EMPOWERING PATIENTS THROUGH
REVELATIONARY
SCIENCE

Company Overview

Dr. Neal Walker
President and CEO
January 2019

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Cautionary Note Regarding Forward-Looking Statements

Any statements contained in this presentation that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "believe", "expect", "may", "plan," "potential," "will," and similar expressions, and are based on Aclaris' current beliefs and expectations. These forward-looking statements include expectations regarding Aclaris' development programs in skin and hair conditions, the clinical development of JAK inhibitors, and the benefits and synergies of Aclaris' acquisition of RHOFADE. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements. Risks and uncertainties that may cause actual results to differ materially include uncertainties inherent in the conduct of clinical trials, Aclaris' reliance on third parties over which it may not always have full control, and other risks and uncertainties that are described in the Risk Factors section of Aclaris' Annual Report on Form 10-K for the year ended December 31, 2017, Aclaris' Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the "SEC filings" section of the Investors page of Aclaris' website at http://www.aclaristx.com. Any forward-looking statements speak only as of the date of this presentation and are based on information available to Aclaris as of the date of this presentation, and Aclaris assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Our Corporate Strategy: Building a Fully-Integrated Biopharmaceutical Company

APPLY UNIQUE LEADERSHIP INSIGHTS

- 250+ years of relevant experience in dermatology
- 300+ years of drug discovery experience in immunology
- Key leadership with track record of executing across multiple development and commercial stage companies

ACCELERATE NOVEL, DIVERSE PIPELINE

- A-101
  - A-101 45%
    - Common Warts
    - Dosed first patient in phase 3 trials in 9/2018
- Immunology Portfolio
  - ATI-501/ATI-502 (JAK 1/3 Inhibitors)
    - Alopecia Areata, Vitiligo
  - ATI-450 (MK-2 inhibitor)
    - RA, Psoriasis, CAPS, HS, PG
  - ATI-1777 (Soft JAK inhibitor)
    - Atopic Derm, Alopecia Areata, Vitiligo
  - ITK/JAK3 (Soft topical inhibitor)
    - Psoriasis, Inflammatory Dermatoses

ASSET AND COMMERCIAL STRATEGY

- Time and capital efficient
- Commercialize ESKATA® (hydrogen peroxide) topical solution, 40% (w/w) as a self-pay treatment administered in-office.
- Focus on large, underserved market segments in dermatology and inflammation.

Pipeline

Program	Indication(s)	Preclinical	Phase 1	Phase 2	Phase 3
A-101(45%) *Topical*	Common Warts				
ATI-502 JAK1/JAK3 Inhibitor *Topical*	Alopecia Areata				
	Vitiligo				
	Androgenetic Alopecia (exploratory)				
	Atopic Dermatitis (exploratory)				
ATI-501 JAK1/JAK3 Inhibitor *Oral*	Alopecia Areata				
ATI-450 MK2 Pathway Inhibitor *Oral*	RA, Psoriasis, Hidradenitis Suppurativa, CAPS, Pyoderma Gangrenosum, Other				
ATI-1777 JAK1/JAK3 Inhibitor *Soft Topical*	Atopic dermatitis, Vitiligo, Alopecia Areata				
ITK/JAK3 Inhibitor *Soft Topical*	Psoriasis, Inflammatory Dermatoses				
ITK/JAK3 Inhibitor *Oral*	Psoriasis, Inflammatory Dermatoses				
MK2 Pathway Inhibitor *Oral*	Oncology				
ITK/JAK3 Inhibitor *Oral, gut-restricted*	Ulcerative colitis / Crohn's disease				

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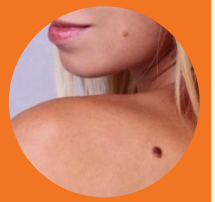
Conditions with Significant Treatment Gaps

SEBORRHEIC KERATOSIS (SK)



83+MM* people[1]

ESKATA® first FDA-approved topical treatment for raised SK

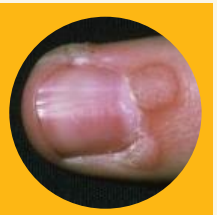
*Includes all types of SKs

ALOPECIA AREATA (AA)

6.8+MM people

in U.S. have had or will develop AA[5]; current available Rx treatment options used off label and have significant limitations

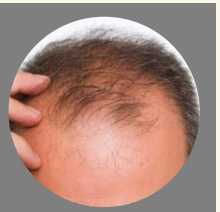
VERRUCA VULGARIS (COMMON WARTS)



22+MM people

in U.S.[2]; current treatments show only modest therapeutic effect and have significant limitations[3,4]

ANDROGENETIC ALOPECIA (MALE / FEMALE PATTERN HAIR LOSS)



35MM men and **21MM women**

in U.S. suffered from hair loss in 2012[6,7]; demand for treatment is high

VITILIGO

1-2% global population impacted[8];

no FDA-approved medication to repigment the skin[9]

[1]Bickers et al. The Burden of Skin Disease. J Am Acad Dermatology. 2006;55:490-500.[2]Nguyen et al. Laser Treatment of Nongenital Verrucae A Systematic Review. JAMA Dermatology. 2016;152(9):1025-1033.[3]Kwok et al. Topical treatments for cutaneous warts (Review). Cochrane Database of Systematic Reviews.2012. Art. No.: CD001781.[4]Mulhem et al. Treatment of Nongenital Cutaneous Warts. American Family Physician. 84:3, 2011; 288-293.[5]National Alopecia Areata Foundation. https://www.naaf.org/alopecia-areata. Last accessed July 2, 2019.[6]International Society of Hair Restoration Surgery. http://www.ishrs.org/node/3094. Last accessed July 24, 2019.[7]Herskovitz, I, et al. Female Pattern Hair Loss. International Journal of Endocrinology and Metabolism. 2013 Oct; 11(4): e9860. [8]Fitzpatrick T, et al. http://www.avrf.org/facts/frequently-asked-questions.html. Last accessed July 24, 2019.[9]The Vitiligo Therapeutics Market is Expected to Show Moderate Growth up to 2019. 2012. https://www.asdreports.com/news-217/vitiligo-therapeutics-market-expected-show-moderate-growth-up-2019. Last accessed July 24, 2019

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RHOFADE® (oxymetazoline HCl) cream, 1%

RHOFADE

The National Rosacea Society (NRS) estimates that approximately 16 million Americans are affected by rosacea.[1] Persistent facial redness is cited as the most common sign of rosacea, and may resemble a flushing or sunburn that does not go away.[2] Typical triggers include sun exposure, stress, weather, food, exercise and/or products.[3] In an NRS survey, 65% of rosacea patients surveyed said their symptoms first appeared between 30-60 years of age.[4]

1 National Rosacea Society, https://www.rosacea.org/rr/2010/winter/article_1.php, 2 National Rosacea Society, https://www.rosacea.org/patients/allaboutrosacea.php, 3 National Rosacea Society, https://www.rosacea.org/rr/2002/summer/article_3.php, 4 National Rosacea Society, https://www.rosacea.org/weblog/risks_answer_why_me, Last accessed on September 30, 2018

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RHOFADE Rationale

Rhofade (oxymetazoline HCl) cream, 1%

- Understanding of RHOFADE by management team due to role in development
- Expected synergies by leveraging current infrastructure and sales force in the U.S.
- Significant overlap (~70%) in existing call points for current field force who will detail both ESKATA and RHOFADE
- Intellectual property includes multiple patents, the last of which expires in 2035
- Deal is expected to be accretive to Aclaris' earnings beginning in the fourth quarter of 2019
- Approved indication for the treatment of persistent facial erythema (redness) associated with rosacea in adults
- Establishes a presence in medical dermatology in advance of A-101 45% for the treatment of common warts, if approved
- Opportunity to acquire a recently launched, but currently non-promoted asset in the rosacea market
- Allergan has agreed to provide financial, distribution, and commercial support to Aclaris for a smooth transition

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RHOFADE Deal and Oxford Debt Terms

Acquisition:

- Asset Purchase for the Worldwide RHOFADE® (oxymetazoline HCl) cream, 1% product rights and additional IP
- RHOFADE trailing twelve-month (TTM) net sales of $17.5 million through June 30, 2018

Consideration to Allergan:

- $65M upfront
- Royalties payable to Allergan:
  - 10% on RHOFADE net sales up to $100m
  - 12.5% on RHOFADE net sales between $100m - $150m
  - 15% on RHOFADE net sales over $150m
- $5m milestone due to Allergan for the achievement of a specified development milestone for potential development of an additional dermatology product
- Assumption of payment obligations to Aspect and Vicept
  - **Aspect**
    - One-time upon achievement of net revs in annual period of $100m
    - Royalties payable at 4.5% on RHOFADE net sales up to $100m.
  - **Vicept**
    - One-time upon achievement of net revs in 12mo period in excess $250m, $350m and $500m

Debt Terms:

- $65M total available for draw through Term Loan with Oxford Finance
- $30M borrowed on October 31, 2019
- $35M balance available from closing of RHOFADE acquisition until March 31, 2019
- Key Terms on new Term Loan
  - Interest only for 36 months, followed by 24 monthly principal payments - 5 year term
  - Coupon = LIBOR + 6.25%; Floor of 8.35%

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ESKATA® (hydrogen peroxide) topical solution, 40% (w/w)

ESKATA

eskata®

(hydrogen peroxide) topical solution, 40% (w/w)

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ESKATA – Practice Value Proposition

Forecasting Tool*

Input	
Unit Cost USD	$130.00
Unit Price USD	$300.00
Target Procedures	2
Number of Locations	1
Number of Providers	1

*For illustration purposes only

Per Unit	
Gross Margin USD	$170.00
Gross Margin	57%

Gross Profit	
Daily	$340.00
Weekly	$1,700.00
Monthly	$6,800.00
Annually	$89,080.00

- Over 1,050 ESKATA accounts opened to date
- Sales force focused on driving clinical and business integration in existing accounts and expanding account base to support national DTC campaign
- Delegation to ancillary healthcare professional staff – nurse, medical assistant, aesthetician
- Ability for practices to supplement incremental income

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U.S. Market Opportunity

83+MM People in the US with SK[1]

18+MM visits to Derm for SK[2]

8+MM SK treatments[2]

Reasons for Not Removing SKs Include[3]:

- High risk of **scarring**
- High risk of **hypopigmentation**
- Want to avoid **cutting, freezing** or **burning**

Opportunity to Engage Motivated Patients via **DTC**

In a survey of patients with SKs (n=406) who were evaluated by a dermatologist

83% Were extremely or somewhat interested **in paying out of pocket** to have their SKs removed if treatment were offered at a reasonable cost[3]

73% of **females** were so bothered by SK that they have tried to **hide**, **disguise** or **remove** their lesions on their own[3]

42% of **males** were so bothered by SK that they have tried to **hide**, **disguise** or **remove** their lesions on their own[3]

[1]Bickers et al. The Burden of Skin Disease. *J Am AcadDermatology.*2006;55:490-500. [2]Data on File. Aclaris Therapeutics, Inc. Burke Screener of 594 dermatologists. 2014. [3]Data on File. Aclaris Therapeutics, Inc. In-Office SK Treatment Study. Final Report. 2016.

