# REVELATIONARY SCIENCE

## Company Overview

Dr. Neal Walker President and CEO June 2019





#### 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 of its drug candidates, including the timing for initiation and completion of clinical trials, the availability of data from these trials and the timing of its regulatory submissions related to these trials, and the growth opportunity for ESKATA and 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, 2018, 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.

# Corporate Strategy: Building a Fully-Integrated Biopharmaceutical Company



#### **LEADERSHIP**

- Physician-founded
- Key leadership with track record of executing across multiple development and commercial stage companies
- Kinome experts chemists and biologists; combined 300+ years of drug discovery experience

Leverage core expertise in drug development and kinase inhibition to develop small molecule therapeutics





#### 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				
	Atopic Dermatitis				
ATI-501 JAK1/JAK3 Inhibitor Oral	Alopecia Areata				
ATI-450 MK2 Pathway Inhibitor Oral	RA (Psoriasis, Hidradenitis Suppurativa, CAPS, Pyoderma Gangrenosum, Oncology)				
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				
ITK/JAK3 Inhibitor Oral, gut-restricted	Ulcerative colitis / Crohn's Disease				
MK2 Pathway Inhibitor Oral	Oncology				



#### Conditions with Significant Treatment Gaps

#### **SEBORRHEIC KERATOSIS** (SK)

83+MM people in U.S.\*1

ESKATA® (hydrogen peroxide) topical solution, 40% (w/w), first FDA-approved topical treatment for raised SKs in adults



#### **ALOPECIA AREATA** (AA)

5-7MM people in U.S.

have or will develop AA<sup>2,7</sup> Currently available Rx treatment options often used off-label and have significant limitations<sup>7</sup>



#### VERRUCA VULGARIS (COMMON WARTS)

**19-22MM** people in U.S.<sup>2,3</sup>

Currently available treatments have modest therapeutic effect and significant limitations<sup>4</sup>



#### ANDROGENETIC ALOPECIA (MALE / FEMALE PATTERN HAIR LOSS)

~50MM men / ~30MM women

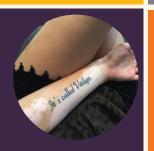
in U.S. affected by AGA hair loss8



#### **VITILIGO**

1-2% of global population impacted<sup>5</sup>

No FDA-approved medication to repigment the skin<sup>6</sup>



#### **ROSACEA**

16+MM people in U.S.<sup>9</sup>

RHOFADE® (oxymetazoline hydrochloride) cream, 1% FDA-approved for the topical treatment of persistent facial erythema (redness) associated with rosacea in adults, a symptom experienced in about 71% of patients with rosacea9



\*Includes all types of SKs ¹Bickers et al. The Burden of Skin Disease. *J Am Acad Dermatology*. 2006;55:490-500.²Data on file, Aclaris Therapeutics, Inc. ³Nguyen et al. Laser Treatment of Nongenital Verrucae A Systematic Review. *JAMA Dermatology*. 2016;152(9):1025-1033.⁴Kwok et al. Topical treatments for cutaneous warts (Review). Cochrane Database of Systematic Reviews.2012. Art. No.: CD001781. ⁵Fitzpatrick T, et al. http://www.avrf.org/facts/frequently-asked-questions.html. Last accessed March 30, 2019.⁵https://www.asdreports.com/news-217/vitiligo-therapeutics-market-expected-show-moderate-growth-up-2019. Last accessed March 30, 2019. ⁵National Alopecia Areata Foundation. https://www.naaf.org/alopecia-areata. Last accessed March 30, 2019. ⁵National Institute of Health Androgenetic Alopecia. https://ghr.nlm.nih.gov/condition/androgenetic-alopecia#statistics. Last accessed March 30, 2019. ⁵National Rosacea Society, https://www.rosacea.org/rosacea-review/2010/summer/new-survey-uncovers-wide-range-of-potential-signs-and-symptoms. Last accessed on March 30, 2019.

#### COMMERCIAL PORTFOLIO

RHOFADE® (oxymetazoline HCI) cream, 1% ESKATA® (hydrogen peroxide) topical solution, 40% (w/w)



#### **RHOFADE Cream**



- National Rosacea Society estimates more than 16 million Americans are affected by rosacea<sup>1</sup>
- Persistent facial erythema (PFE) is the most common sign or symptom of rosacea, experienced in about 71% of rosacea patients according to a survey conducted by this same Society<sup>1</sup>
- RHOFADE Growth Opportunity:
  - Increase prescribing by current RHOFADE prescribers
  - Recapture lost share from HCPs who decreased their prescribing in 2018
  - Capitalize on untapped potential within rosacea-treating HCPs who are not yet prescribing a medication to treat PFE

#### NDICATION

RHOFADE cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

IMPORTANT SAFETY INFORMATION AND WARNINGS

WARNINGS AND PRECAUTIONS

Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. RHOFADE cream should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

The most common side effects of RHOFADE® Cream include application-site reactions of: skin reactions (dermatitis), worsening of rosacea pimples, itching, redness, and pain.



