Ruxolitinib Cream: Phase 2 Data in Vitiligo
Speakers on Today’s Webcast

• **Hervé Hoppenot**  
  *Chief Executive Officer*  
  Incyte

• **John E. Harris, MD, PhD**  
  *Associate Professor and Vice Chair Department of Dermatology*  
  *Director Vitiligo Clinic and Research Center*  
  University of Massachusetts Medical School

• **Jim Lee, MD, PhD**  
  *Group Vice President, Inflammation and Autoimmunity*  
  Incyte
Forward-looking Statements

Except for the historical information set forth herein, the matters set forth in this presentation contain predictions, estimates and other forward-looking statements, including without limitation statements regarding: expectations regarding ruxolitinib cream trial results and implications of those results; expectations to commence and the expected timing of commencement of Phase 3 clinical trials for ruxolitinib cream for vitiligo; our views of the commercial opportunities, including our views of market size and market opportunities, for our drug product candidates, including ruxolitinib cream for vitiligo; and our expectations regarding further clinical development for ruxolitinib cream and the timing of clinical trial results.

These forward-looking statements are based on our current expectations and are subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: unanticipated delays; further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials; determinations made by the FDA; assuming approval of ruxolitinib cream for vitiligo or other indications, the acceptance of ruxolitinib cream in the marketplace and the effects of market competition; manufacturing, sales and marketing requirements; and other risks detailed from time to time in our reports filed with the Securities and Exchange Commission, including our quarterly report on Form 10-Q for the quarter ended March 31, 2019. We disclaim any intent or obligation to update these forward-looking statements.
Incyte has Three Groups within Clinical Development

**Targeted therapies**

Small molecules:
- JAK1/JAK2, JAK1, FGFR1/2/3, PI3Kδ, PIM, LSD1, FGFR4

Immuno-therapies

Small molecules:
- ARG, AXL/MER, IDO1, PD-L1

Large molecules:
- PD-1, GITR, OX40, TIM-3, LAG-3, PDL1xCD137

**Inflammation & Autoimmunity**

Topical delivery: JAK1/JAK2

Oral delivery: JAK1, PI3Kδ
Capitalizing on our Expertise in Inflammation and Autoimmunity

**Atopic dermatitis**
- ✓ Phase 2 data presented at EADV 2018
- ✓ Phase 3 underway; results expected 2020

**Vitiligo**
- ✓ Proof-of-concept achieved; Phase 3 in preparation

- Itacitinib: PoC trial in ulcerative colitis
- INCB54707: PoC trial in moderate to severe hidradenitis suppurativa

**Inflammation & Autoimmunity**

- Oral PI3Kδ
- Ruxolitinib cream

- Oral JAK1
- Parsaclisib: PoC trial in autoimmune hemolytic anemia
- Parsaclisib: PoC trial in Sjögren's syndrome
Targeting JAK signaling as a novel treatment for vitiligo

John E. Harris, MD, PhD
Associate Professor
University of Massachusetts Medical School
Vitiligo

- 1-2% incidence
- 3-6.5 million (US)
- 75-150 million (world)
- 50% onset before age 20

Disease associations
- Type 1 diabetes
- Lupus
- Hashimoto thyroiditis
- Pernicious anemia
- Addison’s disease
**Vitiligo is not a cosmetic disease**

Khaled Ezzadine, MD, PhD, a Vanecta Sheth, MD, b Michelle Rodrigues, MBBS (Hon.), FACD, c Viktoria Eleftheriadou, MD, PhD, a John E. Harris, MD, PhD, a Itilat H. Hamzavi, MD, b and Amit G. Pandya, MD, c on behalf of the Vitiligo Working Group

Bordeaux, France; Boston and Worcester, Massachusetts; Melbourne, Australia; Nottingham, United Kingdom; Detroit, Michigan; and Dallas, Texas

---

**The burden of vitiligo: Patient characteristics associated with quality of life**

May W. Linthorst Homan, MD, a,b Phyllis I. Spuls, MD, PhD, b John de Korte, MA, PhD, a Jan D. Bos, MD, PhD, b Mirjam A. Sprangers, MA, PhD, c and J. P. Wiertz van der Veen, MD, PhD, a,b

Amsterdam, The Netherlands

**Background:** Vitiligo is commonly regarded as a harmless cosmetic skin problem in Western societies, and the importance of treating patients with vitiligo is often underestimated.

**Objective:** We sought to determine the clinical and sociodemographic variables that adversely affect the quality of life in adult patients with generalized vitiligo so that these variables can be considered in the treatment and care.

**Methods:** A total of 245 adult patients with generalized vitiligo completed two quality-of-life questionnaires (the Medical Outcomes Study 36-Item Short-form General Health Survey and the Skindex-29). Physicians assessed sociodemographic and clinical characteristics of these patients.

**Results:** Dark skin type, vitiligo located on the chest, and treatment in the past appeared to have an adverse impact on the psychosocial domains of quality of life. Moreover, itch was reported by 20% of the patients in this study.