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ESKATA Consumer Initiatives

DIGITAL MEDIA & PARTNERSHIPS

NEWBEAUTY realself.

marie claire ELLE

WEBSITE PAGE TAKEOVERS

CONDÉ NAST

HEARST

TV COMMERCIAL

MAGAZINE ADS

ESKATA.COM

STREAMING ONLINE:

YouTube hulu HGTV

usa network E! food network

SOCIAL MEDIA

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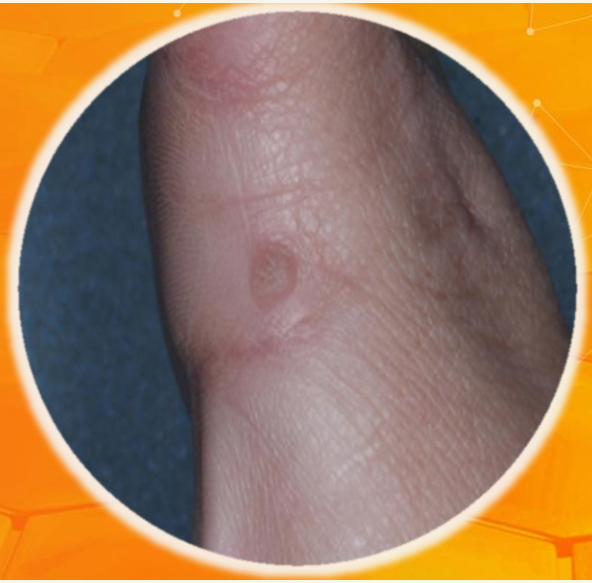
A-101 45% Topical Solution Phase 3 Candidate For Common Warts



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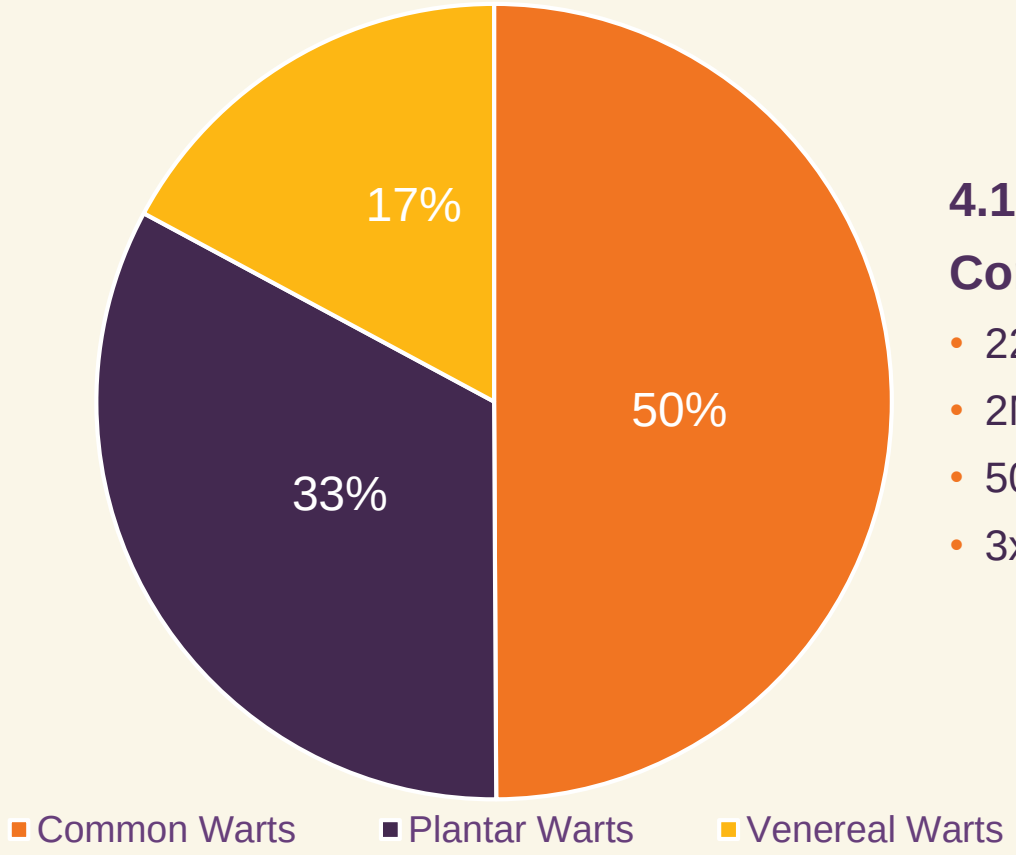
Wart Market: Patient Visits by Wart Type

Patient Visits for Warts



4.1MM Patient Visits for Warts[1]

Common Warts:

- 22MM prevalent population in the US[2]
- 2MM patient visits for common warts[1]
- 50% of all patient visits for warts[1]
- 3x more patient visits than genital warts[1]

[1] IMS National Disease and Therapeutic Index 2016.

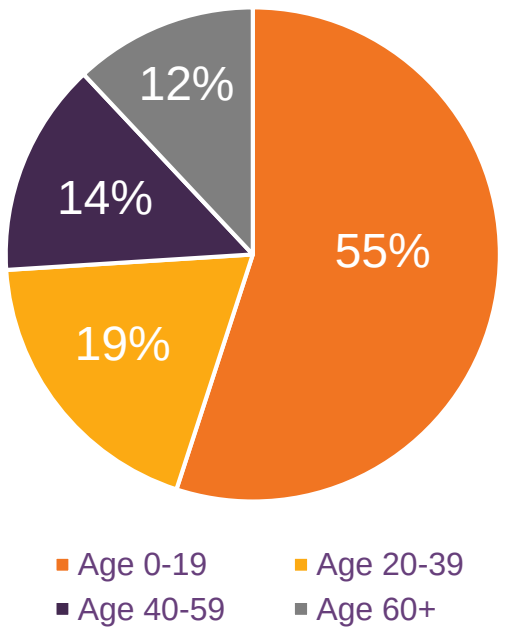
[2] Nguyen et al, Laser Treatment of Nongenital Verrucae A Systematic Review, JAMA Dermatology. 2016;152(9):1025-1033

Common Warts: Patient Desire for Treatment

- 50% of patients report moderate to extreme discomfort[1]
- 39% of patients say warts impact social/leisure activities[1]
- Perceived social stigma,[2] possibly due to contagious nature
- Warts can persist for years[2]
- OTC topical treatments containing salicylic acid are first-line and most common therapy that many patients choose[1]
  - Promote exfoliation; stimulate host immunity[2]
  - Slow to work; require frequent applications for up to 12 weeks[2]
  - Marginally effective; 1.6 times more likely to clear treated warts than placebo[3]

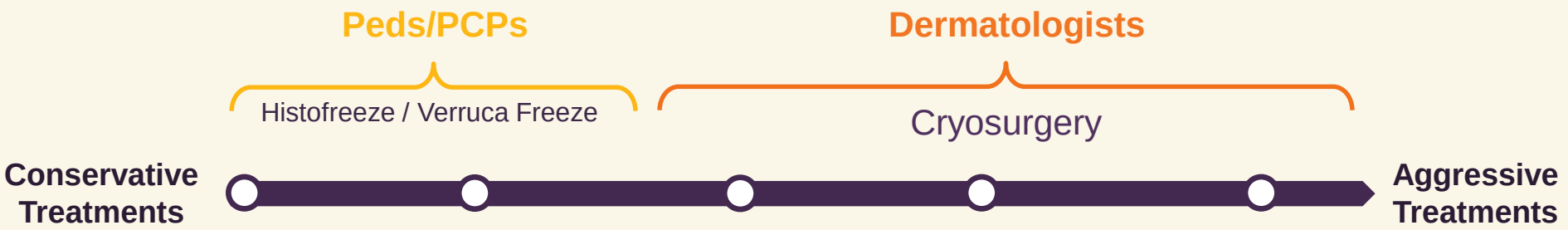
A high percentage of patients with warts are children

Patient Visits by Age[4]



[1] Lipke M., An Armamentarium of Wart Treatments, *Clinical Medicine & Research*,4:4, 2006; 273–293.
[2] Mulhem et al, Treatment of Nongenital Cutaneous Warts, *American Family Physician*; 84:3, 2011; 288-293.
[3] Sterling et al. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014, British Journal of Dermatology; (2014) 171, 696–712.
[4] IMS National Disease and Therapeutic Index 2016

Common Warts: Treatment Paradigm



OTC:
- Freezing products
- Salicylic Acid
- Botanicals

Rx Topicals:
- Imiquimod
- Retinoids
- Other off label prescriptions

- Excision
- Injections (Bleomycin, Candida)
- Laser

Peds/PCPs:
- Difficult and recalcitrant cases are typically referred to Derms
- Less likely to offer procedural treatments and so have need for an efficacious monotherapy

Dermatologists:
- Viewed as the leaders in the treatment of warts; Other specialties tend to follow Derms' lead
- More likely to utilize both in-office procedures and take-home Rx/OTC

- Patient burden comes from the duration of treatment, time commitment, pain and discomfort, as well as the cost of treatments
- A-101 45% is viewed as less burdensome than many of the more aggressive in-office treatments as well as the OTC treatments that must be applied daily

Source: Burke Market Research, January 2016

Summary of WART-203 Phase 2 Trial Results

Trial	Trial Design	Trial Outcome
WART–203 (N=159)	• A randomized, double-blind, vehicle-controlled, parallel-group study of A-101 45% solution in subjects with 1-6 common warts • Self-treated twice weekly for a total of 16 treatments	• Efficacy: Statistically significant results on all primary, secondary, and exploratory endpoints • Favorable safety profile

Primary Endpoint:

- Mean change from baseline in the Physician's Wart Assessment (PWA) score on target wart at day 56 (visit 10) using an analysis of covariance.

