SO MANY DRUGS, SO LITTLE TIME... A THERAPEUTIC UPDATE

JAMES Q. DEL ROSSO, DO
Research Director / Clinical Dermatology
JDR Dermatology Research / Thomas Dermatology

Adjunct Clinical Professor (Dermatology)
Touro University Nevada
Henderson, Nevada
Disclosures

ALMIRALL*^#
ATHENEX*
BIOPHARMX^*
BOTANIX*
CELGENE*^#
DERMIRA^*
ENCORE^#
EPI HEALTH*^#
FERNDALE^#
FOAMIX^*
GALDERMA*^#
GENENTECH*#

LEO PHARMA*^#
LA ROCHE POSAY^
NOVAN^*
ORTHO DERMATOLOGY*^#
PFIZER^#
REGENERON*^#
SANOFI-GENZYME^#
SONOMA (INTRADERM)^
SUN PHARMA*^#
TARO^*
VERRICA^*

* Research Investigator
^ Consultant/Advisor
# Speaker

UPDATED 12-24-2018
Glycopyrronium Cloth Applied Once Daily – Axillary Hyperhidrosis
Phase 3 Randomized Controlled Trials (Pooled ATMOS-1 and ATMOS-2)

Glycopyrronium Cloth Treated Patients Reported Less Severe Sweating

| Proportion of Patients Reporting Clinically Meaningful Decrease in Sweat Severity, (%) |
|---------------------------------|---------------------------------|
| Vehicle N=234                   | Glycopyrronium Cloth N=463      |
| 27.6%                           | 59.5%                           |

Glycopyrronium Cloth Treated Patients Produced Less Sweat

| Median Absolute Change from Baseline in Gravimetrically-Measured Sweat Productiona (mg/5 min) |
|---------------------------------|---------------------------------|
| Vehicle N=234                   | Glycopyrronium Cloth N=463      |
| -61.8                           | -79.8                           |


Patients Aged ≥9 Years - Primary Axillary Hyperhidrosis:
• ≥6 months duration
• Sweat production of ≥50 mg/5 min in each axilla
• AXILLARY SWEATING DAILY DIARY Item 2 Score ≥4
• HYPERHIDROSIS DISEASE SEVERITY SCALE Grade 3 or 4

* Gravimetrically-measured average from the left and right axillae

Intent-to-treat (ITT) population, MCMC used to impute missing values; no statistical analysis performed for post-hoc pooled analyses

Median Sweat Production at Baseline (mg)

<table>
<thead>
<tr>
<th>Vehicle N=234</th>
<th>Glycopyrronium Cloth N=463</th>
</tr>
</thead>
<tbody>
<tr>
<td>112.6</td>
<td>122.1</td>
</tr>
</tbody>
</table>
IMPETIGO/
BACTERIAL SKIN INFECTIONS
Ozenoxacin 1% Cream Twice Daily x 5 Days
New Generation Topical Quinolone – Marked Gram (+) Activity

Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and Pediatric Patients With Impetigo
A Randomized Clinical Trial

Theodore Rosen, MD; Nuria Albareda, MD; Noah Rosenberg, MD; Fernando Garcia-Alonso, MD, PhD;
Sandra Roth, PharmD; Henko Zuidt, MD, PhD; Anastasio A. Hobart, MD

IMPORTANCE: Ozenoxacin, a novel topical antibacterial agent with potent bactericidal activity against gram-positive bacteria, has been developed as a cream with 1% active drug for the treatment of impetigo, a highly contagious bacterial skin infection.

Multicenter, Double-Blind, Placebo-Controlled
Phase 3 Trial (N=411)

Superior Clinical Success vs Placebo
After 5 Days of Therapy
(54.4% vs 37.9%)

More Rapid Microbiologic Clearance
than Topical Retapamulin

Superior Microbiological Success
vs Placebo After 2 Days of Therapy
(87.2% vs 63.9%)

100% of Drug-Resistant Bacteria
Cured/Improved (10/10 Mupirocin-Resistant; 8/8 MRSA)

RESEARCH ARTICLE

For reprint orders, please contact: reprints@futuremedicine.com

Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial

Savion Gropper1, Nuria Albareda1, Klaus Cheliuci1, Dawie Kruger1, Ismail Mitha2, Yacoob Vahed2, Mashra Gani2, Fernando Garcia-Alonso1 & Ozenoxacin in Impetigo Trial Investigators Group1


