

<table>
<thead>
<tr>
<th>Dermatophytes / filamentous fungi</th>
<th>AN2690</th>
</tr>
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<tbody>
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<td><em>E. floccosum</em></td>
<td>≤ 0.5</td>
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<tr>
<td><em>M. audouinii</em></td>
<td>2</td>
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<tr>
<td><em>M. canis</em></td>
<td>2</td>
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<tr>
<td><em>M. gypseum</em></td>
<td>2</td>
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<tr>
<td><em>T. tonsurans</em></td>
<td>2</td>
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<tr>
<td><em>T. mentagrophtes</em></td>
<td>2</td>
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<tr>
<td><em>T. rubrum</em></td>
<td>1</td>
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<tr>
<td><em>M. furfur</em></td>
<td>1</td>
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<tr>
<td><em>C. albicans</em></td>
<td>1</td>
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<tr>
<td><em>F. solari</em></td>
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<tr>
<td><em>A. fumigatus</em></td>
<td>0.25</td>
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Tavaborole penetrates nail 250x better than ciclopirox lacquer.

<table>
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<tr>
<th>Days</th>
<th>Tavaborole</th>
<th>Penlac</th>
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<td>0-3</td>
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<td>4-6</td>
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<td>7-9</td>
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<td>0.0018</td>
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<td>10-12</td>
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<td>0.0014</td>
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<tr>
<td>13-15</td>
<td>0.96</td>
<td>0.0033</td>
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<tr>
<td>Total</td>
<td>2.24</td>
<td>0.0088</td>
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Amount (mg / Sample)
Econazole 1% Foam (Ecoza™) Mycologic Cure and Treatment

- Mycologic Cure: 67.6% (Econazole Nitrate Foam 1% n=173), 16.9% (Foam Vehicle n=166)
- Effective Treatment: 48.6% (Econazole Nitrate Foam 1% n=173), 10.8% (Foam Vehicle n=166)
### Topical Treatments

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<th>Treatment</th>
<th>Pre-clinical</th>
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<td>INCB18424 (ruxolintinib)</td>
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<td>Calcipotriene foam (STF 115469)</td>
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<td>Tofacitinib (CP-690,550)</td>
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<td>M518101</td>
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<tr>
<td>CycloPsorb™</td>
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- **PDE4 inhibitor**
- **TRKA KINASE Inh**
- **MEK inh**
- **JAK inh**
- **NSAID**
- **rose bengal disodium**
- **TNF-α and IFN-γ**
- **JAK inh**
- **Vit D3**
Safety and Efficacy of AN2728 Ointment in a Phase 2b Dose-Ranging, Bilateral Study of Mild-to-Moderate Plaque Psoriasis

Zane LT, Toledo-Bahena M², Hughes MH¹, Heerinckx FA¹

¹Anacor Pharmaceuticals, Palo Alto, CA; ²Instituto Mexicano de Investigación Clínica (IMIC), Mexico City, Mexico

Introduction

AN2728 (5-(4-cyanophenoxo)-1,3-dihydro-1-hydroxy-2,5-benzoxaborole) is a novel oxaborole compound being developed as a topical treatment for inflammatory skin diseases including plaque-type psoriasis. AN2728 demonstrates in vitro activity against a range of pro-inflammatory cytokines implicated in the pathogenesis of psoriasis. 1-3

AN2728 has demonstrated efficacy in 7 psoriasis clinical trials, including 4 Phase 1 microscale studies and 3 Phase 2 randomized, double-blind, vehicle-controlled, bilateral comparison studies. This poster presents the results from a recently completed dose-ranging Phase 2b trial, AN2728-P386-301. 4

Purpose

To determine the safety and efficacy of AN2728 Ointment, 2% and 0.5%, administered once daily (QD) or twice daily (BID), compared to Clobetasol vehicle in the treatment of mild-to-moderate plaque-type psoriasis.

