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

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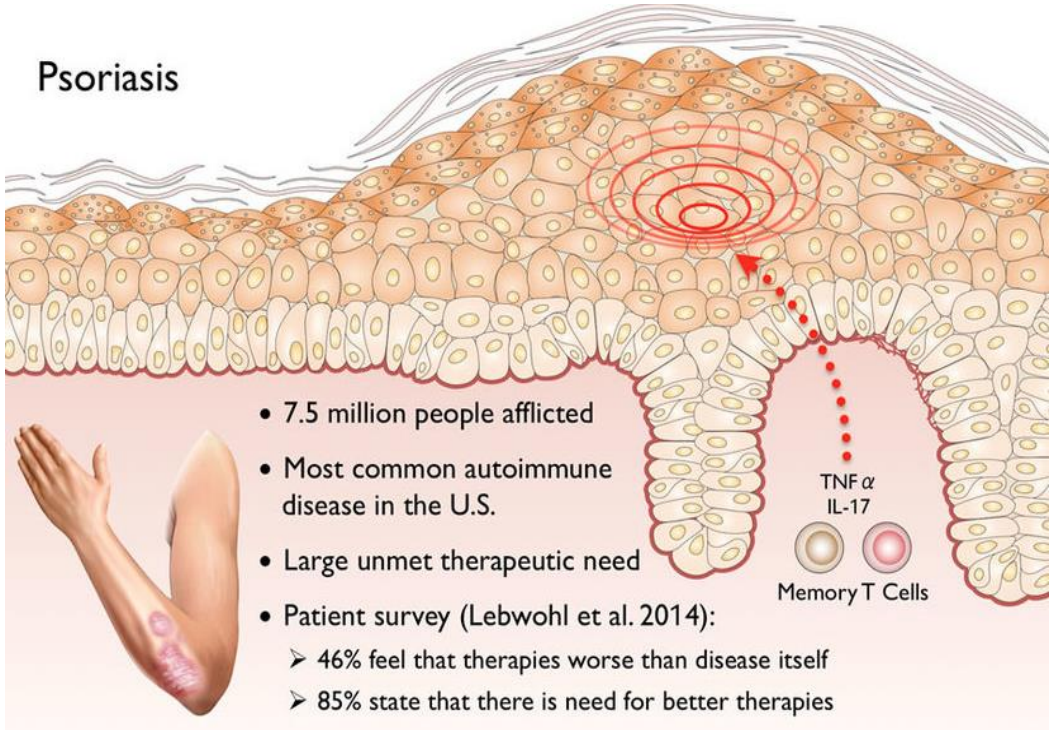
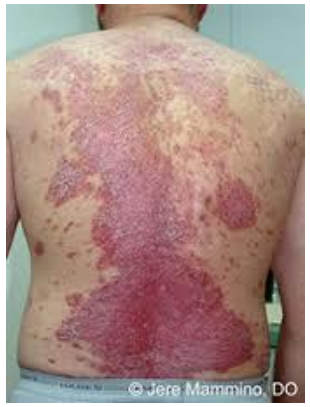
Ticker: CTIX

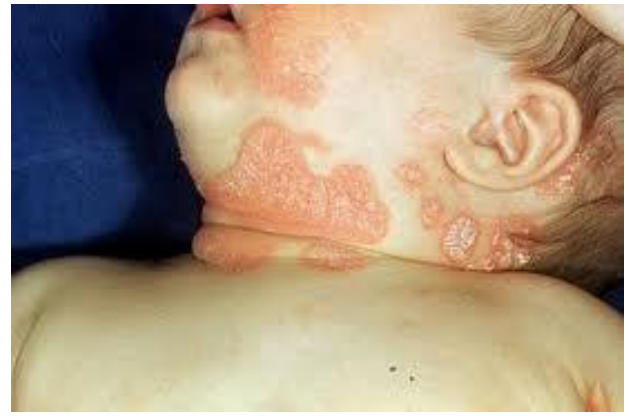
Psoriasis

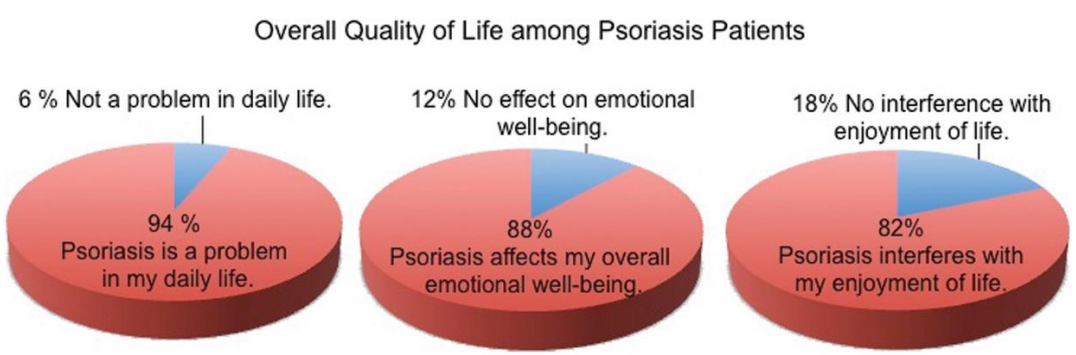
Debilitating Chronic Disease That Affects Millions