#### Core Intellectual Property: RHOFADE

- Three-year CI market exclusivity until January 18, 2020
- Five Orange Book Patents
  - USP No. 7,812,049 (Exp 5/2/28 with 1562 days PTA)
    - Method of treating erythema resulting from rosacea comprising administering topically a composition comprising about 0.05-30% of oxymetazoline as the sole active agent
    - Exclusively licensed from Allergan
  - USP No. 8,420,688 (Exp 8/02/24 with 193 days PTA)
    - Same as '049, but recites "therapeutically effective amount" of oxymetazoline
    - Exclusively licensed from Allergan
  - USP No. 8,815,929 (Expires: 1/22/24)
    - Same as '688, but recites oxymetazoline and other alpha-1 agonists
    - Exclusively licensed from Allergan
  - USP No. 8,883,838 (Exp 12/1/31)
    - A cream composition with certain % of oxymetazoline, % of certain emollient/emulsifier/excip/ etc. (the stabilized cream)
  - USP No. 9,974,773 (Exp 6/11/35)
    - Method of treating facial erythema associated with rosacea comprising topically administering once daily to the site of erythema on the face of the patient a pharmaceutical composition comprising 1.0% or 1.5% w/w oxymetazoline HCl thereof as the sole active ingredient
- Pending applications
  - Families related to Orange Book listed patents have pending applications in the U.S.
  - Pending applications are directed to, for example, methods of treating facial erythema using 1.0% oxymetazoline administered once daily; cream formulations of oxymetazoline; method of treating erythema, telangiectasia or inflammatory lesions associated with rosacea comprising topically administering formulations of oxymetazoline
  - Corresponding pending/issued applications in major international jurisdictions



#### **ESKATA**

#### 83+MM People in the US with SK\*1

18+MM visits to Derm for SK<sup>2</sup>

8+MM SK treatments<sup>2</sup>

## Reasons for Not Removing SKs Include<sup>3</sup>:

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



- Moved to second position in the detail schedule
- Sales team focused on top ESKATA accounts based on productivity in each territory, with the objective of increasing utilization
- Received recent European approvals for ESKATA / ESKERIELE and in active discussions with potential commercial partners



A-101 (hydrogen peroxide) 45%
Topical Solution (Investigational
Drug Candidate) Phase 3 for the Treatment of
Common Warts



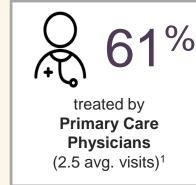


#### Common Warts - Patient/Physician Surveys



19-22 MM<sup>1,2</sup>







- 50% of all patient visits for warts are for common warts<sup>3</sup>
- 3x more patient visits than genital warts<sup>3</sup>
- 50% of patients report moderate to extreme discomfort<sup>4</sup>
- 39% of patients say warts impact social/leisure activities<sup>4</sup>
- Unmet Needs<sup>1</sup>:
  - Would prefer pain-free treatments which work faster and do not have unwanted side effects



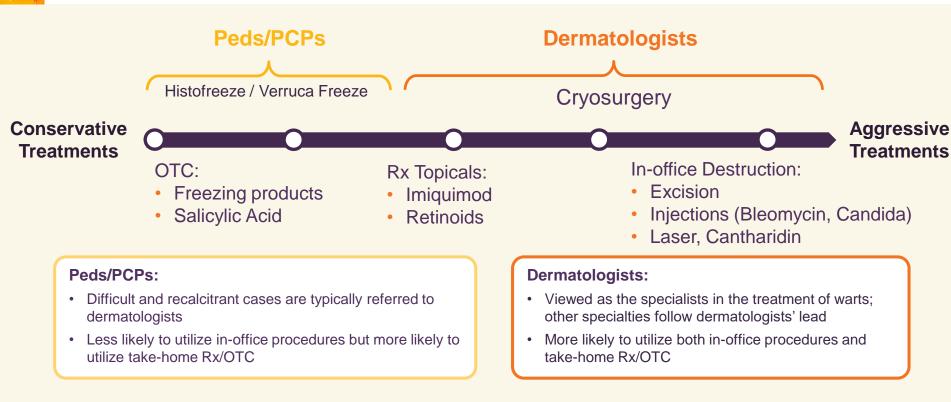
<sup>&</sup>lt;sup>1</sup>Data on file, Aclaris Therapeutics, Inc.

<sup>&</sup>lt;sup>2</sup>Nguyen et al. Laser Treatment of Nongenital Verrucae A Systematic Review. JAMA Dermatology. 2016;152(9):1025-1033.

<sup>&</sup>lt;sup>3</sup> IMS National Disease and Therapeutic Index 2016.