Methods

Protocol Design

This multicenter, Phase 2b, randomized, double-blind, vehicle-controlled, 12-week bilateral comparison study enrolled a total of 145 adult patients with mild-to-moderate plaque psoriasis. Patients were randomized (1:1:1) to 1 of 4 treatment regimens to 2 similar but randomly assigned target plaques on the trunk or upper extremities for 12 weeks. The treatment groups included:

1) AN2728 Ointment, 2% to one target plaque and Clobetasol vehicle to second target plaque; applied QD (AM & PM)
2) AN2728 Ointment, 2% to one target plaque and Clobetasol vehicle to second target plaque; applied QD (AM & PM)
3) AN2728 Ointment, 0.5% to one target plaque and Clobetasol vehicle to second target plaque; applied QD (AM & PM)
4) AN2728 Ointment, 0.5% to one target plaque and Clobetasol vehicle to second target plaque; applied QD (AM & PM)

End Points

Plaque severity was measured using 9-point atopic scales for Overall Target Plaque Severity Score (OTPSS), which ranged from 0 (no evidence of disease) to 9 (very severe). Individual components of psoriatic plaque severity (erythema, scaling, and plaque elevation) were graded on a 3-point scale.

In the primary endpoint analysis, the proportion of patients in whom the AN2728 Ointment, 2% BID-treated plaque achieved a greater decrease in OTPSS from baseline to Day 42 relative to the vehicle-treated plaque was compared to the proportion of patients in whom the reverse was true.

The secondary efficacy analysis compared the proportion of patients across treatment groups who had a greater decrease from baseline to Day 42 relative to the vehicle-treated plaque.

Results

Baseline Characteristics

In this study, 36, 37, 35, and 37 patients were randomized (ITT), respectively, to apply AN2728 Ointment, 0.5%-QD, 0.5%-BID, 2%-QD, and 2%-BID to a target plaque; all 145 patients also applied Clobetasol to a second target plaque. Across treatment groups, the patients ranged in age (mean) from 46.8 to 63.3 years and were primarily male (55%-65%). The patients also presented at baseline with a mean OTPSS that ranged across treatment groups from 3.1 to 3.2, and had similar baseline skin erythema, scaling, and plaque elevation scores. There were no significant differences between treatment groups in any of the demographic or baseline characteristics.

Primary Efficacy Results (ITT)

At Day 42, 54.1% of the patients who applied AN2728 Ointment, 2% BID and Clobetasol vehicle had a greater decrease in OTPSS from baseline in the active-treated plaque than in the vehicle-treated plaque, compared to just 2.7% of the patients where the reverse was true (p<0.001; Figure 1).

An examination of mean improvement in OTPSS scores by treatment group indicated a dose-responsive relationship with respect to concentration and frequency of application (Figure 4).

Within treatment groups, the proportion of patients who had greater decreases in OTPSS from baseline to Day 42 for the active-treated plaque relative to the vehicle-treated plaque was larger than the proportion of patients in whom the reverse was true. The treatment response generally improved with increasing concentration and application frequency (Figure 2).

In an exploratory analysis describing the proportion of patients whose plaques achieved an OTPSS of 0 or 1 and at least a 2-grade improvement from baseline, treatment with AN2728 Ointment, 2% BID demonstrated an early and consistent benefit relative to the other treatment groups and vehicle across the treatment period. At Day 84, 54% of patients who received AN2728 Ointment, 2% BID had an OTPSS of 0 or 1 and at least a 2-grade improvement from baseline in the active-treated plaque (Figure 3).

Safety Results

No serious adverse events were reported. Overall, 51 patients (35%) experienced at least one AE during the study. The majority (89%) of AEs were considered unrelated or unlikely to be treatment-related. The majority of AEs (82%) were not severe. None of the treatment-related events was severe.

The most common AEs included rash (26%) and pruritus (22%). Treatment-related AEs included pruritus (reported by 0.6% of patients, including at least 1 in each treatment group), "dermatitis contact" (reported by 0.5% of patients, including at least 1 in the AN2728 Ointment, 2% BID group), and "transaminase increased" (reported by 1.0% of patients in the AN2728 Ointment, 2% BID group).