Secondary Endpoints:

- The proportion of subjects whose target wart is judged to be clear on the PWA at day 56.
- The proportion of subjects with all treated wart(s) clear, stratified by baseline number of warts at day 56.

Exploratory Endpoints:

- The percentage of all treated warts that were clear at day 56.

Current Status

- Initiated Phase 3 clinical trials September 2018.

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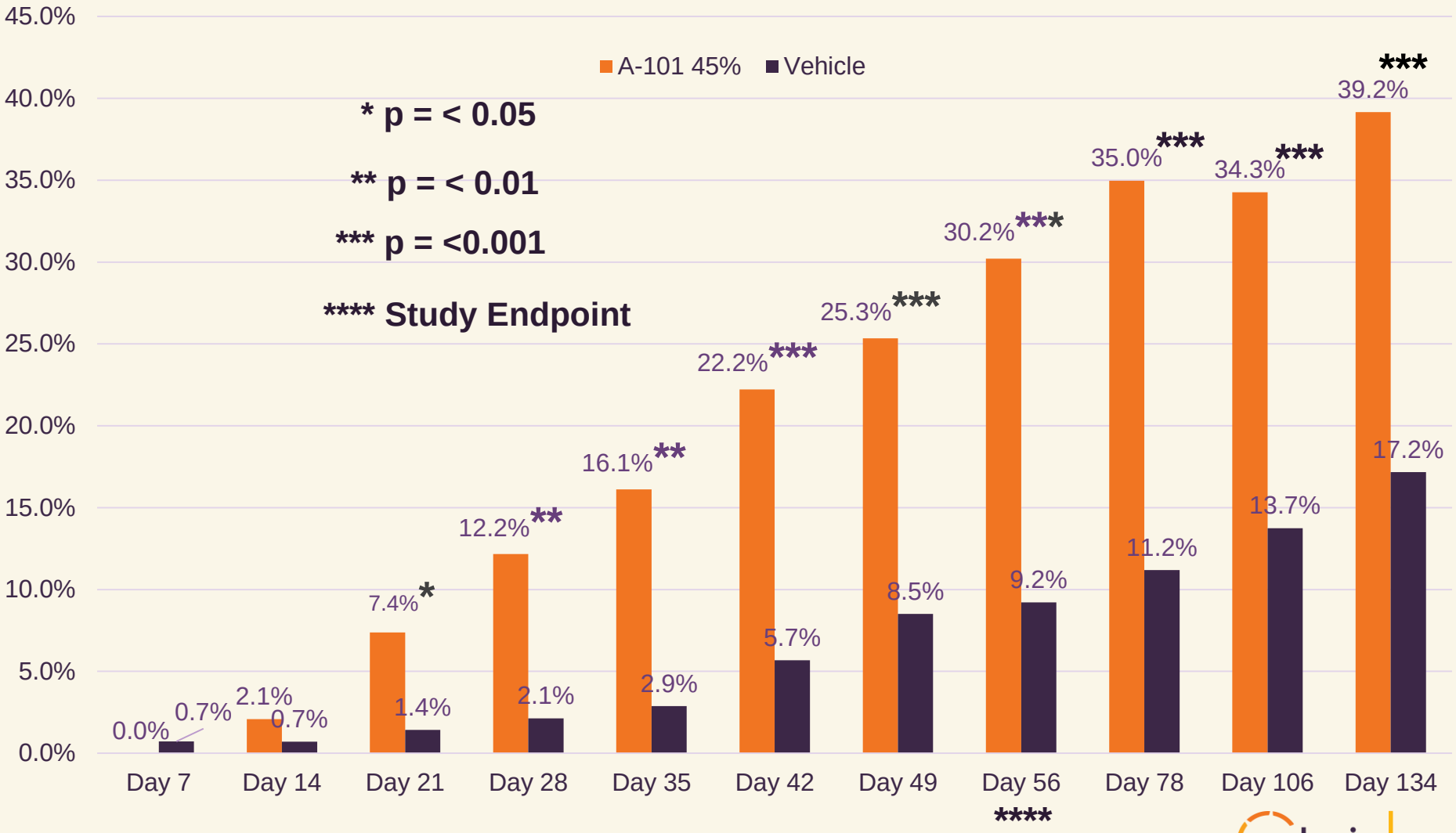
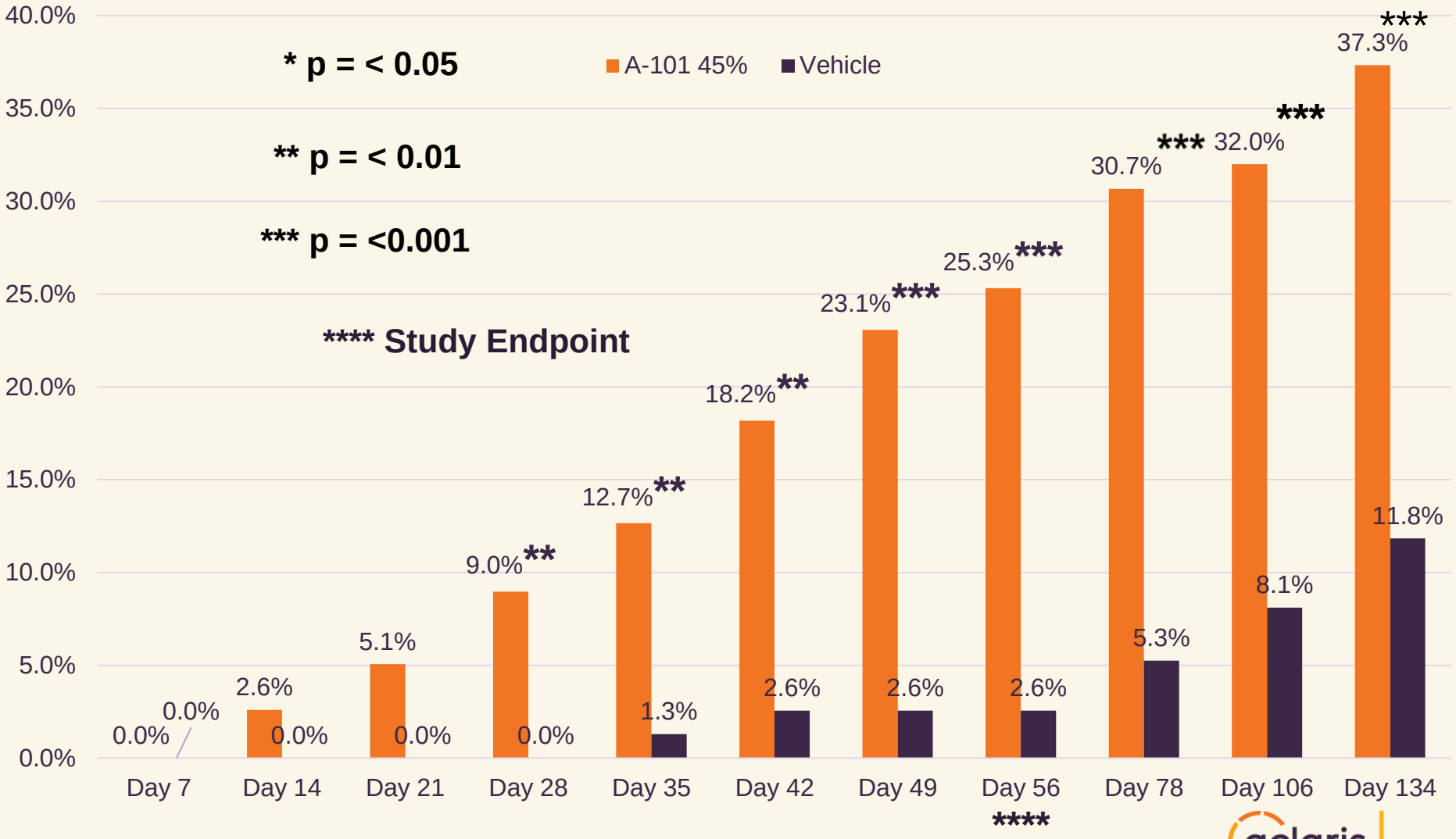
WART-203: The Percentage of All Treated Warts that are Clear on the PWA for Each Post-baseline Visit (N=159)



WART-203: Proportion of Subjects Achieving Target Wart Clearance at each Post-Baseline Visit (N=159)