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









Sources:
https://www.novartis.com/news/media-releases/largest-global-psoriasis-survey-shows-84-people-face-discrimination-and
http://www.cytherapharm.com/
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0052935

Prurisol

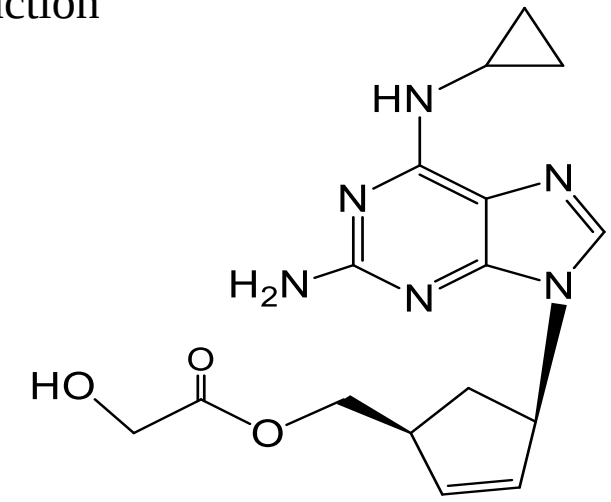
MOA and Attributes

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]



Prurisol

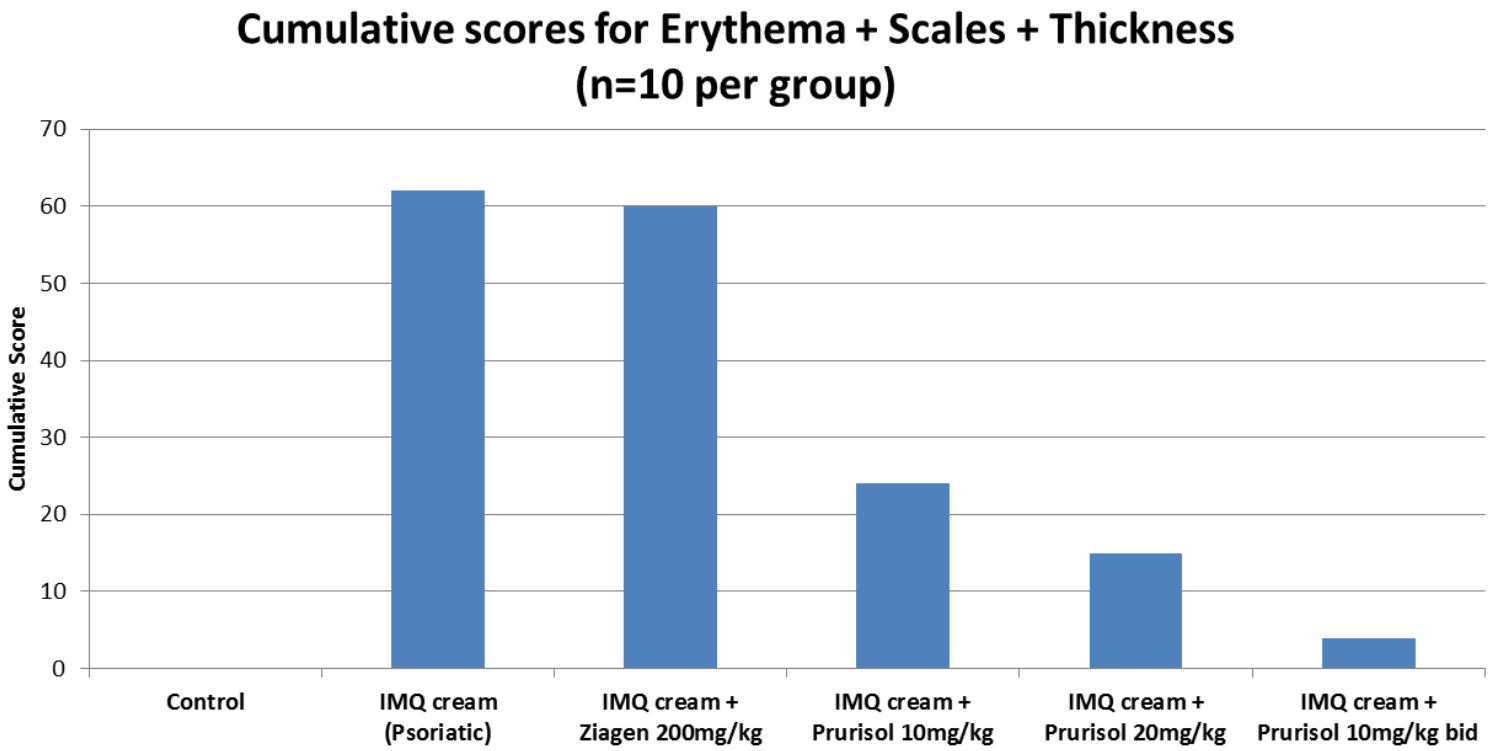
[Abacavir (α-hydroxyl) acetate; abacavir glycolate]