<sup>&</sup>lt;sup>4</sup> Lipke M., An Armamentarium of Wart Treatments, *Clinical Medicine & Research*,4:4, 2006; 273–293. © Copyright 2019 Aclaris Therapeutics, Inc. All rights reserved

#### **Common Warts: Treatment Paradigm**



- Patient burden comes from the duration of treatment, time commitment, pain and discomfort, as well as the cost of treatments
- Opportunity to position A-101 45% as Rx treatment with convenience of home use



#### Summary of WART-203 Phase 2 Trial Results

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

#### **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.

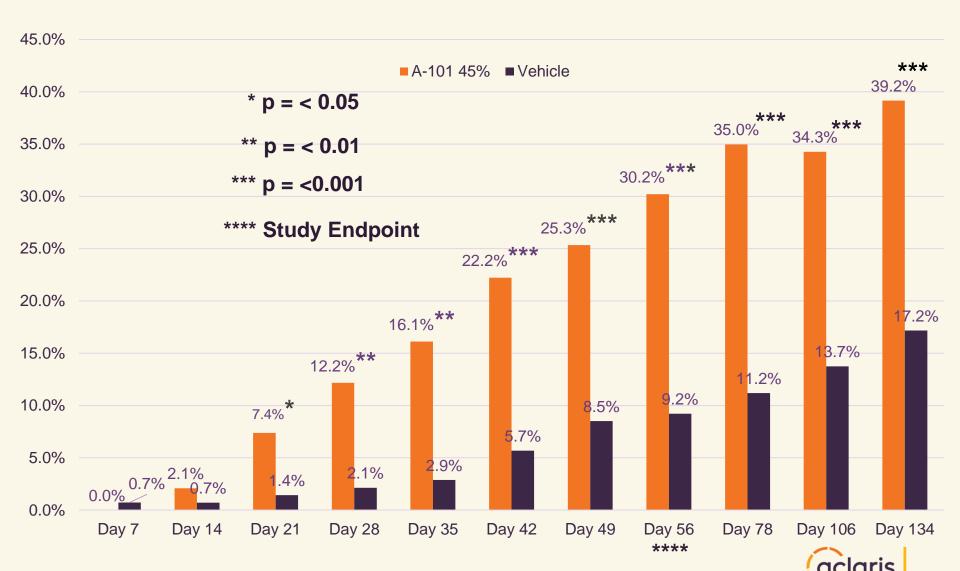
#### **Secondary Endpoints:**

- The proportion of subjects whose target wart is judged to be clear (PWA=0) at day 56.
- The proportion of subjects with all treated wart(s) clear, stratified by baseline number of warts at day 56.
- The percentage of all treated warts that were clear at day 56.

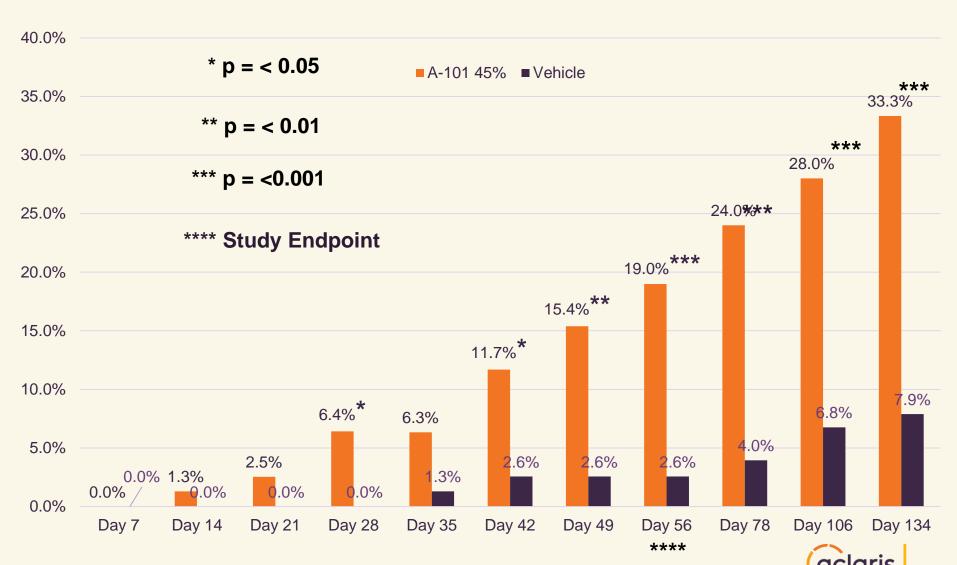
#### **Current Status**

Phase 3 Data expected 2H19.