**Limitations:** Psychiatric comorbidity was not evaluated in the analyses.

**Conclusion:** Generalized vitiligo is a serious skin disorder with an adverse impact on the emotional state, comparable with that of other major skin diseases. (J Am Acad Dermatol 2009;61:411-20.)

---

**Dermatology Life Quality Index (DLQI)**

Vitiligo

![Vitiligo DLQI](image)

51%

Psoriasis

![Psoriasis DLQI](image)

56%

Vitiligo – unmet medical need

• Poor Quality of Life: Similar to psoriasis/eczema
• Willingness to pay for a cure: Greater than eczema
• No FDA-approved medical treatments!
• Current topicals used off-label have significant side effects
Current vitiligo treatments
Segmented and Incomplete

• Topical steroids (striae, atrophy)
• Topical calcineurin inhibitors (burning sensation, hyperpigmentation)
• nbUVB phototherapy (time-consuming-3x/wk >1yr, moderately effective)
• Surgical transplantation (for stable disease only, <5% are candidates)
• Depigmentation (for very severe disease only, <1%, worsens vitiligo)

Current treatments have significant limitations and thus have only penetrated a small part of market, likely <20%
My (simple) Treatment Algorithm

- Signs of activity?
  - Yes → Oral pulse steroids x3 months
  - No → >5% BSA?
    - Yes → Alternate bid
      - Clobetasol x 1 week
      - Tacrolimus x 1 week
    - No → Interest in nbUVB?
      - Yes → Consider Excimer laser
      - No → Consider surgery for segmental vitiligo

- >5% BSA?
  - Yes → Alternate bid
    - Clobetasol x 1 week
    - Tacrolimus x 1 week
  - No → Interest in nbUVB?
    - Yes → Willing to apply topicals?
      - Yes → nbUVB 2-3x/wk
      - No → nbUVB 2-3x/wk + Alternate bid
        - Clobetasol x 1 week
        - Tacrolimus x 1 week
    - No → nbUVB 2-3x/wk
Vitiligo – “Severity”
Data from 3 vitiligo specialty clinics

<table>
<thead>
<tr>
<th>Percentage</th>
<th>BSA Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>58%</td>
<td>&lt;5% BSA</td>
</tr>
<tr>
<td>25%</td>
<td>5-10% BSA</td>
</tr>
<tr>
<td>11%</td>
<td>&gt;10-25% BSA</td>
</tr>
<tr>
<td>5%</td>
<td>&gt;25-50% BSA</td>
</tr>
<tr>
<td>2%</td>
<td>&gt;50% BSA</td>
</tr>
</tbody>
</table>

Worcester  | Dallas  | Paris
Vitiligo – “Severity”
Decision Tree

1. **Signs of activity?**
   - Yes → **Systemic + Topical** 20%
   - No
     - **More than 5% BSA?**
       - Yes → **Systemic + Topical** 32%
       - No → **Topical** 48%

2. **Topical only**
   - US 1.6M
   - World 37M

3. **Topical + Systemic**
   - US 1.6M
   - World 37M
Phototherapy, a current vitiligo treatment, is reimbursed at a high level:

- $24,000 per year
- $42,000 per year
Vitiligo – The Opportunity

- Vitiligo analogous to psoriasis market 30 years ago: topicals, phototherapy, oral immunosuppressant (methotrexate)

- Psoriasis (7.4M in US/125M worldwide) – now with effective therapies, $8B annual market, estimated to be $21B by 2022; mostly shared by 10-12 drugs

- Vitiligo (3-6M in US/75-150M world) with no effective, FDA-approved medication
A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN-γ for Autoreactive CD8⁺ T-Cell Accumulation in the Skin

John E. Harris¹, Tajie H. Harris², Wolfgang Weninger³,⁴, E. John Wherry⁵, Christopher A. Hunter² and Laurence A. Turka⁷

Journal of Investigative Dermatology advance online publication, 2 February 2012; doi:10.1038/jid.2011.463

Melanocyte-specific CD8⁺ T cells

CD8⁺

6-7 wks
• Clinical and histological appearance same as human
• Gene expression in mouse and human identical
• Only mouse model of skin depigmentation (not hair)
• Only reversible model of vitiligo
• Ongoing studies parallel observations in mouse and human
• Has predicted therapies now in clinical trials (JAK)
• Many companies using this model for preclinical testing
Gene expression is similar in mouse and human vitiligo
A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN-γ for Autoreactive CD8⁺ T-Cell Accumulation in the Skin

John E. Harris¹, Tajie H. Harris², Wolfgang Weninger³,⁴, E. John Wherry⁵, Christopher A. Hunter² and Laurence A. Turka⁶

Journal of Investigative Dermatology advance online publication, 2 February 2012; doi:10.1038/jid.2011.463

CXCL10 Is Critical for the Progression and Maintenance of Depigmentation in a Mouse Model of Vitiligo

Mehdi Rashighi,¹ Priti Agarwal,¹ Jillian M. Richmond,¹ Tajie H. Harris,²* Karen Dresser,³ Ming-Wan Su,⁴ Youwen Zhou,⁴ April Deng,³ Christopher A. Hunter,² Andrew D. Luster,⁵ John E. Harris¹
CXCL10 antibody reverses vitiligo
Emerging Treatments

IFN-γ

IFNγR

CXCL9
CXCL10

CXCR3

Keratinocytes

STAT1

T cell

Harris et al. JID 2012
Rashighi et al. STM 2014
Richmond et al. JID 2017a
Richmond, et al. JID 2017b
Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA)

Ongoing Trials:
- Aclaris
- Incyte
- Pfizer
Where does JAK signaling matter?