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

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

Prurisol

Mouse Psoriasis Model: Comparison with Ziagen® (Abacavir)



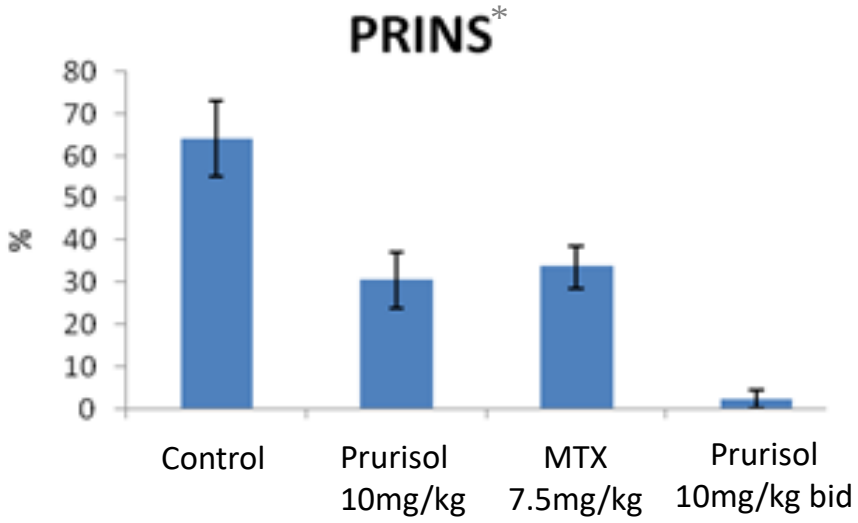
- BALB/C mice treated daily with IMQ cream or control cream on the back of the animal close to the tail
- 16 days of treatment; assessed every 2nd day for erythema, scales and thickness; Scale 0 to 4
- Calculated a cumulative score of erythema + scaling + thickness of the skin
- 2 daily doses of Prurisol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

New Imiquimod-induced Psoriasis Mouse Model for In Vivo Efficacy Screening
www.criver.com/about-us/news.../psoriasis-mouse-model

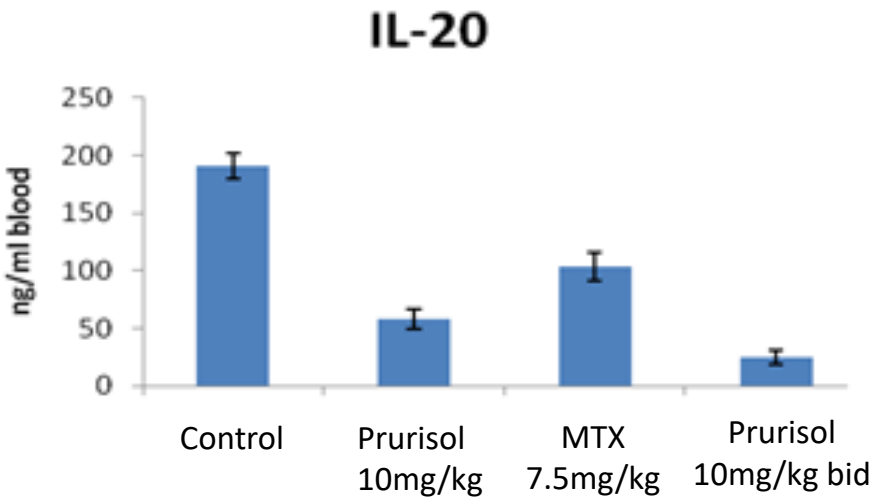
Imiquimod-Induced Psoriasis Efficacy Studies - The Jackson Laboratory
https://www.jax.org/...mice.../imiquimod-induced-psoriasis

Prurisol

Human Psoriatic Xenograft Model: PRINS & IL-20



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



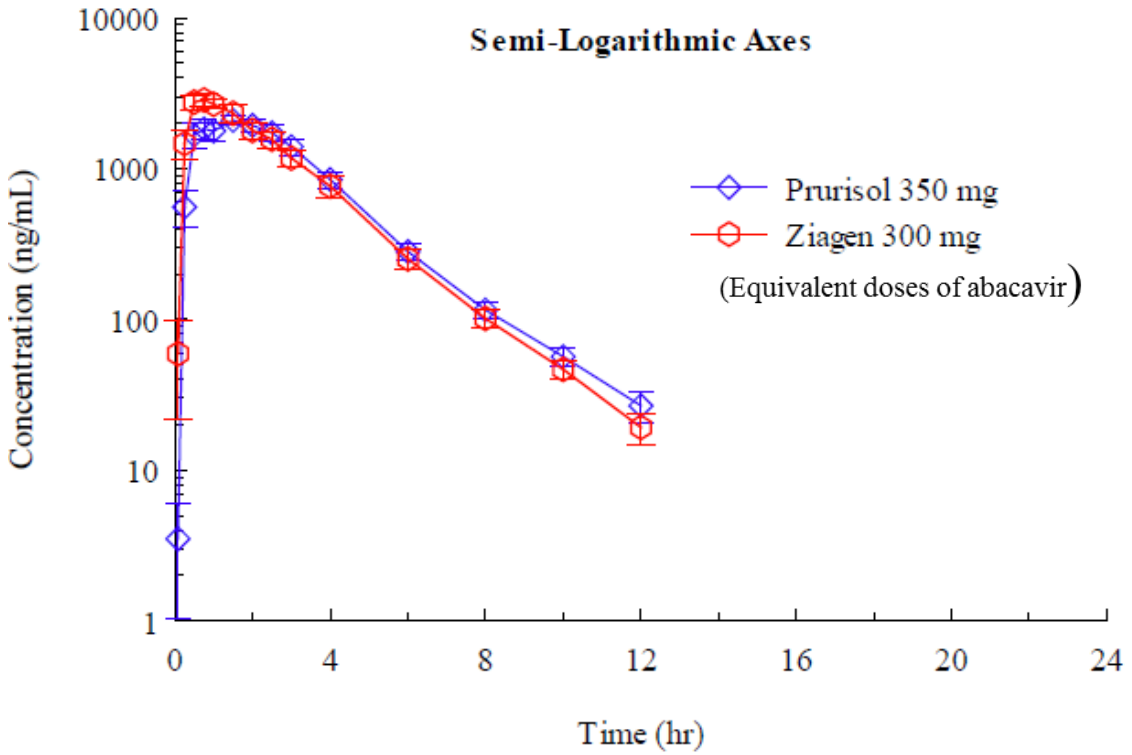
- Human psoriatic skin xenograft model; SCID mice received 350 rad total body irradiation, then transplanted with psoriatic human tissue
- Four groups:
  - 10 mg/kg Prurisol orally once per day for 21 days
  - 10 mg/kg Prurisol orally twice per day for 21 days
  - 7.5 mg/kg methotrexate (MTX) intraperitoneally 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

CTIX-0001

Prurisol Bioequivalence Trial

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



Parameter*	Prurisol 350 mg	Ziagen 300 mg
Cmax (ng/mL)	2,816 ± 703 (16)	3,617 ± 885 (16)
Tmax (hr)	0.88 (16) [0.50 – 2.50]	0.75 (16) [0.25 – 2.50]
AUC(0-t) (hr×ng/mL)	7,781 ± 2,072 (16)	8,420 ± 2,573 (16)
AUC(inf) (hr×ng/mL)	7,901 ± 2,079 (16)	8,523 ± 2,582 (16)
λz (1/hr)	0.3854 ± 0.1103 (16)	0.4033 ± 0.1183 (16)
t½ (hr)	2.00 ± 0.84 (16)	2.02 ± 1.30 (16)
CL/F (L/hr)	46.0 ± 12.8 (16)	38.5 ± 12.2 (16)
Vz/F (L)	136 ± 78.1 (16)	109 ± 67.5 (16)

*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

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

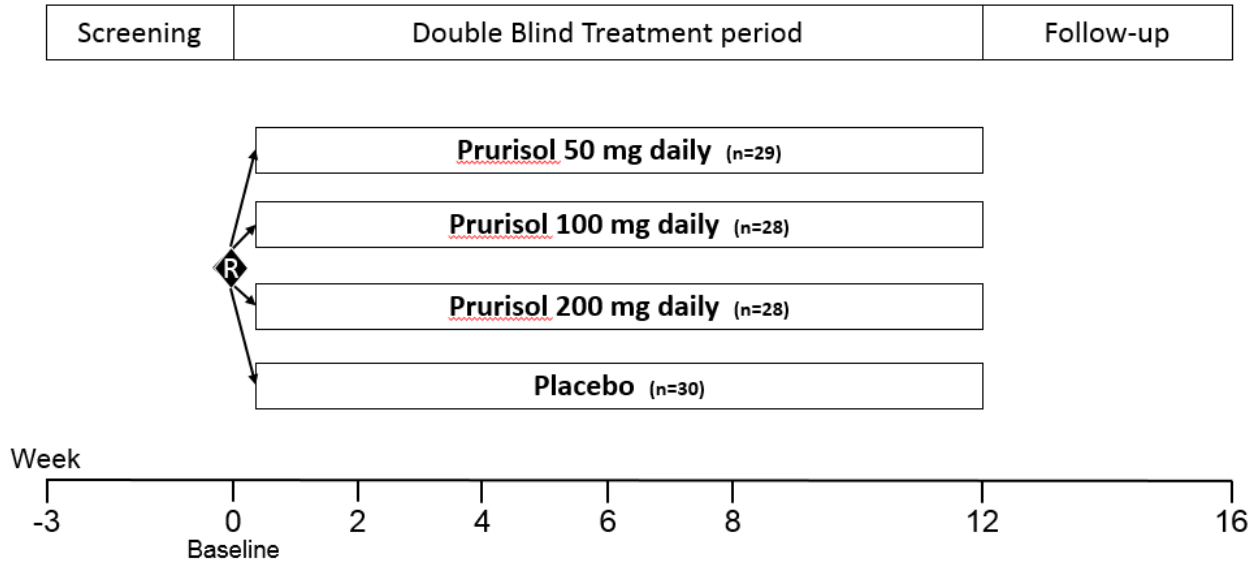
CTIX-0002 Proof of Concept

Trial Design

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

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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

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

Source: Table 14.1.2.2 (ITT Population)

CTIX-0002

Primary Efficacy Endpoint (Percentage of Subjects ≥ 2-point improvement in IGA at Week 12)

At Week 12 (200 mg group), 25.9% subjects (ITT) and 35.0% subjects (PP) achieved ≥ 2-point improvement in IGA

		Prurisol 200 mg	Placebo
Week 12 Analysis			
ITT population (LOCF imputation)	n/N1, (%)	7/27 (25.9)	4/30 (13.3)
	Difference in % vs placebo	+12.6 *(p=0.3179)*	
PP population	n/N1, (%)	7/20 (35.0)	3/18 (16.7)
	Difference in % vs placebo	+18.3 *(p=0.2778)*	

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

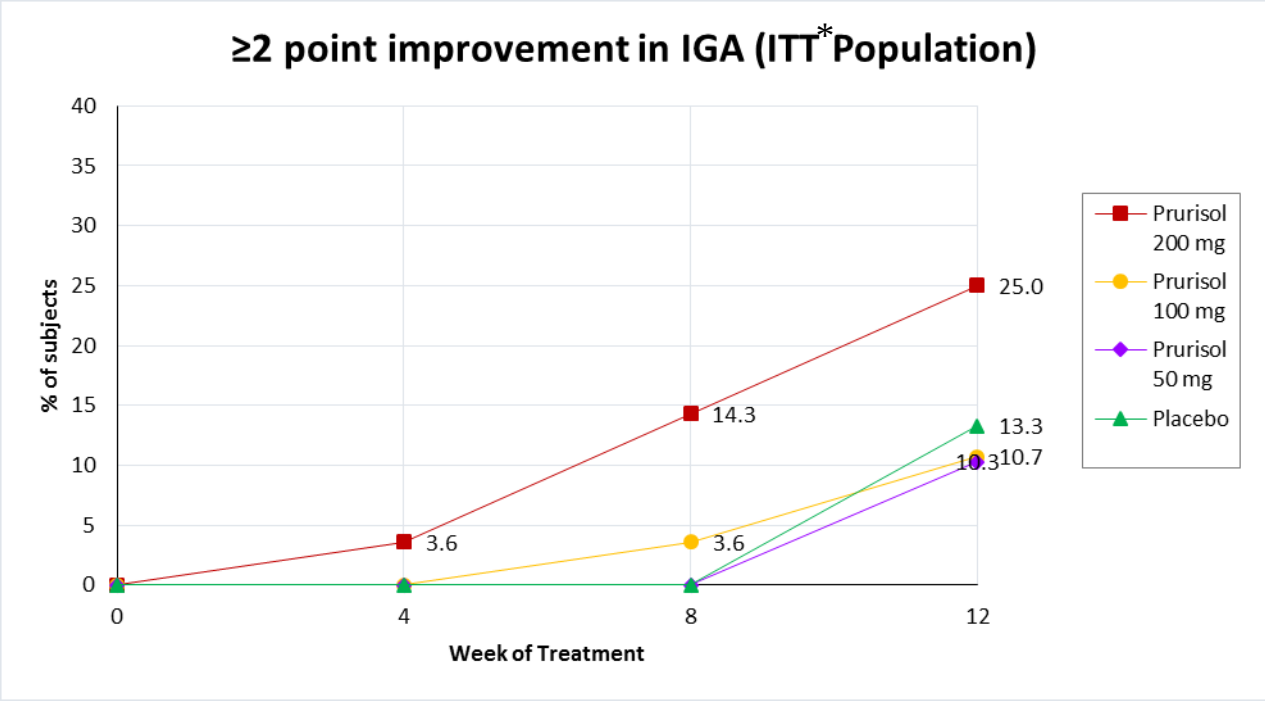
Note: The p-values generated from this study were for informational purposes only and statistical significance was not a criterion for study success (cf protocol section 9.8)

n = number of subjects with ≥ 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