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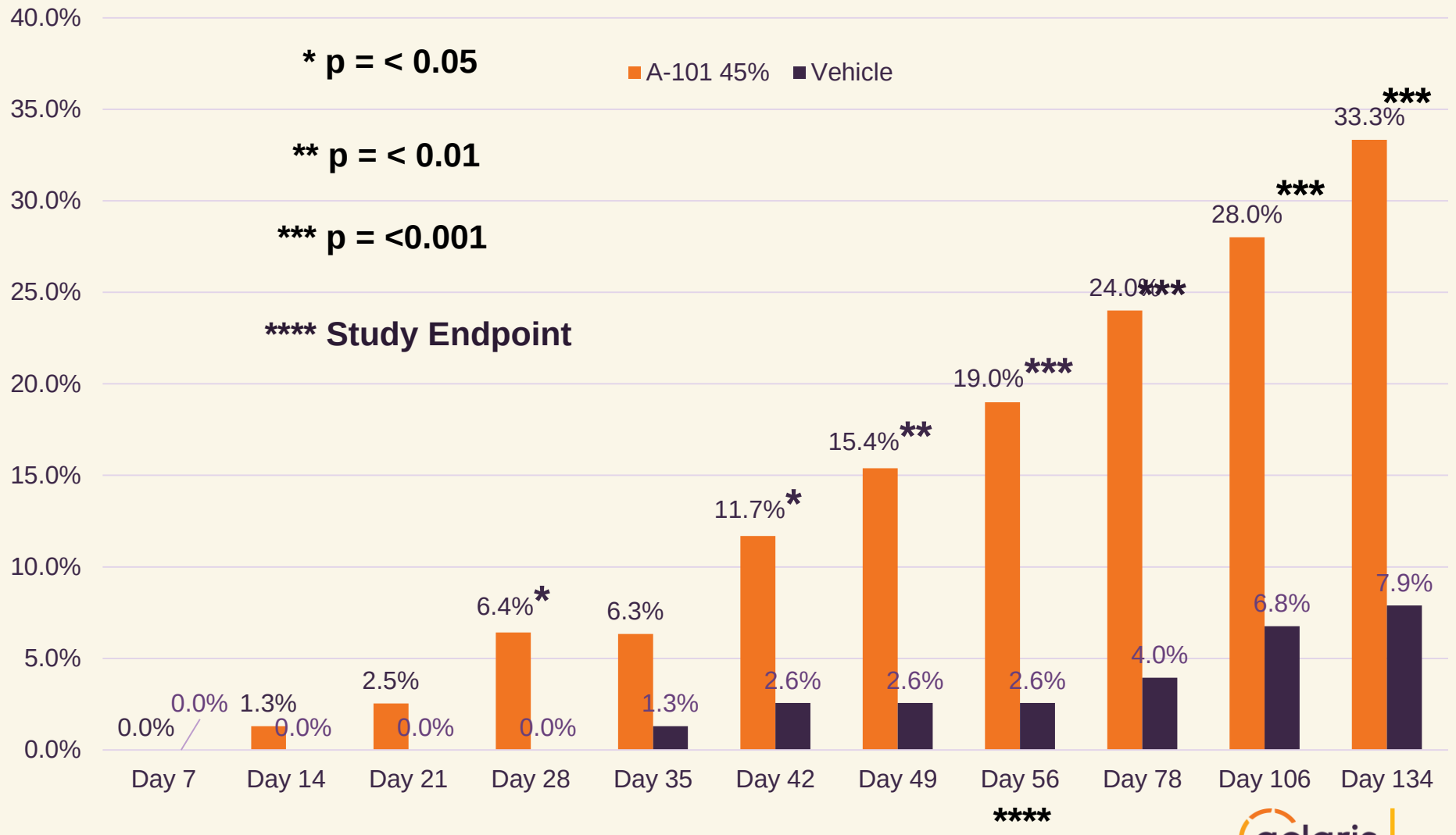
WART-203: Proportion of Subjects with all treated Wart(s) (1-6) Clear, Stratified by Baseline Number of Warts, at each Post-Baseline Visit (N=159)



Core Intellectual Property: A-101

- **Issued US Patent # 7,381,427**
  - Directed to methods of treating/removing SK with high concentration hydrogen peroxide.
  - Orange Book listed for ESKATA; estimated expiry date w/ potential PTE of 2½ yrs ~ 2025.
- **Issued US Patent # 9,675,639**
  - Directed to topical compositions of high concentration hydrogen peroxide with 2-propanol, methods of use and applicators ~ total of 70 claims
  - Orange Book listed for ESKATA; expires July 2035
- **Issued US Patent # 9,980,983**
  - Directed to methods of treating/removing SK with 40% “stabilized” hydrogen peroxide ~ total of 25 claims
  - Orange Book listed for ESKATA; expires April 2035
- **Issued US Patent # 10,098,910**
  - Directed to an applicator containing a formulation of high concentration hydrogen peroxide and methods of using such an applicator to treat seborrheic keratosis (SK), warts and other indications ~ total of 18 claims
  - Orange Book listed for ESKATA; expires April 2035
- **Pending Applications**
  - In US, directed to additional applicator and methods of treating warts with 45% hydrogen peroxide; subject matter of ‘639 and ‘983 Patents and foregoing also being pursued in major foreign markets; would expire in April 2035
  - Directed to results of Aclaris Wart-201 Study data; would expire in August 2037.
- **Exclusive supply agreement with only cGMP manufacturer of Active Pharmaceutical Ingredient**
  - Exclusivity for 10 years from date of 1st commercial sale of product.
- **Granted 3-year exclusivity, actively seeking 5-year exclusivity**

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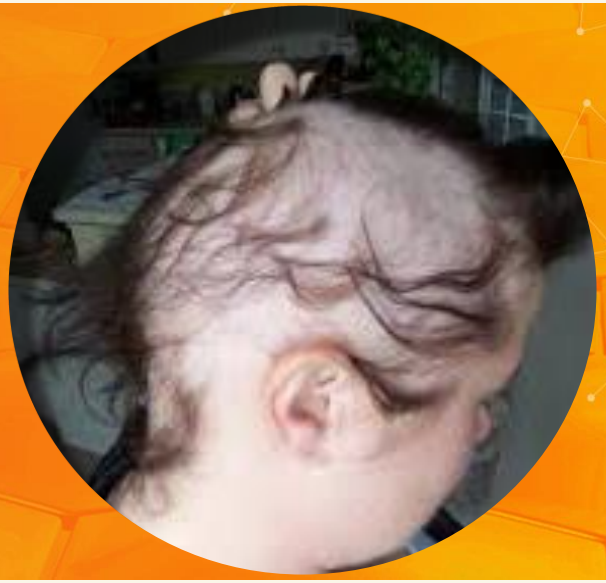
JAK Inhibitor Candidates



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ATI-501/ATI-502: Investigational Selective JAK 1/3 Inhibitors in Alopecia Areata, Vitiligo and Androgenetic Alopecia

Portfolio and IP Estate:

ATI-501 (oral) and ATI-502 (topical) – Selective JAK 1/3 inhibitor

Additional topical JAK inhibitors in development

- Oral and topical rights
- Known MOA and observed biological response in humans
- Promoted hair regrowth in mouse model[1]
- Broad IP estate
- Know-how and methods of use covering JAK inhibitors for the treatment of:
  - Alopecia areata
  - Androgenetic alopecia (male and female pattern hair loss)
  - Additional hair loss disorders

ATI-501 JAK1/JAK3

Oral treatment for alopecia totalis and alopecia universalis

ATI-502 JAK1/JAK3

Topical treatment for patchy alopecia areata, androgenetic alopecia, and vitiligo

JAK1/JAK3 Inhibitor

“Soft Topical” treatment for atopic dermatitis, alopecia areata, and vitiligo

[1] Data on File. Aclaris Therapeutics Inc.

Alopecia Areata (AA)

- 6.8+ million people in the U.S. have had or will develop AA during their lives[1]
  - 25-50% of patients have persistent patchy AA[2]
  - 14-25% of patients progress to alopecia totalis or universalis[2]
- AA is an autoimmune condition which ranges in severity:
  - Patchy Alopecia Areata – patchy hair loss on scalp
  - Alopecia Totalis – complete hair loss on scalp
  - Alopecia Universalis – complete hair loss on scalp, face and body
- 2/3 of affected individuals <30 years old at disease onset[3]
- Translational research work by Dr. Angela Christiano at Columbia University

[1]National Alopecia Areata Foundation. hhttps://www.naaf.org/alopecia-areata. Last accessed July 2. 2019.
[2]MacDonald, et al. Guidelines for the Management of Alopecia Areata. *Brit J Derm*. 2003
[3]Gilhar, A. et al. Alopecia Areata *NEJM* 366;16 nejm.org. 2012

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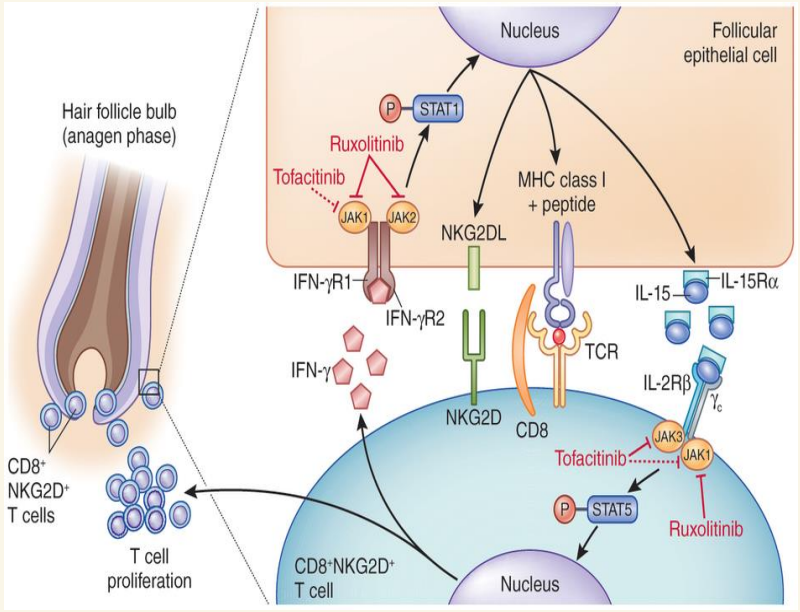
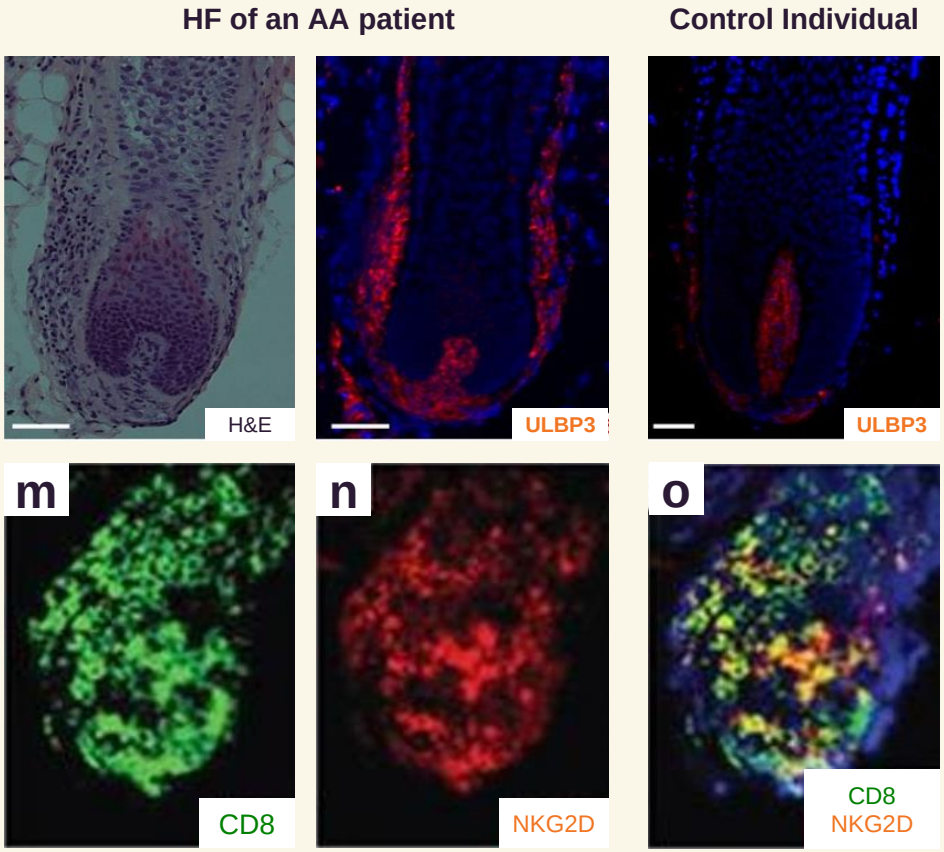
Mechanism of JAK Inhibitors in Alopecia