TOPICAL THERAPY for PLAQUE PSORIASIS
Calcipotriene 0.005%-Betamethasone Dipropionate 0.064% (Cal/BD) Foam Use in Psoriasis Patients with Incomplete Response to Biologics ~ Long-Term Management (N=25)

- Open-label, prospective; after ≥24 weeks biologic therapy
  - Persistent areas of plaque psoriasis (<5% Body Surface Area)
- Cal/BD once daily x 4 weeks THEN twice per week (on 2 consecutive days x 12 weeks)
- Assessed Physician Global Assessment, BSA, BSA x PGA
- Greater improvement in all parameters vs Baseline
- WEEK 4: 76% achieved Target BSA ≤1% and PGA <1
- WEEK 16: 68% achieved Target BSA ≤1% and PGA <1
- Favorable skin tolerability

Moderate-Severe Plaque Psoriasis Phase III Trials
Topical Halobetasol 0.01%/Tazarotene 0.045% x 8 Weeks
Evaluation of Investigator Global Assessment (IGA) Results (Pooled Phase 3 Data)

IGA 2-Grade Improvement +
Clear/Almost Clear

Low Adverse Events
Dermatitis (6.3%) – Stinging (2.6%) – Itching (2.2%)

Two Multicenter Double-Blind Vehicle-Controlled Phase 3 Studies (N=418)

Moderate Plaque Psoriasis – Target Sign Score
Betamethasone Dipropionate 0.05% SPRAY BID vs Augmented Betamethasone Dipropionate 0.05% Lotion BID vs Vehicle BID

- Reduction in TSS was greater with BDSp at Day 4 (-17.3% vs -10.6%; \( P = .009 \))
- At Day 4 BDSp was also significantly different from AugBD for both TSS_{50} (13.2% vs 5.6%, \( P = .044 \)) and TSS \leq 1 for any sign (13.8% vs 5.6%, \( P = .031 \))

Clobetasol 0.025% Cream
Pharmacokinetic/dynamic Properties vs 0.05% Cream

MODERATE TO SEVERE PLAQUE PSORIASIS / TWICE DAILY APPLICATION
N=45 / 20-50% BODY SURFACE AREA

PLASMA CONCENTRATION

Day 15

<table>
<thead>
<tr>
<th>Systemic Clobetasol Propionate Plasma Concentration (pg/mL)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasol Propionate 0.025% Cream</td>
<td>56.3 pg/mL</td>
</tr>
<tr>
<td>Clobetasol Propionate 0.05% Cream</td>
<td>152.5 pg/mL</td>
</tr>
</tbody>
</table>

Low Incidence of HPA Axis Suppression*

<table>
<thead>
<tr>
<th>Patients With Abnormal ACTH Stimulation Test Results (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasol Propionate 0.025% Cream</td>
<td>12.5%</td>
</tr>
<tr>
<td>Clobetasol Propionate 0.05% Cream</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

Flurandrenolide Tape (4 mcg/cm²) for Corticosteroid Responsive Dermatoses


Both occlusive tape alone and steroid incorporated/occlusive tape inhibit of enzyme activities in psoriatic lesions and normal-appearing skin.

Steroid Tape >> Tape Alone
ADJUNCTIVE PHOTOPROTECTION
Polypodium Leucotomos Extract (PLE)
New Information of Specific Formulation

▪ Analysis of different PLE extracts to determine relative antioxidant content (by HPLC) and ability to prevent UV damage (Vanillic, Ferulic, Caffeic, Protocatechuic, Others)
  ▪ Results showed marked differences in content between different extract formulations and part of fern used (leaves > root)
  ▪ Specific brand PLE with most efficient photoprotection based on cellular assay testing (ie cell survival, cyclobutane dimers)

▪ Assessment of oral PLE on Visible Light-induced Pigmentation (VLP)
  ▪ IGA scores do not indicate an effect of PLE on VLP
  ▪ Spectral measurements support an effect of PLE on VLP
  ▪ Preliminary histology results indicate an effect of PLE on visible light induced DNA damage and inflammation

ROSACEA
Ivermectin (IVM) 1% Cream + Subantibiotic Dose Doxycycline (Doxy MR 40 mg/day) vs IVM 1% Cream Alone
Severe Rosacea / Mean Lesion Count ~39 / Multiple Prior Therapies

147% more subjects on combination therapy achieved 100% lesion reduction vs. monotherapy

Mean percentage Reduction in Inflammatory Lesions from Baseline (%)