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



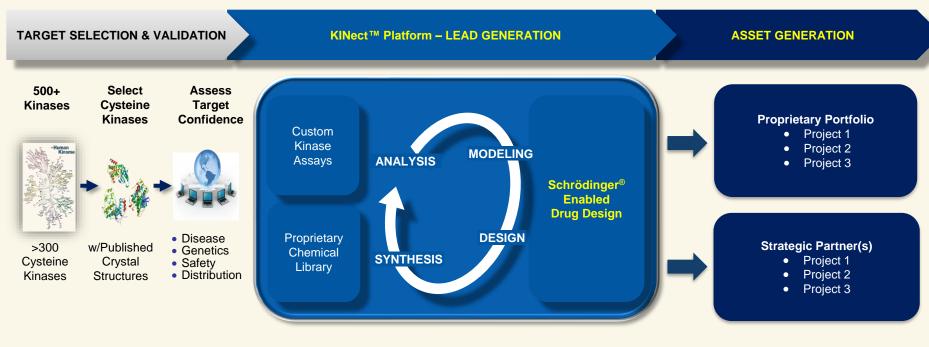
# WART-203: Proportion of Subjects with all treated Wart(s) (1-6) Clear, Stratified by Baseline Number of Warts, at each Post-Baseline Visit (N=159)



### Inflammation and Immunology Platform



# KINect™ Platform – Developing Better Kinase Drug Candidates Rapidly & Efficiently



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

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

#### **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

#### 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<sup>™</sup> platform allows rational targeting of validated kinase targets

## Kinase Drugs Represented \$240B in Aggregate Global Sales from 2011-2015<sup>1</sup>



#### 500 member class, representing 2% of the human genome



#### Investigational Selective JAK 1/3 Inhibitors

#### Portfolio and IP Estate:

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

#### Additional topical JAK inhibitors in development

- Known MOA and observed biological response in humans
- Promoted hair regrowth in mouse model<sup>1</sup>
- Broad IP estate Methods of use covering JAK inhibitors for the treatment of:
  - Alopecia areata
  - Androgenetic alopecia (male and female pattern hair loss)

#### ATI-501 JAK1/JAK3 inhibitors

Oral treatment for alopecia totalis and alopecia universalis

#### ATI-502 JAK1/JAK3 inhibitors

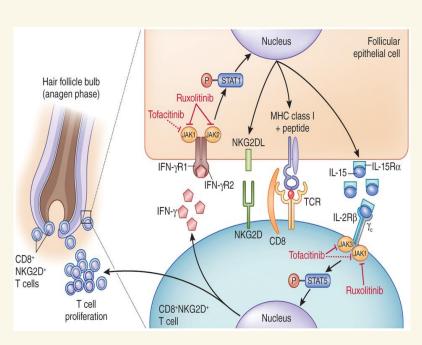
Topical treatment for hair loss disorders: patchy alopecia areata and androgenetic alopecia

#### ATI-1777 JAK1/JAK3 inhibitors

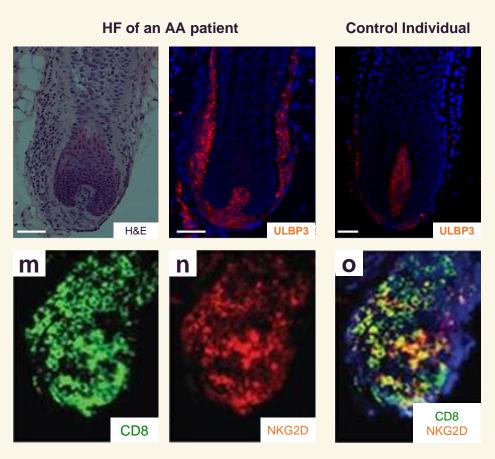
"Soft Topical" treatment for atopic dermatitis, alopecia areata, and vitiligo



#### Mechanism of JAK Inhibitors in Alopecia Areata



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



Christiano Laboratory, Columbia University

#### ATI-502 – Topical Proof of Concept

Baseline Follow up 33/M (334 Days on Drug) 23/F (353 Days on Drug) 45/F (385 Days on Drug with a 47 day gap)

- Of the 8 patients who received at least 6 months of drug, 3 had evidence of eyebrow hair regrowth (defined by at least a 2 grade categorical shift in eyebrow score in at least 1 eyebrow [scale 1-5]).
- The 3 patients pictured above were the only patients who completed ~12 months of drug treatment.

#### Alopecia Areata - Patient/Physician Surveys



**Patients with Alopecia** Areata in the US

 $5 - 7 \, \text{MM}^{12}$ 

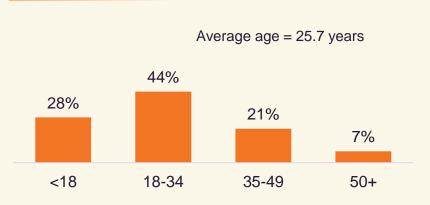


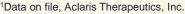
treated by **Primary Care Physicians** (6.7 avg. visits)1

treated by **Dermatologists** (7.1 avg. visits) 43% of pts are referrals1









<sup>&</sup>lt;sup>2</sup>National Alopecia Areata Foundation. https://www.naaf.org/alopecia-areata.