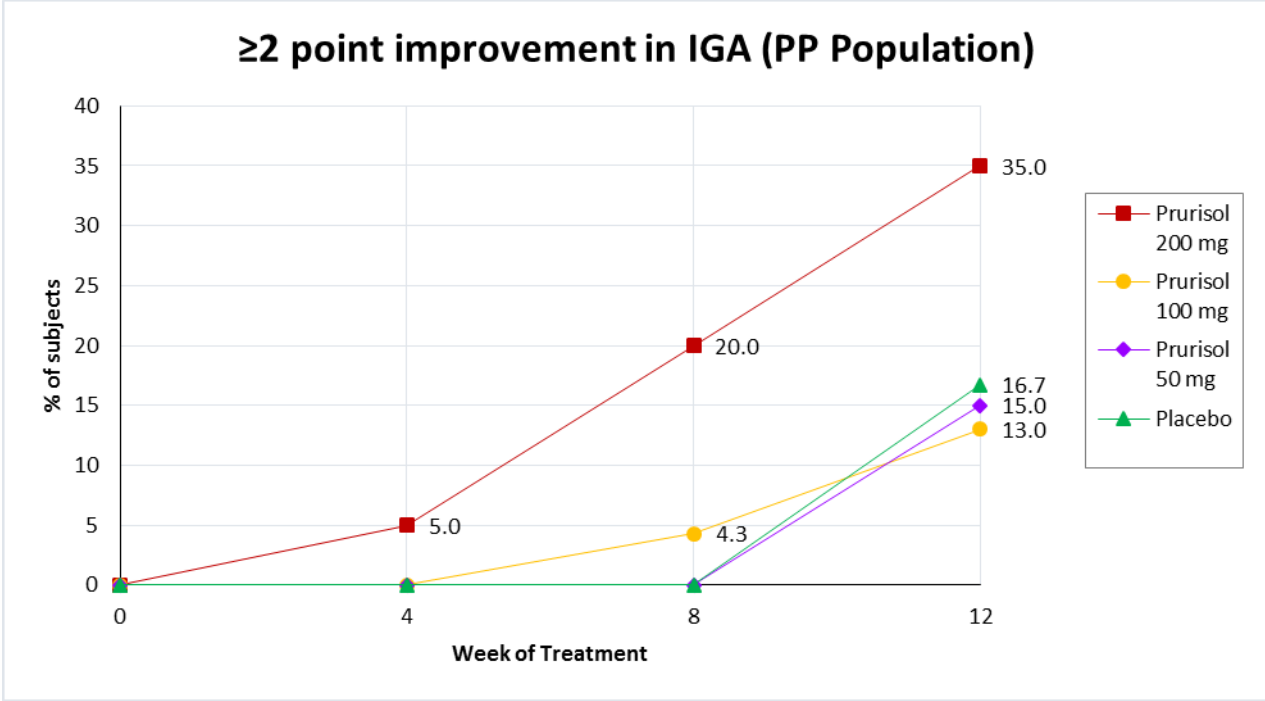
CTIX-0002

≥ 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)



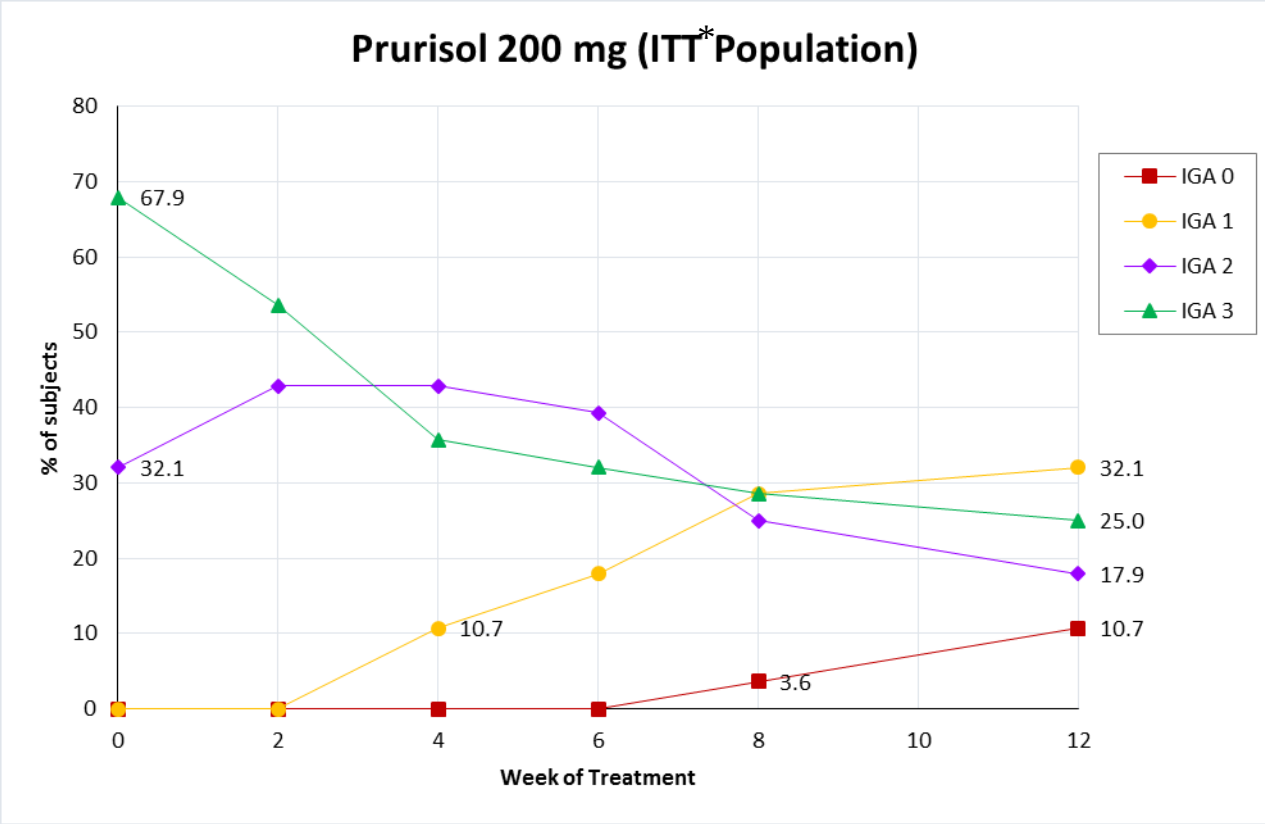
Source: Table 14.2.1.2.4 (PP Population)

* ITT population denominator for % calculation based upon subject population at baseline

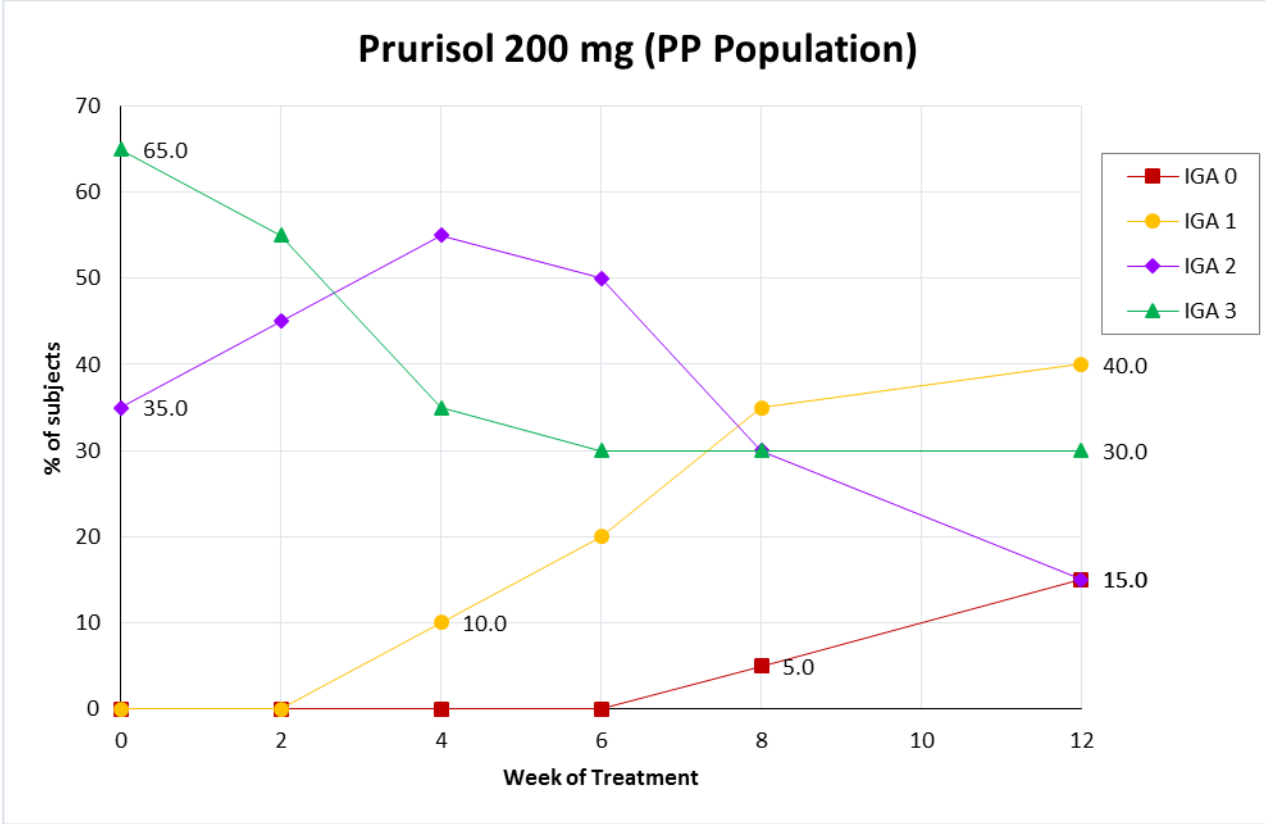
CTIX-0002

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



Source: Table 14.2.1.2.1 (ITT Population)



Source: Table 14.2.1.2.2 (PP Population)

* Where % subject total <100%, basis is attrition without data imputation

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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

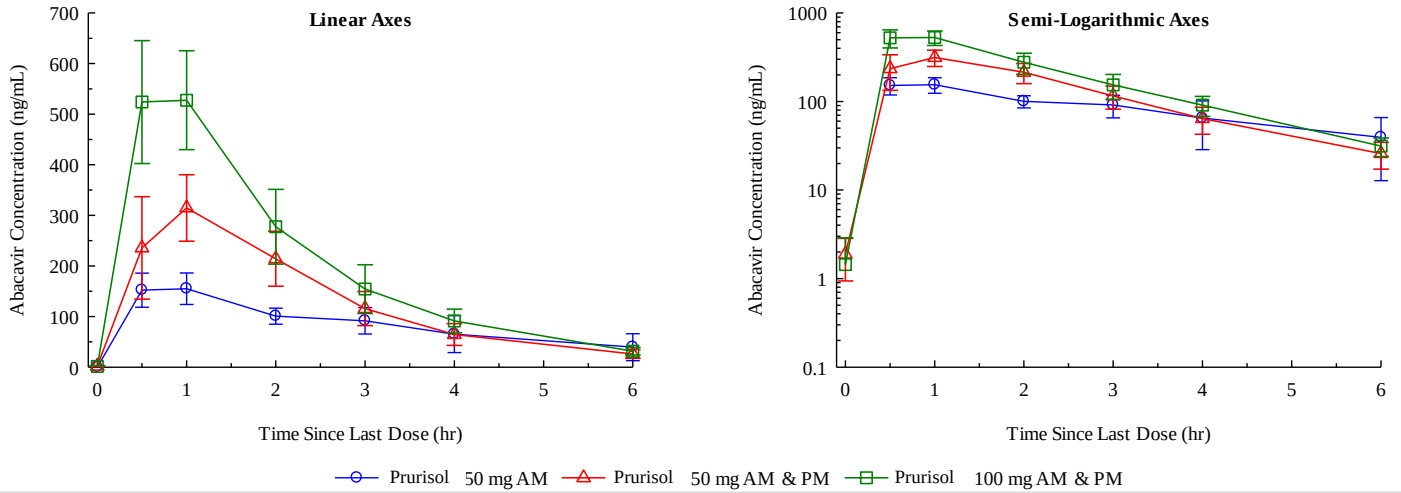
CTIX-0002

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)

Mean ± SE plasma concentrations of abacavir



Summary of abacavir PK parameters

Parameter*	Prurisol Dose		
	50 mg AM	50 mg AM & PM	100 mg AM & PM
Cmax (ng/mL)	209 ± 87.6 (8)	371 ± 209 (7)	661 ± 47.9 (3)
Tmax (hr)	1.00 (8) [0.50 – 4.00]	1.00 (7) [0.50 – 1.00]	0.50 (3) [0.50 – 1.00]
AUC(0-t) (hr×ng/mL)	522 ± 228 (8)	806 ± 490 (7)	1,258 ± 332 (3)
AUC(inf) (hr×ng/mL)	462 ± 161 (6)	859 ± 531 (7)	1,320 ± 341 (3)
λz (1/hr)	0.5801 ± 0.1340 (6)	0.5607 ± 0.1078 (7)	0.5144 ± 0.1149 (3)
t½ (hr)	1.24 ± 0.24 (6)	1.27 ± 0.23 (7)	1.40 ± 0.35 (3)
CL/F (L/hr)	107 ± 62.5 (6)	68.6 ± 42.2 (7)	66.1 ± 18.2 (3)
Vz/F (L)	194 ± 120 (6)	117 ± 56.0 (7)	139 ± 73.1 (3)

*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 ≥ 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 ⅔rd 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

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