Mean Reduction in % Inflammatory Lesions from Baseline to Week 12

% Subjects with 100% Clearance of Inflammatory Lesions at 12 Weeks

ANSWER Study. Poster Presentation, Fall Clinical Dermatology, Las Vegas, NV, October 2018 / Soolantra Product Information, Galderma Laboratories, Fort Worth, TX.
Oxymetazoline 1% Cream: Phase 4 vs Phase 3 Study Outcomes
≥1-Grade Improvement in CEA

Phase 4 Trial

Phase 3 Pivotal Trials

\[ \text{Patients With CEA} \geq 1\text{-Grade Change} (\%) \]

Postdose on Day 1

\[ \text{Hour 1} \quad \text{Hour 3} \quad \text{Hour 6} \quad \text{Hour 9} \quad \text{Hour 12} \]

\[ \text{Oxymetazoline (n=446)} \quad \text{Vehicle (n=439)} \]

\[ 54.9^{\$} \quad 85.3^{\$} \quad 84.1^{\$} \quad 74.7^{\$} \quad 65.3^{\$} \]

\[ 17.9 \quad 26.7 \quad 28.8 \quad 29.8 \quad 27.6 \]

\[ \text{P}<0.0001 \text{ for the comparison to vehicle.} \]

\[ 54.6^{+} \quad 81.9^{+} \quad 78.9^{+} \quad 73.0^{+} \quad 59.8^{+} \]

\[ 30.3 \quad 48.9 \quad 51.9 \quad 47.2 \quad 39.3 \]

\[ +P<0.001 \text{ for the comparison to vehicle.} \]

CEA, Clinician Erythema Assessment
ATOPIC DERMATITIS
Pathophysiologic Circuits in Atopic Dermatitis (AD)
Role of Interleukin-4 (IL-4) and Interleukin-13 (IL-13)

- **IGE PRODUCTION**
- **T2 HELPER DIFFERENTIATION**
- **INFLAMMATION IN SKIN AND BLOOD**
  - **PROMOTES EOSINOPHIL MIGRATION**
  - **IL-31 EXPRESSION**

IL-4

IL-13

**STRATUM CORNEUM AND EPIDERMAL BARRIER FUNCTION**
- **ANTIMICROBIAL PEPTIDES**
- **CERAMIDES**
- **LORICIN and INVOLUCRIN**
- **FILAGGRIN**

**IL-4**

**INFLAMMATION IN SKIN AND BLOOD**
- **PROMOTES EOSINOPHIL MIGRATION**
- **IL-31 EXPRESSION**

**SIGNS AND SYMPTOMS OF ATOPIC DERMATITIS**
- **XEROSIS / ECZEMA**
- **PRURITUS**

Safety of Dupilumab for Atopic Dermatitis (AD) Analysis of Adverse Events / Infection Rates

- Adverse Events reported in 8 clinical trials (4 publications)
- Marked reduction in AD exacerbation
- 54% DECREASED RISK of Skin Infections
- Similar to Negligible Risk of Herpes Simplex Infections (RR 1.21)
- Similar Risk of Upper Respiratory Tract Infections
- Similar Risk of Nasopharyngitis
- Similar Risk of Urinary Tract Infections
- Increased risk for Conjunctivitis (RR 2.64)

Dupilumab in the “Real World”
Emerging Data and Experience with Clinical Uses

PEDiATRIC ATOPIC DERMATITIS
Pharmacokinetics, Safety, and Efficacy of Dupilumab in a Pediatric Population with Moderate-to-Severe Atopic Dermatitis: Results from an Open-Label Phase 2a Trial

Michael J. Cork1, Diamant Thaci2, A. Thomas DiCioccio3, John D. Davis3, Qin Zhang3, Marius Ardeleanu3, Bolanle Akinlade3, Neil M.H. Graham3, Gianluca Pirozzi4, Ashish Bansal5

1 Sheffield Dermatology Research, Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, UK; 2 Comprehensive Center for Inflammation Medicine, University Hospital Schleswig-Holstein, Lübeck, Germany; 3 Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; 4 Sanofi, Bridgewater, NJ, USA

HAND DERMATITIS
Dupilumab Treatment of Very Severe Refractory Atopic Hand Eczema

Jørt A.F. Oosterhaven, MD; Gertrudia L. E. Remeij, BSc; Marie L. A. Schaukelj, MD, PhD

DUPILUMAB FOR HAND ECZEMA


Author Affiliations


ALLERGIC CONTACT DERMATITIS
Dupilumab use in allergic contact dermatitis.

MacCraith BC1, Sung CT2, Darwin E3, Jacob SE4

DYS HIDROSIS

Dupilumab in the Treatment of Dyshidrosis: A Report of 2 Cases

Gillian K. Weston MD; Jette Hooper; Bruce E Strober MD PhD

University of Connecticut, Farmington, CT

BULLOUS PEPHIGOID

Dupilumab for the Treatment of Recalcitrant Bullous Pemphigoid

Alex Kaye, BA1; Samantha C. Gordon, MD2; Sandhya C. Deverapalli, MD2; et al

Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis.

Snast I, Reiter O, Hodak E, Friedland R, Mimouni D, Leshem YA.

NEMOLIZUMAB (ANTI-IL-31) SQ
- Demonstrated Efficacy for Pruritus (Phase 2)
- Improvement of Pruritus and Dermatitis (52 Weeks)

LEBRIKIZUMAB (ANTI-IL-13) SQ
- Phase 2b Dose Ranging SQ Q4W + TCs x 12 Wks
  - 125 mg Q4 Weeks
- Significantly Greater % Reaching EASI-50 vs Placebo (82.4%; P = .026)
- Adverse Events Similar to Placebo

TRALOKINUMAB (ANTI-IL-13) SQ
- Phase 2b 300 mg Q2W + TCs x 12 Wks
- Superior Improvement in EASI and IGA Success vs Placebo
  - Improved SCORAD, DLQI, Pruritus
  - Response Correlation with Higher IL-31 Biomarkers

FUTURE ???

LACK OF EVIDENCE SUPPORTING EFFICACY WITH INFLIXIMAB, RITUXIMAB, OMAлизумаб, AND USTEKINUMAB


Baricitinib / Moderate-Severe Atopic Dermatitis in Adults
2 MG QD or 4 MG QD + TCS vs Placebo + TCS / 16-Week Phase 2 (N=124)

Primary Outcome
% Achieving EASI-50 at Week 16

Change in EASI Score Over Time (16 Weeks)

ORAL
Run-in TCS x 4 Weeks
EASI Score >12


* p<0.05, ** p≤0.01, *** p≤0.001

EASI=Eczema Area and Severity Index; MMRM= mixed-effects model of repeated measures; TCS=topical corticosteroids
COMMON CUTANEOUS VIRAL INFECTIONS

Molluscum Contagiosum
Verruca Vulgaris
Topical Cantharidin (0.7% w/v) Refined Formulation Phase 2 Pilot Study in Molluscum Contagiosum (N=30)
Pharmaceutical Grade / Ether-Free Formulation

12-Week, Open-label Trial; Age 2-17 Years; <50 Lesions
Applied Every 21 Days Up to 4 Treatments or Until Clearance
Treatment Washed Off at 6 Hours (14/30, 46.7%) or 24 Hours (16/30, 53.3%)

The mean ± SD lesion count was reduced from 23.0 ± 15.6 at baseline to 6.8 ± 11.7 at EOS (p < 0.0001). Note that data is pooled from the 6 hour and 24 hour cohorts.
Hydrogen Peroxide 45% Formulation (HP45% [A-101])
Two Phase 2 Clinical Trials for Common Warts

HP45% vs Placebo Twice Weekly x 8 Weeks
16 Applications by Self-Application
Multiple Assessments including Physician’s Wart Assessment (PWA) of Target Wart

WART 203 TRIAL (N=159)
PRIMARY ENDPOINT (Day 56)
- Mean Reduction PWA 0.87 vs 0.17 (p<0.001)
SECONDARY ENDPOINTS (Day 56)
- % ALL Warts CLEAR 30.2% vs 9.2% (p<0.001)
- % ALL Warts CLEAR/NEAR CLEAR 45.6% vs 15.6% (p<0.001)
- % Target CLEAR 25.3% vs 2.6% (p<0.0001)

WART 202 TRIAL (N=157)
PRIMARY ENDPOINT (Day 56)
- Mean Reduction PWA 0.77 vs 0.23 (p<0.001)
SECONDARY ENDPOINTS (Day 56)
- % ALL Warts CLEAR 20.8% vs 2.9% (p<0.001)
- % ALL Warts CLEAR/NEAR CLEAR 52.8% vs 13.7% (p<0.001)
- % Target CLEAR 15.7% vs 1.4% (p<0.0001)