#### Spectrum of Hair Loss







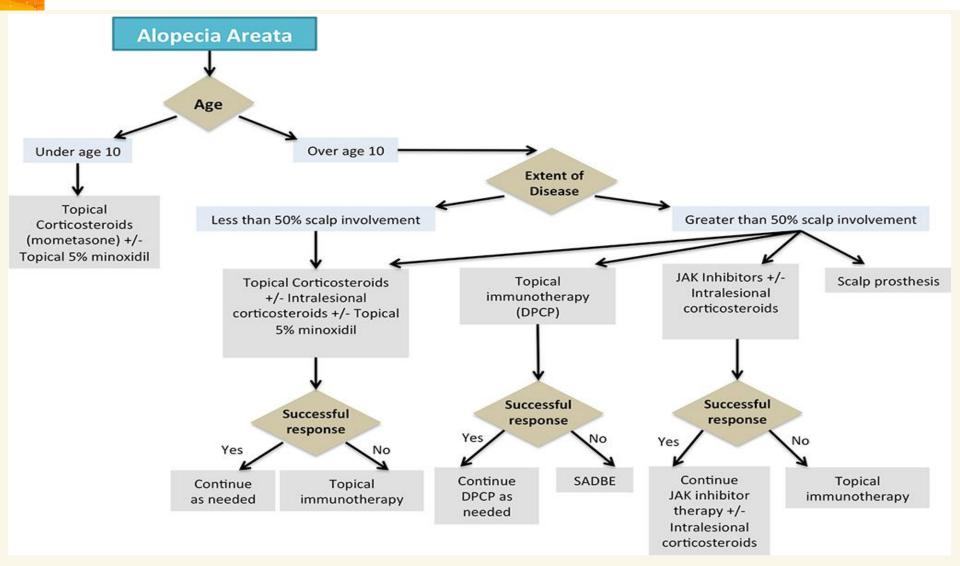




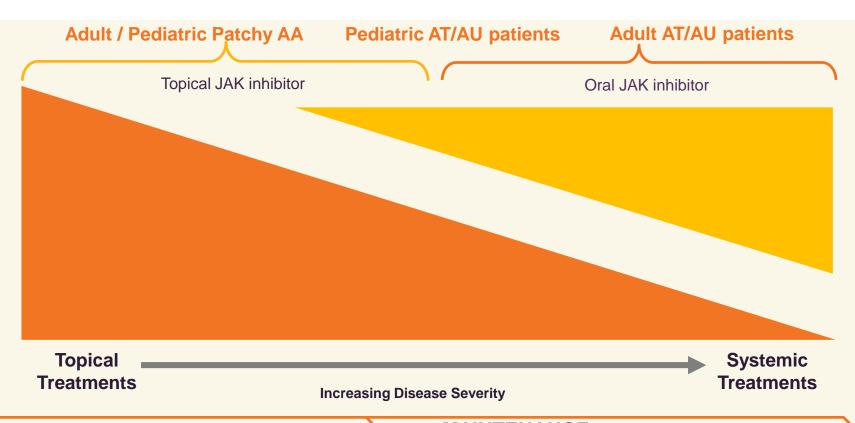
- 25-52% of patients have persistent patchy AA<sup>1</sup>
- 14-25% of patients progress to alopecia totalis or universalis<sup>1</sup>

\*Pictures from data on file

#### Current treatment paradigm



#### Alopecia Areata: Potential Treatment Paradigms



#### **INDUCTION:**

Topical JAK inhibitor may be efficacious in patients with less severe patchy AA

Oral JAK inhibitor may be best option in patients with more severe AT/AU phenotypes

#### **MAINTENANCE:**

AT/AU patients may be able to maintain hair with topical JAK inhibitor

Concomitant topical therapy may decrease reliance on longer term oral therapy in some patients



# Androgenetic Alopecia (AGA)

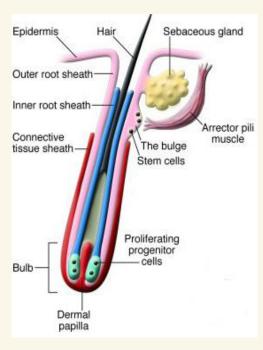


#### Androgenetic Alopecia (AGA): Male/Female pattern hair loss

- AGA is a genetic disorder and the most common cause of hair loss<sup>1</sup>
- Experienced by 70% of men and 40% of women at some point in their lives<sup>1</sup>; affects ~50 million men and ~30 million women in the US<sup>2</sup>
- Affected individuals highly motivated to seek treatment<sup>1</sup>
- Potential benefits of topical JAK inhibitor in AGA:
  - New mechanism of action
  - Minimal systemic side effects
  - Non-hormonal
  - Novel option women with AGA







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



#### AGA - New Mechanism of Action Postulated

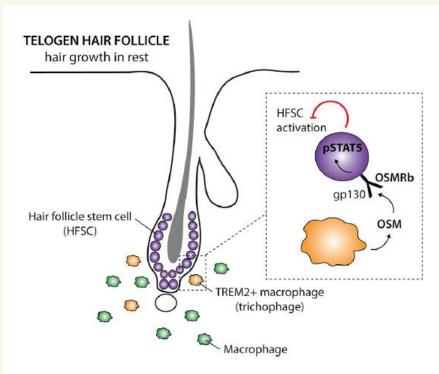


Figure 1. Role of TREM2+ Macrophages in Skin

Dermal TREM2+ macrophages, now termed "Trichophages," reside in close proximity to hair follicles. During telogen—the hair cycle phase when hair is not growing—trichophages produce the cytokine OSM that binds to OSM receptors on hair follicle stem cells (HFSCs). This triggers phosphorylation of STAT5 within HFSCs, impairing their activation, and therefore resulting in maintenance of telogen.

- Tissue-resident immune cells with potent sensing and effector functions are wellplaced to fundamentally aid tissue homeostasis via crosstalk with stem cells.
- A dermis-resident TREM2+ macrophage subpopulation that promotes hair follicle stem cell quiescence via cytokinemediated JAK-STAT signaling has been identified.
- pSTAT5 (the p indicates that STAT5 is in the ON position – ie: active, and then a red curved arrow blocks HFSC activation (this is telogen)
- The administration of a JAK inhibitor would turn the pSTAT5 to the OFF position, and then opens the red arrow and <u>PROMOTES</u> HFSC activation.



#### 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 for the treatment of AA
  - 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 6 issued U.S. patents and 1 pending application directed to methods of treating AA, AGA or hair loss disorders by administering ruxolitinib, deuterated ruxolitinib, baricitinib, decernotinib, topical tofacitinib or monotherapy tofacitinib.
  - This portfolio also includes an issued patent in Europe for tofacitinib or decernotinib for use in treating hair loss disorders and a pending European application for ruxolitinib or baricitinib to treat hair loss disorders, 3 issued patents in Japan to ruxolitinib, baricitnib, tofacitinib (topically or as monotherapy) and a pending Japanese application, and 1 issued patent in South Korea to methods of treating hair loss disorders using JAK 1 and/or JAK 2 inhibitors and 2 pending applications in South Korea to methods of treating hair loss disorders using JAK3 inhibitors.
  - Natural expiry in US 2031; naturally expiry in EU, JP, KR 2031-2033



# ATI-450 (MK2 Inhibitor) (Investigational Drug Candidate)



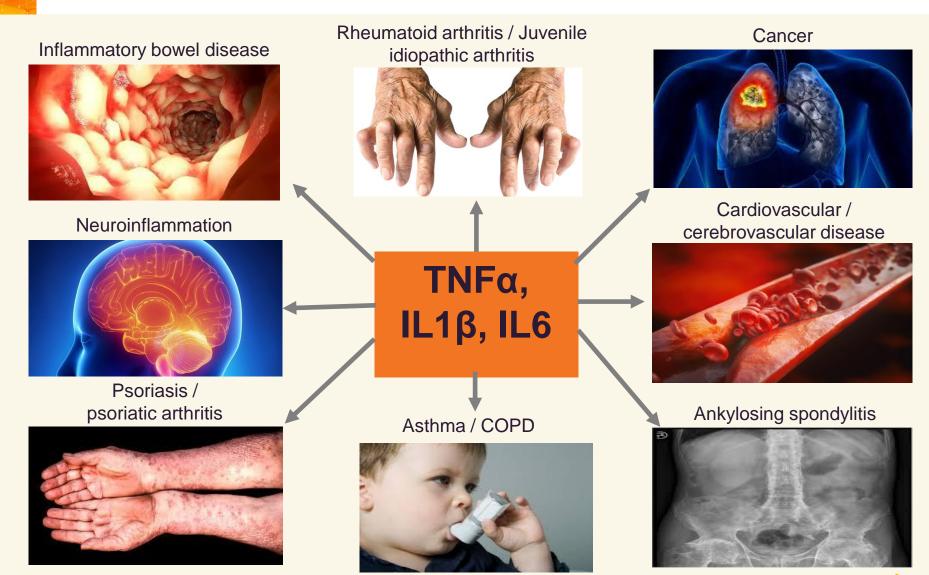
#### MK2 Pathway Inhibitor (MK2 PI) ATI-450