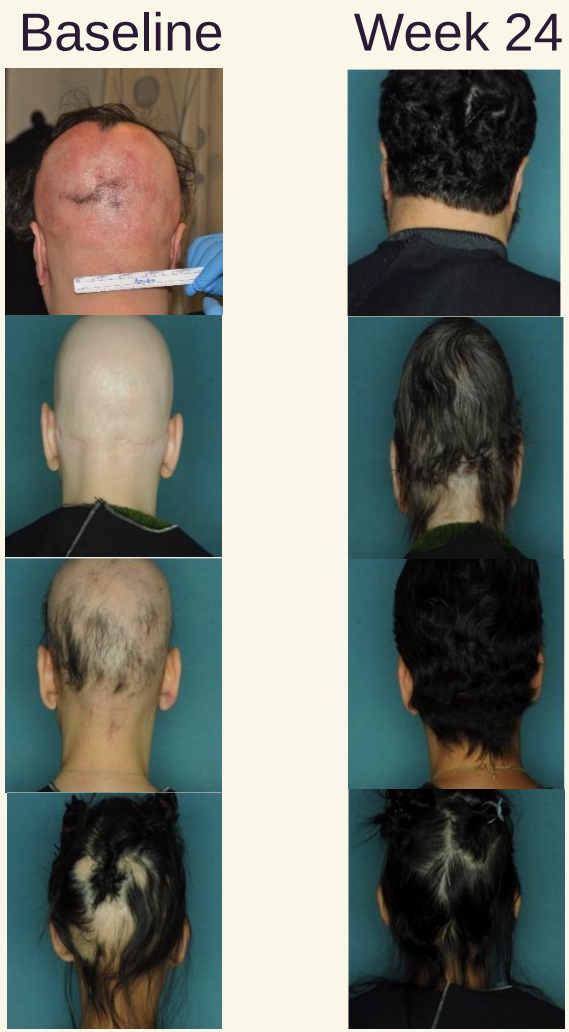


Divito & Kupper, Nature Medicine 20, 989–990 (2014).



Christiano Laboratory, Columbia University

Ruxolitinib and Tofacitinib in Alopecia Areata[1]



RUXO - Baseline SALT 64%. Duration of hair loss 12 years. 6 months 20mg BID. Last SALT 1%

TOFA - Baseline SALT 100%, 5 months 5mg BID, 2 months 10/5 mg BID, 3 months 10mg BID ongoing. Last SALT 39%.

TOFA - Baseline SALT 84%, 6 months 5mg BID, 0 months 10/5mg, 0 months 10mg. Last SALT 0%.

TOFA - Baseline SALT 46%, 5 months at 5mg BID, 2 months at 10/5mg, 2 months 10mg ongoing. Last SALT 12%.

[1]Mackay-Wiggan, et al. JCI Insight. 2016 15:e89790.

Additional Potential Indications: Vitiligo

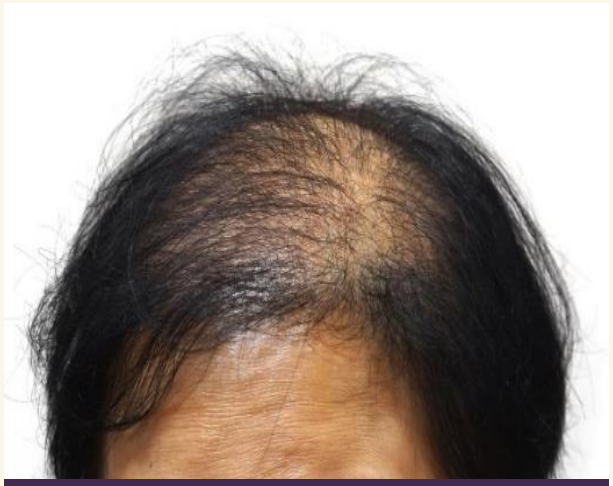
- Vitiligo is a common autoimmune disease where melanin (pigment) is absent, causing lighter patches of skin to appear on various parts of the body[1,2]
- Vitiligo impacts 0.5-2% of the global population irrespective of sex, race or age[3]
- Disease onset occurs in about one-half of sufferers before the age of 20 years[3]
- Drug candidates: ATI-502 (topical) JAK inhibitors

[1] Roddick, J. Autoimmune Diseases. Healthline. 07.22.2015.
[2] Oakley, A. Vitiligo. DermnetNZ. 08.2015.
[3] Picardo_2015_Nature Reviews Disease Primers_Vitiligo.

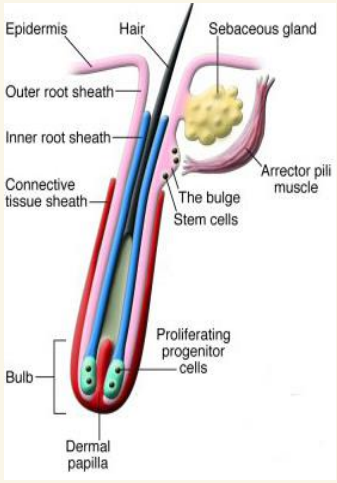
Additional Potential Indications: AGA

- Androgenetic alopecia (male/female pattern hair loss)
- AGA, a genetic disorder, is the most common cause of hair loss[1]
- Experienced by 70% of men and 40% of women at some point in their lives.[1] In 2012, 35 million men and 21 million women suffered hair loss[2,3]
- Sufferers are highly motivated to seek treatment[1]
- Drug candidate: Topical “Soft” JAK inhibitors in development

Male with AGA



Female with AGA



Cotsarelis , J Clin Invest. 2006;116(1):19-22.

[1] McElwee J., et al. Promising Therapies for Treating and/or Preventing Androgenic Alopecia. Medscape. 2012
[2] International Society of Hair Restoration Surgery, http://www.ishrs.org/. Last accessed July 24, 2019.
[3] Herskovitz, I, et al. Female Pattern Hair Loss. *International Journal of Endocrinology and Metabolism*. 2013 Oct; 11(4): e9860.

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Core Intellectual Property: JAK inhibitor

- US & Global JAK IP estate consisting of >150 patents/applications (issued and/or pending)
- Exclusive license with Rigel Pharmaceuticals for ATI-501 & ATI-502 (COM) in dermatology
  - US Natural expiry dates 2030-2034 + potential applicable PTE
  - Corresponding patents & applications in 18 additional jurisdictions (EU, AU, CA, IN, JP, others) - Natural expiry dates 2030 + potential applicable PTE
- Exclusive license under Columbia University
  - Covers the use of certain JAK inhibitors for the treatment of AA, AGA, and other hair loss disorders and biomarkers to identify potential responders
  - This portfolio includes a recently issued U.S. patent and recently allowed U.S. applications directed to methods of treating AA, AGA and other hair loss disorders by administering ruxolitinib, baricitinib, decernotinib, or tofacitinib, and a recently issued patent in Japan directed to pharmaceutical compositions comprising ruxolitinib, baricitinib, or tofacitinib for use in treating AA, AGA and other hair loss disorders
  - Natural expiry date 2031
  - Pending applications in Europe, Japan and Korea

Inflammation and Immunology Platform

Inflammation and Immunology

Walter Smith	Joseph Monahan, PhD	Jon Jacobsen, PhD	Paul Changelian, PhD
Former VP Research & Global Head, Pfizer Inflammation, co-leader of Pfizer Licensing Team Delivered 8 clinical candidates, 6 INDs and 1 NDA in inflammation and cancer	Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team >95 publications and patents (>30 total on kinases)	Former Research Fellow and Director, Pfizer Chemistry >100 publications and patents (15 total on kinases) Project Lead for PFE JAK Program	Immunologist/drug discovery leader at pharma (Pfizer) & biotech (Lycera, Infinity) Validated JAK 1/3 as target for transplant/RA/psoriasis, leading to approval of Xeljanz®

PLATFORM

- KINect™ platform – drug discovery engine
- Proprietary compound library and computational chemistry capability
- Medicinal chemistry, disease biology, immunology, pharmacology and preclinical development expertise

PEOPLE

- Co-inventors of tofacitinib and former leaders of Pfizer kinase program (including JAK inhibitors)
- Kinome experts - chemists and biologists; combined 300+ years of drug discovery experience
- Significant experience in small molecule drug discovery through Phase 2

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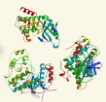
KINect Platform – *Developing Better Kinase Drug Candidates Rapidly & Efficiently*

TARGET SELECTION & VALIDATION | **KINect Platform – LEAD GENERATION** | **ASSET GENERATION**

500+ Kinases

>300 Cysteine Kinases

Select Cysteine Kinases



w/Published Crystal Structures

Assess Target Confidence

- Disease
- Genetics
- Safety
- Distribution

Leveraging key opinion leaders, data in public domain and internal validation

Custom Kinase Assays

Proprietary Chemical Library

ANALYSIS

MODELING

DESIGN

SYNTHESIS

Schrödinger ™ Enabled Drug Design

High affinity/selective drug scaffolds more rapid target to candidate selection

Proprietary Portfolio
- Project 1
- Project 2
- Project 3

Strategic Partner(s)
- Project 1
- Project 2
- Project 3

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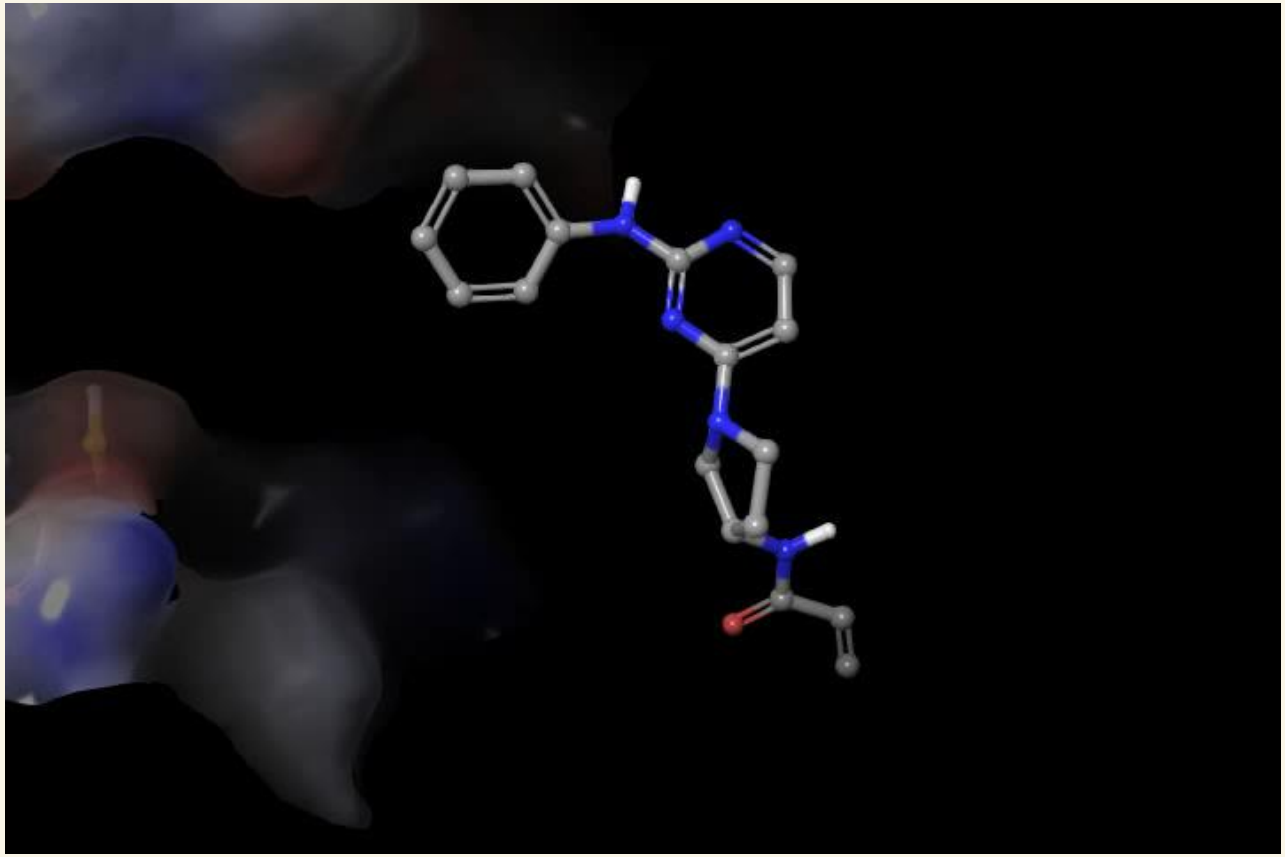
KINect™ Discovery of Covalent Kinase Inhibitors

- Leverage interaction with cysteine free -SH to address issues of potency, selectivity and biochemical efficiency
- Precise placement of reactive group provides significant rate enhancement for covalent bond formation
- **Maximizing** reversible affinity and **Minimizing** reactivity to with the intent of developing efficacious and safe drugs



Kinase **+** ***KINect Library Compound***

Reversible → ***Covalent***

Reactivity

Research and Development Capabilities

BIOCHEMISTRY & ENZYMOLOGY

- Leaders in Mechanistic Enzymology
- Custom Assay Development
- Compound: Target Interaction
- Enzyme Inhibitor Mechanisms
- Direct Binding Kinetics
- High Throughput Screening

TRANSLATIONAL RESEARCH

- Biomarker Assay Development
- Clinical Biomarker Assessment
- *In vivo* Efficacy and PK Studies
- PK/PD Relationship
- Release Assay Validation

BIOANALYTICAL CHEMISTRY

- Non-GLP Analytical
- Bioanalytical Method Development
- Bioanalytical Method Validation
- Pharmacokinetic/Toxicokinetic Analysis
- Ab Solubility and Aggregation

CELL & MOLECULAR BIOLOGY

- Target Clone/Express/Purification
- Translatable Cellular Assays
- Target Modulation/Disease Assays
- Cell Pathway Interrogation
- Custom Assay Development
- Multiple Assay Platforms

IMMUNOLOGY & IMMUNO-ONCOLOGY

- Cytokine Expression
- Th Cell Differentiation/Activation
- CTL Differentiation and Function
- B Cell and NK cell Function
- Ag Specific Cell and *In Vivo* Models
- HWB/PBMC/Monocyte Assays

COMPUTATIONAL & MEDICINAL CHEMISTRY

- Schrödinger ™ Enabled Structure Based Drug Design
- Computational Chemistry
- Library Design
- Compound Synthesis

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The Kinase Opportunity: Rational Targeted Drug Discovery

Creating New Medicines Targeting Previously Inaccessible Parts of the Kinome

KINect™ Technology Platform

Proprietary chemical library and integrated capabilities for interrogating the Kinome

- Solves challenges encountered in the class
  - Selectivity
  - Biochemical efficiency
- Validity of targeting kinases is commercially established
- Plethora of validated kinase targets are inadequately drugged
- KINect™ platform allows rational targeting of validated kinase targets

Kinase Drugs Represented $240B in Aggregate Global Sales from 2011-2015[1]

500 member class, representing 2% of the human genome

[1] https://www.nature.com/nrd/posters/druggablegenome/nrd_druggablegenome.pdf. Last Accessed 8-2-18

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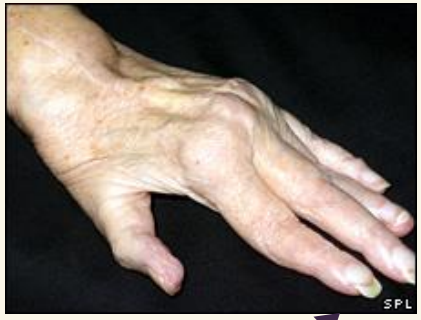
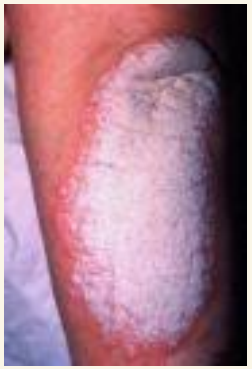
MK-2 Inhibitor: Inflammatory Cytokines Drive Disease Pathophysiology

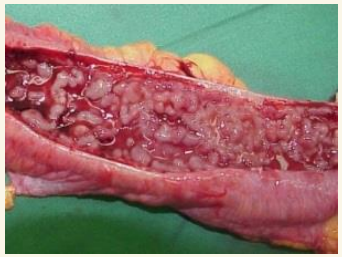
Rheumatoid Arthritis (RA)
Juvenile Idiopathic Arthritis



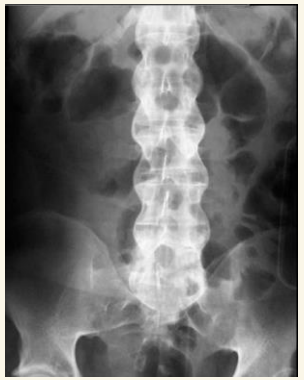
Psoriasis
Psoriatic Arthritis



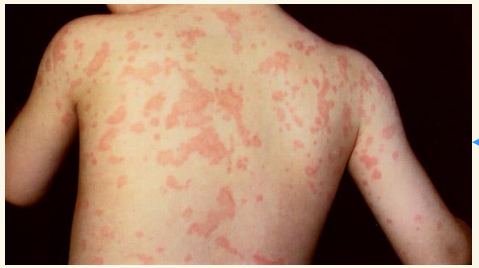
Inflammatory Bowel Disease



Ankylosing Spondylitis



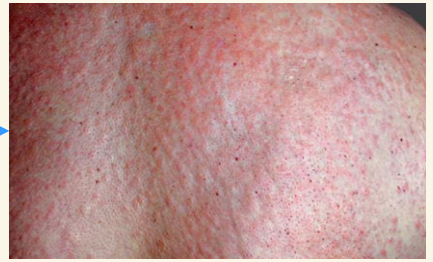
CAPS / Autoinflammatory Disease



TNFα

IL-1

Still's Disease



Anti-TNF Biologic Drugs: Humira®, Enbrel®, Remicade® (>$30B sales)
Anti IL-1 Biologic Drugs: Kineret®, Ilaris®, Arcalyst® (~$1B Sales)