K5-cre/STAT1$^{\text{flox}}$

**Diagram:**

- **IFN-γ**
  - Arrows leading to **IFNγR** and **Keratinocytes**
  - **IFNγR** leading to **JAK1/2**
  - **JAK1/2** leading to **STAT1**

- **CXCL9** and **CXCL10**
  - Arrows leading from **Keratinocytes** to **CXCR3**
  - **CXCR3** on **T cell**

- **Keratinocytes** and **T cell** are denoted by circles.
Is there a functional role for keratinocytes?

K5-cre/STAT1\textsuperscript{flox}

Melanocyte-specific CD8\textsuperscript{+} T cells

K5-cre\textsuperscript{+} STAT1\textsuperscript{flox/flox}

6-7 wks
STAT1: wt/wt  fl/fl
K5-cre:  +  +

Richmond, et al. JID 2017
Topical ruxolitinib for vitiligo

Rothstein R, et al. JAAD 2017
Ruxolitinib cream: Phase 2 data in vitiligo

Jim Lee, MD, PhD
Efficacy and Safety of Ruxolitinib Cream for the Treatment of Vitiligo: Results of a 24-Week, Randomized, Double-Blind, Dose-Ranging, Vehicle-Controlled Study

David Rosmarin, MD,1 Amit G. Pandya, MD,2 Mark Lebwohl, MD,3 Pearl Grimes, MD,4 Iltefat Hamzavi, MD,5 Alice B. Gottlieb, MD, PhD,6 Kathleen Butler, MD,7 Fiona Kuo, PhD,7 Michael D. Howell, PhD,7 Kang Sun, PhD,7 John E. Harris, MD, PhD8

1Tufts Medical Center, Boston, MA, USA; 2University of Southwestern Medical Center, Dallas, TX, USA; 3Mount Sinai Hospital, New York, NY, USA; 4The Vitiligo & Pigmentation Institute of Southern California, Los Angeles, CA, USA; 5Henry Ford Medical Center, Detroit, MI, USA; 6Icahn School of Medicine at Mount Sinai, New York, NY, USA; 7Incyte Corporation, Wilmington, DE, USA; 8University of Massachusetts Medical School, Worcester, MA, USA
Eligibility Criteria and Study Design

Key Inclusion Criteria
- Patients aged 18–75 years with clinical diagnosis of vitiligo
- Depigmented areas including both of the following
  - ≥0.5% of total BSA on the face
  - ≥3% of total BSA on nonfacial areas

Key Exclusion Criteria
- Current or recent clinically meaningful infection
- Dermatologic disease besides vitiligo
- Use of biological, investigational, or experimental therapy within 12 weeks of screening
- Use of laser or light-based treatments within 8 weeks of screening
- Use of immunomodulating systemic drugs or topical treatments within 4 weeks of screening
- Prior JAK inhibitor therapy

Primary endpoint: F-VASI50 at Week 24
Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographics and Clinical Characteristics</th>
<th>Total (N=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>48.3±12.85</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>73 (46.5)</td>
</tr>
<tr>
<td>Skin type, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>II</td>
<td>50 (31.8)</td>
</tr>
<tr>
<td>III</td>
<td>50 (31.8)</td>
</tr>
<tr>
<td>IV</td>
<td>31 (19.7)</td>
</tr>
<tr>
<td>V</td>
<td>10 (6.4)</td>
</tr>
<tr>
<td>VI</td>
<td>10 (6.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Total (N=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline F-VASI, mean ± SD</td>
<td>1.26±0.82</td>
</tr>
<tr>
<td>Baseline T-VASI, mean ± SD</td>
<td>17.95±15.46</td>
</tr>
<tr>
<td>Facial BSA, mean ± SD, %</td>
<td>1.48±0.86</td>
</tr>
<tr>
<td>Total BSA, mean ± SD, %</td>
<td>22.05±18.38</td>
</tr>
<tr>
<td>Duration of disease, median (range), years</td>
<td>14.0 (0.3–67.9)</td>
</tr>
<tr>
<td>Diagnosed in childhood, n (%)</td>
<td>35 (22.3)</td>
</tr>
<tr>
<td>Other autoimmune disorders, * n (%)</td>
<td>42 (26.8)</td>
</tr>
<tr>
<td>Prior therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>72 (45.9)</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>70 (44.6)</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>55 (35.0)</td>
</tr>
</tbody>
</table>

T-VASI, total Vitiligo Area Scoring Index.

* