Prurisol: A New Small Molecule under investigation for the treatment of Psoriasis

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Disclosure: full-time employee of Cellceutix
Psoriasis
Debilitating Chronic Disease That Affects Millions

84% of those with moderate-to-severe psoriasis report suffering discrimination and humiliation

Sources:
http://www.cytherapharm.com/
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0052935

6% Not a problem in daily life.
12% No effect on emotional well-being.
18% No interference with enjoyment of life.

94% Psoriasis is a problem in my daily life.
88% Psoriasis affects my overall emotional well-being.
82% Psoriasis interferes with my enjoyment of life.
Prurisol
MOA and Attributes

Mechanism of Action (MOA)
• Nonclinical data: Acts through immune modulation and PRINS* reduction
  • Reduces IL-20
  • Reduces skin cell proliferation rate

Attributes
• Strong Intellectual Property(IP) and patent protections
• Small-molecule (<500 MW) (an ester of abacavir)
• Bioavailable
• Excellent in-vivo and in-vitro activity
• Efficacy in xenograft model
• Oral dosing
• Development plan utilizing advantages of 505(b)(2) approach
  [reference drug: Ziagen®; Abacavir]

*PRINS – Psoriasis-associated non-protein coding RNA induced by stress

Prurisol

[Abacavir (α-hydroxyl) acetate; abacavir glycolate]

Molecular formula: $C_{16}H_{20}N_6O_3$
Molecular weight: 344.37
**Prurisol**

*Mouse Psoriasis Model: Comparison with Ziagen® (Abacavir)*

New Imiquimod-induced Psoriasis Mouse Model for In Vivo Efficacy Screening


Imiquimod-Induced Psoriasis Efficacy Studies - The Jackson Laboratory

[https://www.jax.org/...mice.../imiquimod-induced-psoriasis](https://www.jax.org/...mice.../imiquimod-induced-psoriasis)

- BALB/C mice treated daily with IMQ cream or control cream on the back of the animal close to the tail
- 16 days of treatment; assessed every 2\textsuperscript{nd} day for erythema, scales and thickness; Scale 0 to 4
- Calculated a cumulative score of erythema + scaling + thickness of the skin
- 2 daily doses of Prurisol 10mg/kg had greatest reduction in cumulative score (94% compared to IMQ cream alone)
- Ziagen® (Abacavir) similar to IMQ cream alone
**Prurisol**

*Human Psoriatic Xenograft Model: PRINS & IL-20*

- Human psoriatic skin xenograft model; SCID mice received 350 rad total body irradiation, then transplanted with psoriatic human tissue

- Four groups:
  - 10 mg/kg Prurisol orally once per day for 21 days
  - 10 mg/kg Prurisol orally twice per day for 21 days
  - 7.5 mg/kg methotrexate (MTX) intraperitoneally daily for 5 days
  - Saline control

- 96% reduction in PRINS with 2 daily doses of Prurisol compared to controls

- Single daily doses of Prurisol reduced levels of PRINS to comparable extent as MTX

- IL-20 reduced by 69% and 87% after treatment with one or two daily doses of Prurisol; 46% reduction with MTX

*PRINS – Psoriasis-associated non-protein coding RNA induced by stress*
Single-Dose, Crossover Pharmacokinetic and Bioequivalence Study Evaluating Oral Prurisol** and Oral Abacavir Sulfate (Ziagen®) in Healthy Volunteers

- AUC values were comparable for both Prurisol and Ziagen, within 80% to 125% equivalence window, indicating equivalent systemic exposure
- No serious adverse events, or other significant adverse events occurred over the course of the study

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Prurisol 350 mg</th>
<th>Ziagen 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>2.816 ± 0.703 (16)</td>
<td>3.617 ± 0.885 (16)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.88 (16)</td>
<td>0.75 (16)</td>
</tr>
<tr>
<td>AUC(0-t) (hr×ng/mL)</td>
<td>7.781 ± 2.072 (16)</td>
<td>8.420 ± 2.573 (16)</td>
</tr>
<tr>
<td>AUC(0-inf) (hr×ng/mL)</td>
<td>7.901 ± 2.079 (16)</td>
<td>8.523 ± 2.582 (16)</td>
</tr>
<tr>
<td>λz (1/hr)</td>
<td>0.385 ± 0.1103 (16)</td>
<td>0.4033 ± 0.1183 (16)</td>
</tr>
<tr>
<td>t½ (hr)</td>
<td>2.00 ± 0.84 (16)</td>
<td>2.02 ± 1.30 (16)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>46.0 ± 12.8 (16)</td>
<td>38.5 ± 12.2 (16)</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>136 ± 78.1 (16)</td>
<td>109 ± 67.5 (16)</td>
</tr>
</tbody>
</table>

*Arithmetic mean ± standard deviation except for Tmax for which the median range is reported. (N) Number of subjects.

For study details, see [https://clinicaltrials.gov/ct2/show/NCT02101216](https://clinicaltrials.gov/ct2/show/NCT02101216)

**[Abacavir (α-hydroxyl) acetate; abacavir glycolate]
Primary efficacy endpoint: percentage of subjects with ≥ 2 point improvement in IGA rating at 84 days (12 weeks)

- Investigator Global Assessment (IGA) rating: clear (0), almost clear (1), mild (2), moderate (3), severe (4), very severe (5)

- Randomized, double blind, parallel group, placebo-controlled
- 4 treatment groups, 1:1:1:1 randomization, 12 weeks treatment
  - Prurisol
    - 50 mg daily (50 mg AM)
    - 100 mg daily (50 mg AM & 50 mg PM)
    - 200 mg daily (100 mg AM & 100 mg PM)
  - Placebo AM & PM

- Trial conducted at 9 sites in U.S.
- 115 subjects, 4 arms, ~29 per arm
- Efficacy, Safety & PK

For study details, see https://clinicaltrials.gov/ct2/show/NCT02494479
CTIX-0002
Disease Burden Entry Criteria

Individuals with **mild-to-moderate** chronic plaque psoriasis

- Clinical diagnosis of stable (at least 6 months) plaque psoriasis, not including scalp or intertriginous areas
- Body surface area (BSA) affected by plaque psoriasis of 10% to 20% inclusive
- Investigator Global Assessment (IGA) score of “mild” (2) or “moderate” (3) (using IGA rating scale; 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe)
- Identification of a target psoriatic lesion with a score of at least “moderate” (3) on the Target Lesion Assessment for Scaling (TLA) scale

(HLA-B*5701- negative subjects)
CTIX-0002
Subject Demographics

Characteristics at Baseline were similar for all 4 treatment groups

<table>
<thead>
<tr>
<th>ITT Population Baseline Characteristic</th>
<th>Prurisol 50 mg (N=29)</th>
<th>Prurisol 100 mg (N=28)</th>
<th>Prurisol 200 mg (N=28)</th>
<th>Placebo (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (SD)</td>
<td>57.7 (11.11)</td>
<td>55.2 (13.55)</td>
<td>56.9 (15.02)</td>
<td>55.9 (11.25)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48.3</td>
<td>60.7</td>
<td>64.3</td>
<td>53.3</td>
</tr>
<tr>
<td>Female (%)</td>
<td>51.7</td>
<td>39.3</td>
<td>35.7</td>
<td>46.7</td>
</tr>
<tr>
<td>Hispanic or Latino (%), [ethnicity]</td>
<td>89.7</td>
<td>89.3</td>
<td>89.3</td>
<td>90.0</td>
</tr>
<tr>
<td>White (%), [race]</td>
<td>93.1</td>
<td>89.3</td>
<td>92.9</td>
<td>93.3</td>
</tr>
<tr>
<td>Weight (kg), Mean (SD)</td>
<td>80.66 (17.75)</td>
<td>81.41 (16.84)</td>
<td>83.43 (18.65)</td>
<td>80.44 (16.98)</td>
</tr>
<tr>
<td>BSA Affected (%), Mean (SD)</td>
<td>14.19 (3.57)</td>
<td>14.23 (3.56)</td>
<td>14.11 (3.56)</td>
<td>14.42 (3.44)</td>
</tr>
<tr>
<td>Baseline IGA=2, n (%)</td>
<td>12 (41.4)</td>
<td>8 (28.6)</td>
<td>9 (32.1)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Baseline IGA=3, n (%)</td>
<td>17 (58.6)</td>
<td>20 (71.4)</td>
<td>18 (64.3)</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>Baseline IGA Missing, n (%)</td>
<td>-</td>
<td>-</td>
<td>1 (3.6)</td>
<td>-</td>
</tr>
</tbody>
</table>

Source: Table 14.1.2.2 (ITT Population)
At Week 12 (200 mg group), 25.9% subjects (ITT) and 35.0% subjects (PP) achieved \( \geq 2 \)-point improvement in IGA.

<table>
<thead>
<tr>
<th></th>
<th>Prurisol 200 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12 Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT population (LOCF imputation)</td>
<td>n/N1, (%)</td>
<td>7/27 (25.9)</td>
</tr>
<tr>
<td>Difference in % vs placebo</td>
<td>+12.6 ((p=0.3179))</td>
<td></td>
</tr>
<tr>
<td>PP population</td>
<td>n/N1, (%)</td>
<td>7/20 (35.0)</td>
</tr>
<tr>
<td>Difference in % vs placebo</td>
<td>+18.3 ((p=0.2778))</td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 14.2.1.1.1 (ITT Population) and 14.2.1.1.2 (PP Population)

Note: The p-values generated from this study were for informational purposes only and statistical significance was not a criterion for study success (cf protocol section 9.8)

\(n\) = number of subjects with \(\geq 2\)-point improvement in IGA, with missing IGA scores imputed with LOCF

\(N1\) = number of subjects with available IGA score

\(p\)-value from Fisher’s exact test comparing proportions in Prurisol and Placebo group
CTIX-0002
≥ 2-point Improvement in IGA Over Time

• Clinical improvement observed in 200 mg group as early as 4 weeks
• ≥ 2-point IGA improvement (200 mg group) at Week 12 was 25.0% subjects (ITT) and 35.0% subjects (PP)

Source: Table 14.2.1.2.3 (ITT Population)
Source: Table 14.2.1.2.4 (PP Population)

* ITT population denominator for % calculation based upon subject population at baseline
IGA Scores: Distribution Over Time (200 mg group)

- IGA changes noted as soon as Week 2
- Progressive decrease of IGA scores to lower values over 12 weeks
- At Week 12, 42.8% subjects (ITT) and 55.0% subjects (PP) achieved “clear” (0) or “almost clear” (1) in IGA

* Where % subject total <100%, basis is attrition without data imputation
CTIX-0002
Safety Summary: Generally Well Tolerated

• Adverse Events
  For the Prurisol dose groups combined:
  • Headache was the most frequently reported AE (6 AEs, 7.1%)
  • One Serious Adverse Event (preferred term “hepatic enzyme increased”) reported in 50 mg dose group
  • Liver function test increases reported as AEs, with following frequency:
    • Aspartate Aminotransferase (AST) increased, 4 AEs; Alanine Aminotransferase (ALT) increased, 3 AEs; Hepatic enzyme increased, 1 AE

• Clinical laboratory review
  • Blood chemistry changes of clinical significance observed for a small number of subjects, most notable in AST and ALT
    • Seven (7) subjects had on-treatment ALT and/or AST elevations >2xULN
    • Elevations in ALT and/or AST do not appear dose related; n=2 in each active group, n=1 in placebo group
    • No associated increases noted for bilirubin
  • Hematology changes were generally not clinical significant, no trending (increasing or decreasing) noted
  • Urinalysis findings were not clinically significant

• Vitals signs assessments were without clinically significant changes
CTIX-0002
Pharmacokinetics of Abacavir

Dose-related increase in exposure and plasma concentrations observed

- Comparable plasma concentrations expected for 50 mg AM and 50 mg AM & PM doses due to short t½ (1.24 hr and 1.27 hr, respectively); however values higher for the AM & PM regimen
- Less than dose proportional increase in mean plasma concentrations, Cmax and AUC, between 50 mg AM & PM (100 mg daily) and 100 mg AM & PM (200 mg daily)

**Summary of abacavir PK parameters**

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Prurisol Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg AM</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>209 ± 87.6 (8)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.00 (7)</td>
</tr>
<tr>
<td>AUC(0→t) (hr×ng/mL)</td>
<td>522 ± 228 (8)</td>
</tr>
<tr>
<td>AUC(0→∞) (hr×ng/mL)</td>
<td>462 ± 161 (6)</td>
</tr>
<tr>
<td>t½ (1/hr)</td>
<td>0.5801 ± 0.1340 (6)</td>
</tr>
<tr>
<td>Vd/F (L/hr)</td>
<td>1.24 ± 0.24 (6)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>107 ± 62.5 (6)</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>194 ± 120 (6)</td>
</tr>
</tbody>
</table>

*Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

- Median Tmax, ranged from 0.5 hr to 1.0 hr
- Mean t½, ranged from 1.24 hr to 1.40 hr, appears to be independent of dose or regimen
- Small numbers of subjects per group
  (Note: larger sample size planned in next study for more definitive PK parameter calculations)
Current Perspectives

Looking Forward

• The primary efficacy endpoint of percentage of subjects with $\geq 2$-point improvement in IGA was met with the 200 mg Prurisol dose group achieving highest magnitude of effect

• A clear progressive decrease of IGA scores to lower values was seen as early as 2 weeks and further improved out through 12 weeks (200 mg group)

  [Note: The p-values from this study were generated for informational purposes only and statistical significance was not a criterion for study success]

• Sufficient clinical improvement was observed to warrant more detailed examination of clinical responses to treatment at 200 mg and higher dosing levels

• Prurisol was generally well tolerated

• As $\frac{2}{3}$rd of these subjects (200 mg group) had Baseline IGA=3 ("moderate” psoriasis), their favorable responses serve as a bridge to investigate Prurisol in a moderate-to-severe psoriasis population

• A Phase 2b trial is planned to begin 2H 2016 evaluating higher dosing regimens (300mg and 400mg) in moderate-to-severe psoriasis, using proportion of subjects achieving PASI75 at Week 12 as the primary endpoint

19Sep2016