Strategy: develop an oral drug with efficacy paralleling anti-TNF and anti-IL1 biologics

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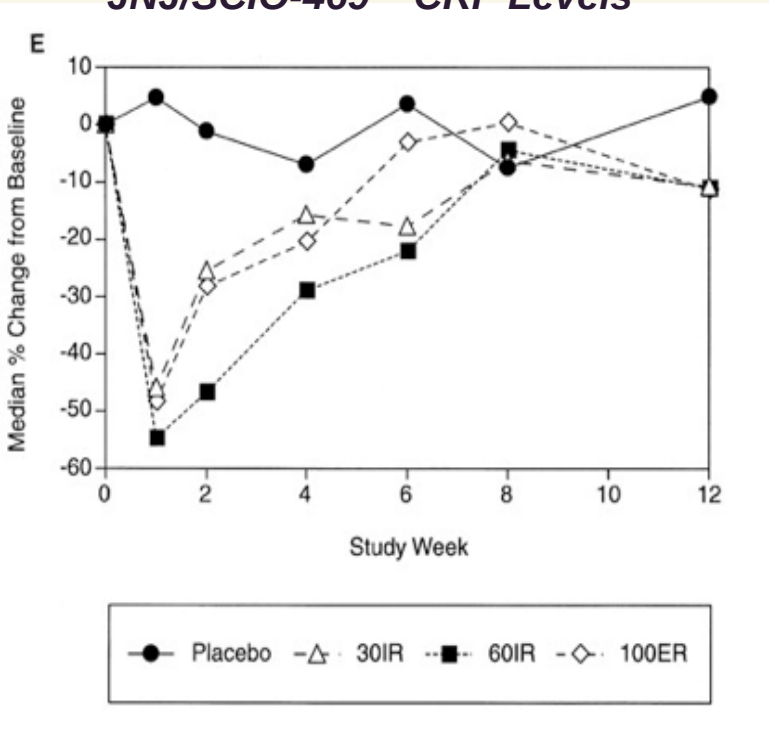
Challenge of Traditional p38 Inhibitors

Transient Efficacy or Tachyphylaxis

Tachyphylaxis: Rheumatoid Arthritis Study*

JNJ/SCIO-469 CRP Levels

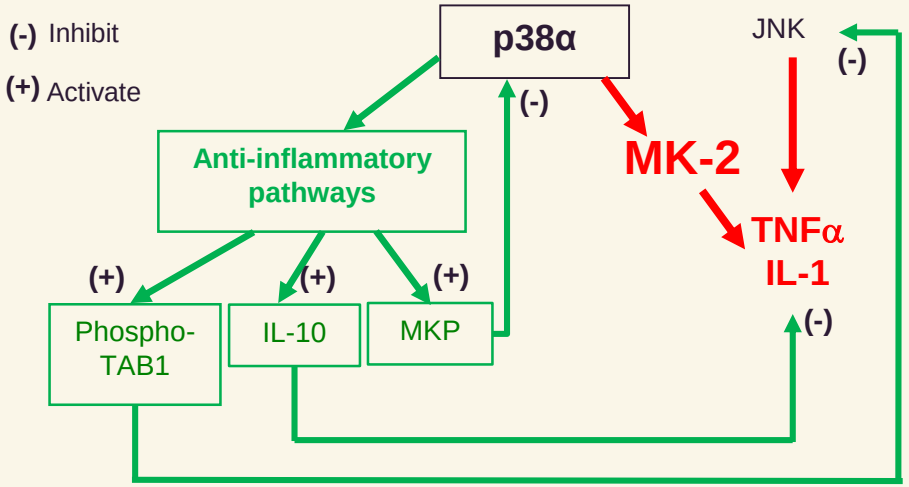


**Genovese, et al., J Rheumatology (2011)*

- Safety - Transient ⇑ LFT, Rash
- Transient Efficacy - No Go for RA
- Also seen in IBD, ACS

Hypothesis:

- Global p38 inhibition blocks inflammatory **and** anti-inflammatory pathways
- MK2 pathway inhibitor is expected to maintain efficacy through selective inhibition of the inflammatory pathways



Schematic of MK2 dependent inflammatory pathway and other anti-inflammatory pathways downstream of p38MAPK

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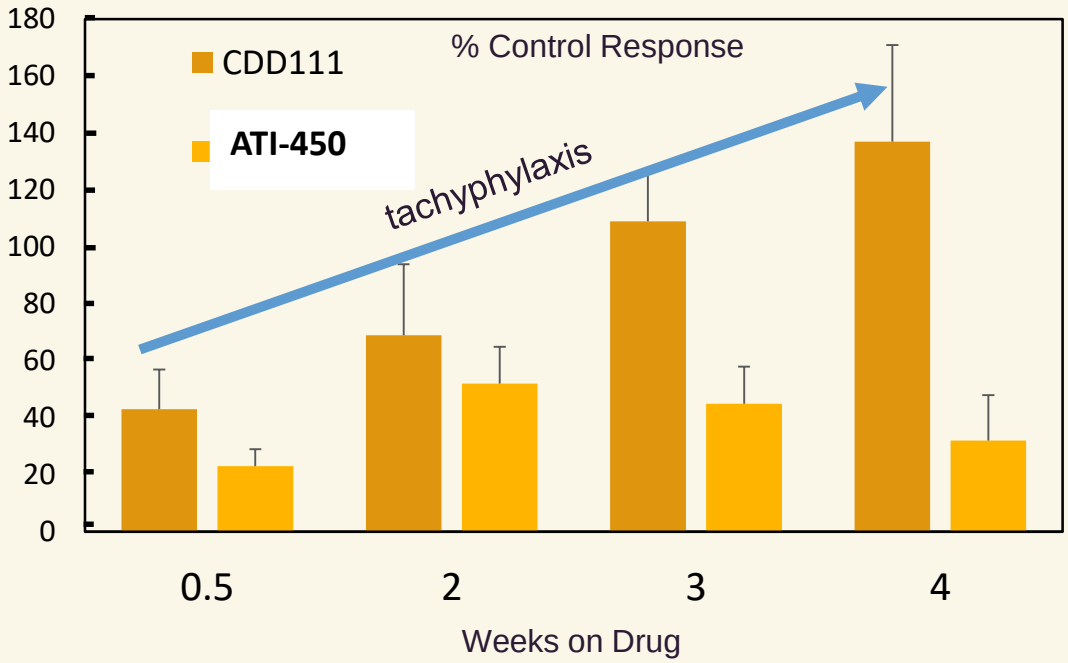
Mouse LPS-Induced TNFα Production

ATI-450 demonstrated durable response (no tachyphylaxis)

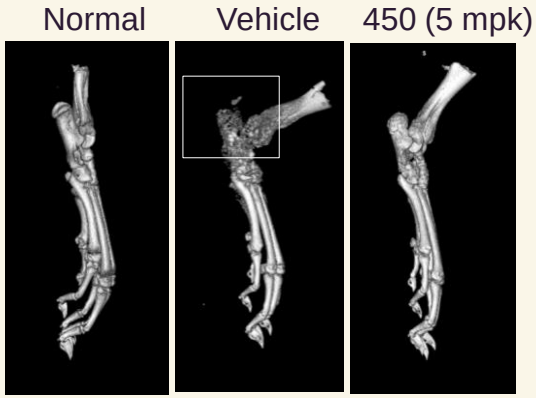
- Global p38 inhibitor CDD-111 lost efficacy as a function of dosing duration over 4 weeks
- This lack of durable efficacy was similar to that observed in IBD and RA clinical studies with global p38 inhibitors
- **This investigational MK2 pathway inhibitor ATI-450 demonstrated durable responses in this model (no tachyphylaxis)**



- Conventional p38 (CDD-111) and MK2PI (ATI-450) administered to mice in feed starting day 1 and continuing through day 28
- At the time point indicated, mice were LPS challenged and blood TNFα levels determined

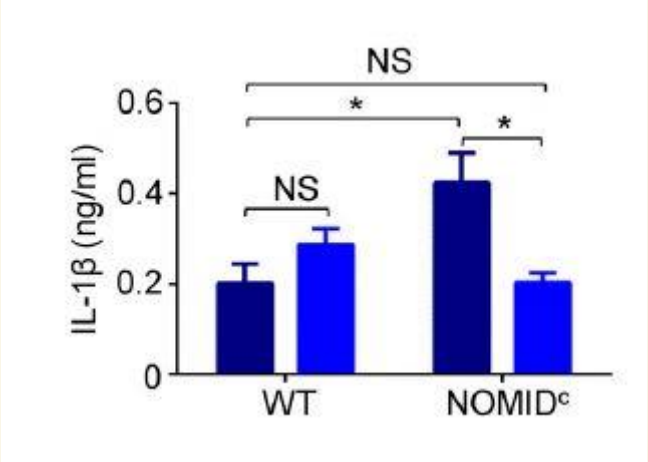
In vivo Results of MK2 Pathway Inhibitor ATI-450

Joint Protection in Rat Arthritis Model[1]

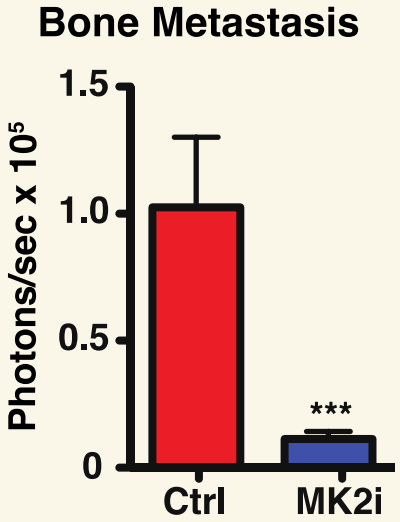


Blockade of Gut Inflammatory Infiltrate in Murine Adoptive Transfer Ulcerative Colitis Model[3]

Cytokine Modulation in Orphan Autoinflammatory Disease (CAPS)[1]



Reduction in Breast Cancer Bone Metastasis in Mice[2]



[1] Wang C, et al. J Exp Med. 2019;215(5):1315-1325.
[2] Murali B, et al. Cancer Res. 2019;78(19)5618-5630.
[3] Data on File. Aclaris Therapeutics Inc.