Only 2 events led to discontinuation of treatment: "dermatitis contact" (related to treatment, mild in severity, in a patient assigned to the AN2728 Ointment, 2% BID group, and worsening of psoriasis (unrelated to treatment, moderate in severity, in a patient assigned to the AN2728 Ointment, 2% QD group).

Overall, AN2728 was generally well tolerated and no significant safety concerns were identified in this study.

Conclusions

- These Phase 2b efficacy results show that AN2728 Ointment is effective in reducing the severity and signs of plaque-type psoriasis.
- Increasing treatment effects are generally correlated with increasing concentration and frequency of application.
- Of the 4 treatment regimens, AN2728 Ointment, 2% BID may provide the greatest therapeutic benefit.
- In general, AN2728 Ointment appears safe and well-tolerated in adult patients with mild-to-moderate plaque-type psoriasis.

References


AN2728 (5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole)

- Boron based Topical PDE4 inhibitor
- *in vitro activity against* TNF-α, IL-12, and IL-23.1
- Phase 2b trial, AN2728-PSR-203
  - 2% vs. 0.5% ointment vs vehicle, applied qd vs bid
  - 145 pts, 4 arms, assess at 6 and 12 weeks
  - AEs: pruritus, application site reaction, contact derm
- AN2728-PSR-202
  - 5% ointment bid for 12 weeks
12 week improvement

Figure 4. Mean Improvement from Baseline Plaque Severity in OTPSS by Study Day: All Treatment Groups

Improvements were also seen in all individual component signs of plaque severity (erythema, scaling, and plaque elevation).

Figure 2. Proportion of Patients with Greater Improvement in OTPSS for AN2728-Treated vs. Vehicle-Treated Plaques by Study Day

<table>
<thead>
<tr>
<th>Study Day</th>
<th>AN2728 Superior</th>
<th>Vehicle Superior</th>
<th>P (Sign test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>10%</td>
<td>13%</td>
<td>0.0213</td>
</tr>
<tr>
<td>Day 14</td>
<td>43%</td>
<td>10%</td>
<td>0.0001</td>
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<tr>
<td>Day 28</td>
<td>60%</td>
<td>3%</td>
<td>0.0004</td>
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<tr>
<td>Day 42</td>
<td>60%</td>
<td>7%</td>
<td>0.0168</td>
</tr>
<tr>
<td>Day 56</td>
<td>60%</td>
<td>17%</td>
<td>0.0639</td>
</tr>
<tr>
<td>Day 70</td>
<td>57%</td>
<td>23%</td>
<td>0.2295</td>
</tr>
<tr>
<td>Day 84</td>
<td>53%</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>
E6201
Topical MEK Inhibitor

- mitogen-activated protein kinase/ extracellular signal-regulated kinase
- Anti-inflammatory
  - Suppressed PMNs and lymphs in animal models
- Anti-proliferative
  - interleukin (IL)-23-induced epidermal hyperplasia.
  - E6201 also suppressed T cell receptor-stimulated IL-17 production from human T cells

Muramoto K et al, J Pharmacol Exp Ther. 2010 Oct;335(1):23-31
Janus Kinase Inhibitors: Ruxolintinib and Tofacitinib

- Family of 4 tyrosine kinases:
  - JAK 1, 2, 3 and Tyk 1, promote cellular signals
  - STAT: Signal Transducer and Activator of Transcription Proteins
  - Growth and Activation signals sent to nucleus

- Overactivity of JAK results in hyperproliferation—psoriasis, myelofibrosis

Rose Bengal disodium
(protocol PH-10-PS-23)

**Phase 2 Data, purified from ophthalmic**
- aqueous hydrogel formulation
- 3 forms (0.002%, 0.005%, and 0.01%)

- 99 subjects randomized
  - once daily for 28 consecutive days
- 79% of 29 subjects improved
- 83% resolved the pruritus

www.clinicaltrials.gov  Phase 2 Dose-Randomized, Vehicle-Controlled Study of PH-10-Aqueous Hydrogel for the Treatment of Plaque Psoriasis
Mahalo!