- IND for treatment of RA allowed in May 2019
- Plan to initiate a Single Ascending Dose / Multiple Ascending Dose Phase 1 trial in approximately 80 patients in the second half of 2019
- If the Phase 1 trial is successful, plan to advance ATI-450 into Phase 2 trials in patients with RA and an additional inflammatory indication
- Pharmacologically unique MOA
- MK2 pathway inhibitors target the production and activity of key inflammatory cytokines including TNFα, IL-1α, IL-1β and IL-6
- ATI-450 inhibits the cytokine targets of established biologics:
  - Anti-TNFs: Humira<sup>®</sup>, Enbrel<sup>®</sup>, Remicade<sup>®</sup>
    - RA, psoriasis, psoriatic arthritis, IBD, ankylosing spondylitis
  - Anti-IL1s: Kineret<sup>®</sup>, Ilaris<sup>®</sup>, Arcalyst<sup>®</sup>
    - CAPS, Still's disease, SJIA, cardiovascular disease
  - Anti-IL6: Kevzara<sup>®</sup>, Actemra<sup>®</sup>
    - RA, Castleman's disease
- Aclaris is developing MK2 pathway inhibitors for chronic inflammatory disease and autoimmune disease

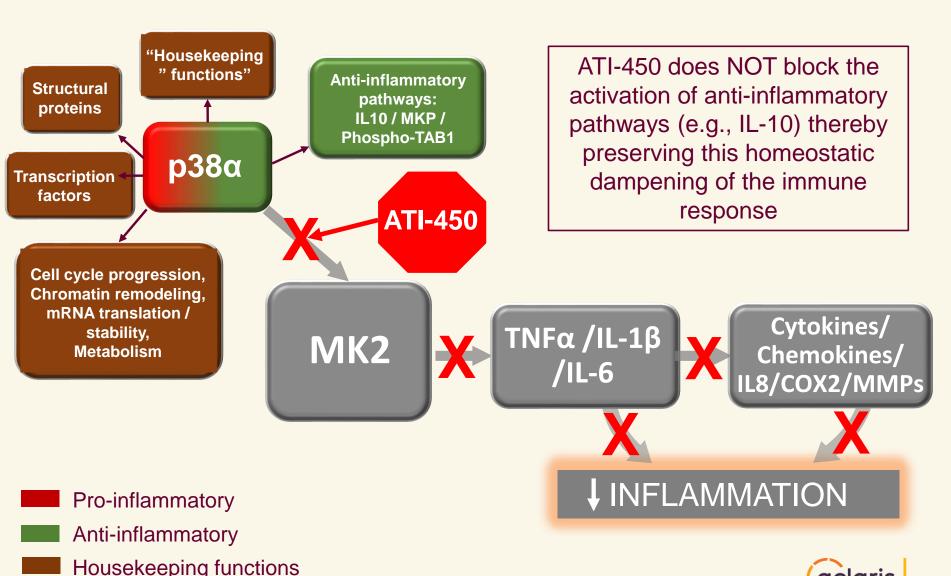
MK2 = mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) RA = rheumatoid arthritis; IBD = inflammatory bowel disease; SJIA = systemic juvenile idiopathic arthritis



#### MK2-driven cytokines are central to many diseases

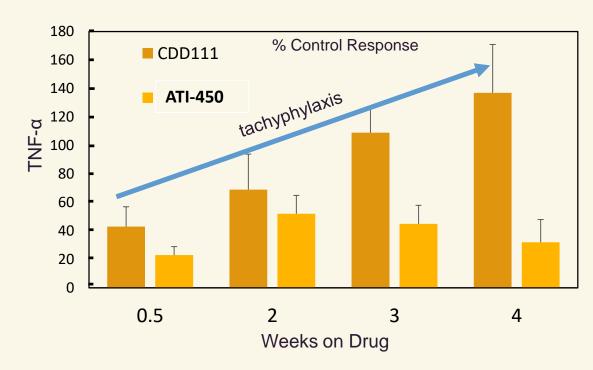


# ATI-450 Inhibits the Expression of Key Inflammatory Cytokines: TNFα, IL-1β and IL-6



# Mouse LPS-Induced TNFα Production *ATI-450 demonstrated durable response (no tachyphylaxis)*

- Global p38 inhibitor
   CDD-111 lost inhibition over time
- This investigational MK2 pathway inhibitor ATI-450 demonstrated durable responses in this mouse model (no tachyphylaxis)

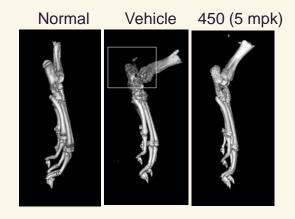


- Conventional p38 (CDD-111) and MK2PI (ATI-450) administered to mice in feed starting day 1 and continuing through day 28
- At the time point indicated, mice were LPS challenged and blood TNFα levels determined

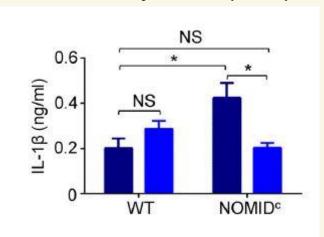


#### In vivo Results of MK2 Pathway Inhibitor ATI-450

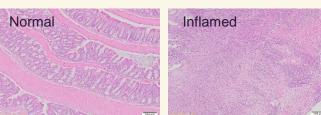
#### Joint Protection in Rat Arthritis Model<sup>1</sup>

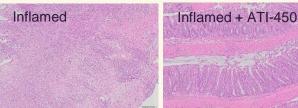


Cytokine Modulation in Orphan Autoinflammatory Disease (CAPS)1



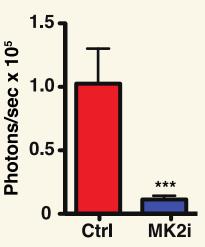
#### Blockade of Gut Inflammatory Infiltrate in Murine Adoptive Transfer Ulcerative Colitis Model<sup>3</sup>





Reduction in Breast Cancer Bone Metastasis in Mice<sup>2</sup>

#### **Bone Metastasis**



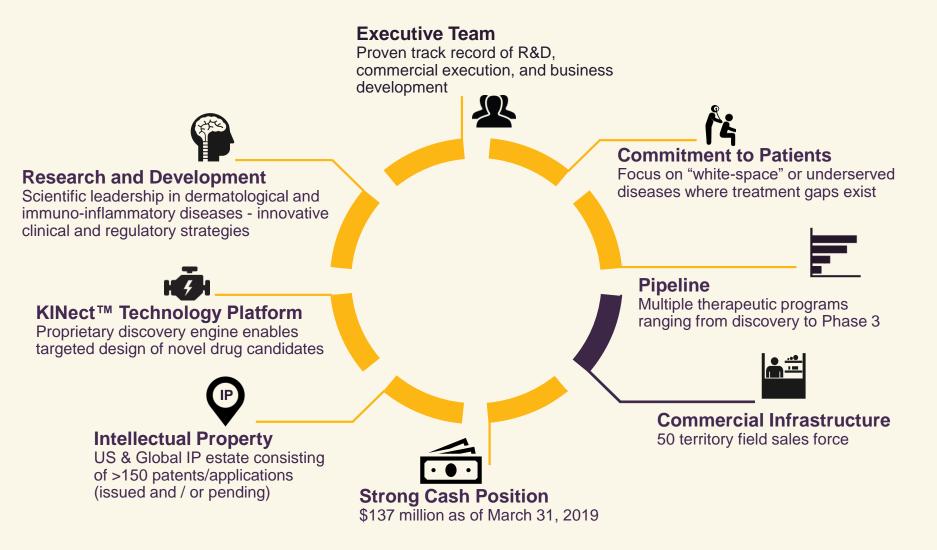
<sup>&</sup>lt;sup>1</sup> Wang C, et al. *J Exp Med*. 2019;215(5):1315-1325.



<sup>&</sup>lt;sup>2</sup> Murali B, et al. Cancer Res. 2019;78(19)5618-5630.

<sup>&</sup>lt;sup>3</sup> Data on File. Aclaris Therapeutics, Inc.

#### Fully Integrated Biopharmaceutical Company



ATI-501/ATI-502 (Oral/Topical JAK Inhibitor)

A-101 45% Common Warts

ATI-501 - Phase 2 AT/AU Dose Range Data

ATI-501 - AT/AU End of Phase 2 FDA mtg

ATI-502 - Initiate Phase 3 Patchy AA Trial1

ATI-502 - Phase 2 Open-label Vitiligo Data<sup>2</sup>

ATI-502 - Phase 2 Open-label AGA Data<sup>3</sup>

ATI-502 - Phase 2 Open-label Atopic Dermatitis Data

ATI-450 (MK2 Inhibitor) - Initiate Phase 1 Trial

ATI-1777 (Soft JAK) - Initiate Phase 1/2 Trials

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VITI-201: 6-month data interim expected mid-2019; 12-month data expected fourth quarter of 2019
 AGA-201: 6-month data expected second quarter of 2019; 12-month data expected fourth quarter of 2019

ATI-502 - Initiate Phase 2 AGA Trial

**Inflammation / Immunology** 

ATI-450 (MK2 Inhibitor) - Phase 1 Data

ATI-1777 (Soft JAK) - Submit IND

for AA in the first half of 2020.

ATI-502 - Phase 2 Patchy AA Dose Range Data

Phase 3 Data

Submit NDA

2019

Q3

Q4

Q1

Q2

Q1

1 If the results from the AA-201 trial are positive, our next steps may include holding an end of Phase 2 meeting with the FDA, and initiating a Phase 3 trial of ATI-502 as a topical treatment

2020

Q3

Q4

Q2