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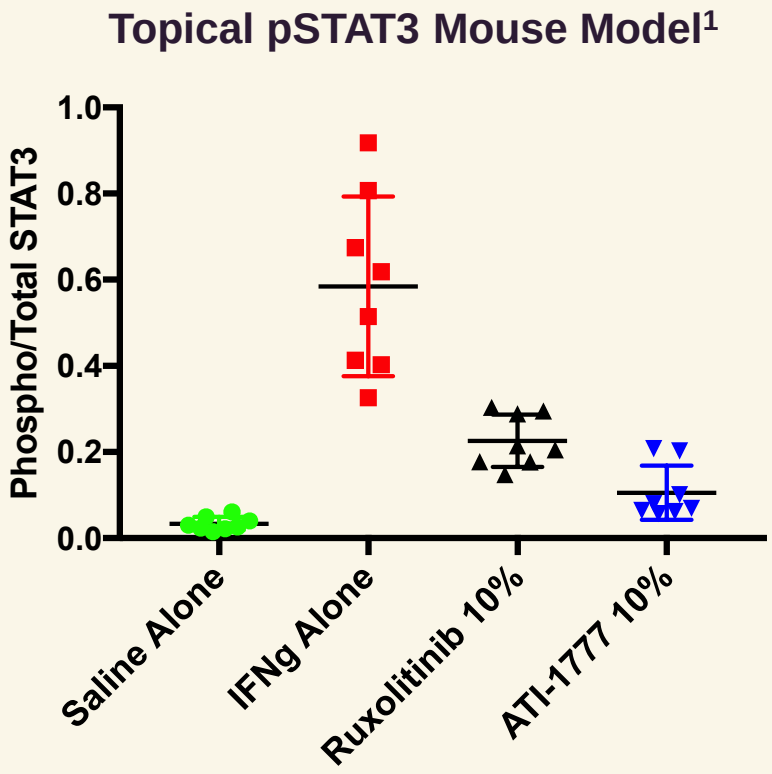
ATI-1777: Soft Topical JAK1/3 Drug Candidate Preclinical Results

- ATI-1777 demonstrated low nM potency against JAK1 and JAK3 enzymes and cellular assays
- Good skin penetration and topical anti-inflammatory effect observed
- Rapidly metabolized and cleared by the liver from blood plasma
- Clean in CEREP pharmacology panel, high kinome selectivity, negative in Ames and high margin in hERG and rat IVT

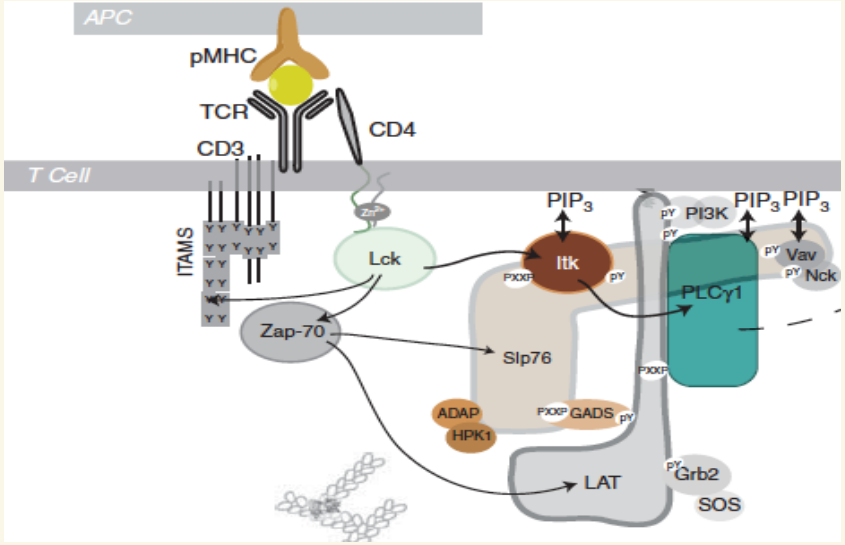


[1] Data on File. Aclaris Therapeutics Inc.

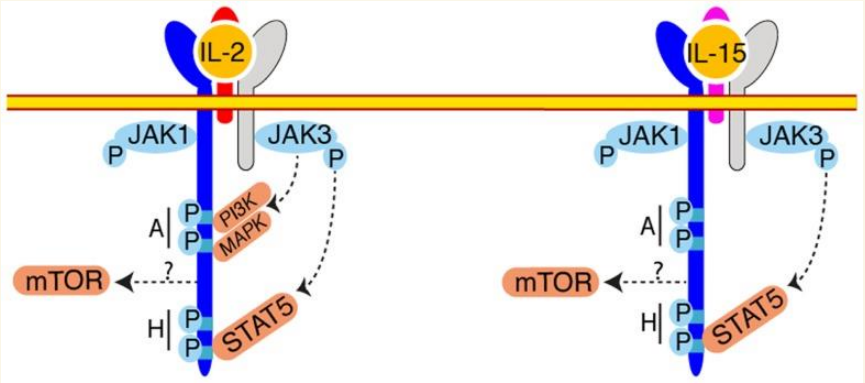
ITK/JAK3 Inhibitors as Anti-Inflammatory Drug Candidates

- Autoimmune diseases are driven by both T cell and cytokine receptors
- Inhibitors of **ITK** act as small molecule inhibitors of Th17 and Th1 cells, primary drivers of autoimmune disease
- **JAK3** regulates IL-2, IL-4 and IL15, three cytokines that drive autoimmune diseases in general, but dermatological diseases in particular
- Aclaris has generated covalent ITK/JAK3 drug candidates specifically designed for oral delivery or as soft topical drugs for potential treatment of autoimmune disease

ITK Regulates the T Cell Receptor[1]

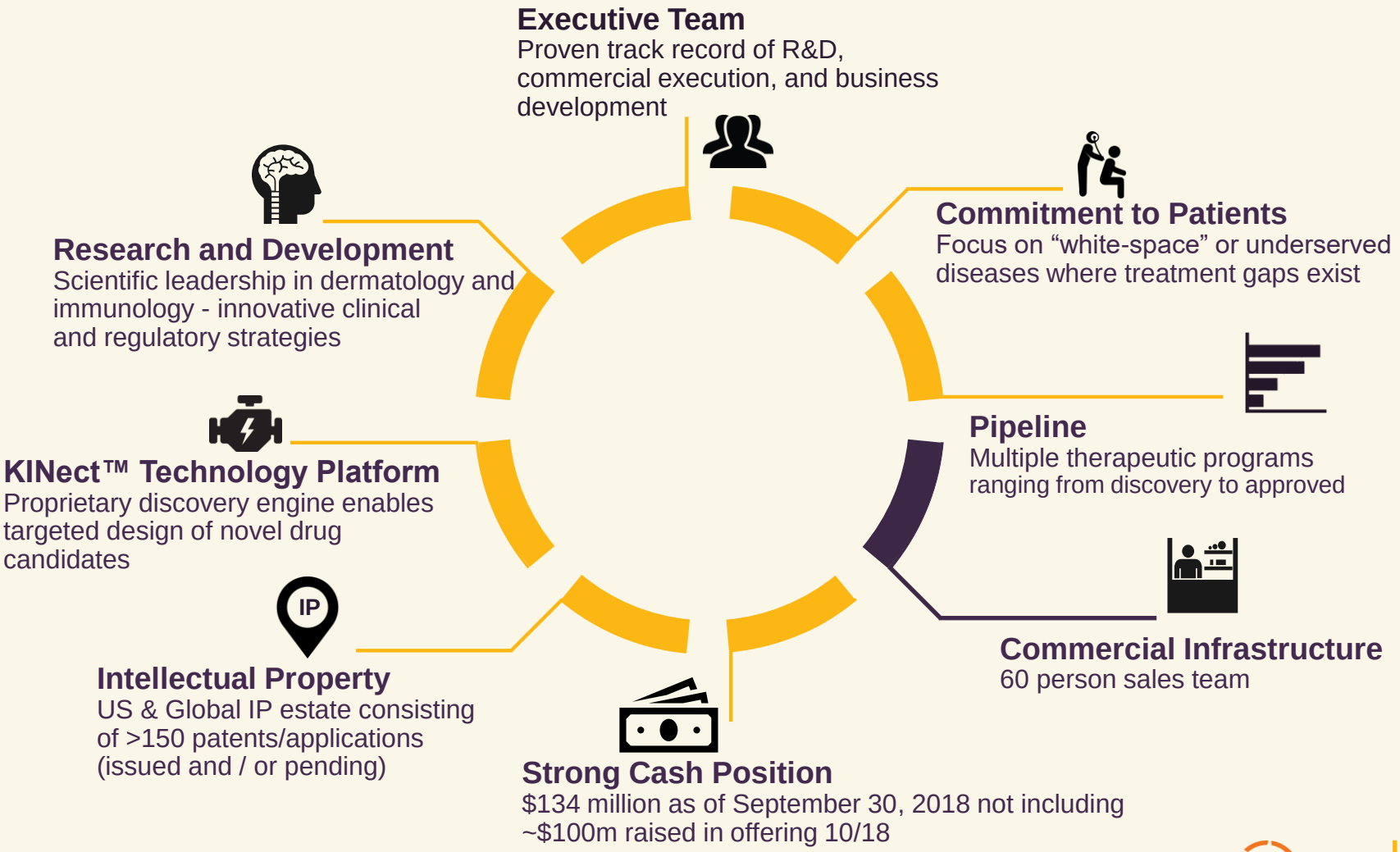


JAK3 Regulates Key Autoimmune Cytokines[2]



[1] Andreotti, et al. *Cold Spring Harb Perspect Biol 2010;2:*a002287
[2] Marcais, et al. *Frontiers in Immunology*. 2013;4:1-14.

Fully Integrated Biopharmaceutical Company



THANK YOU

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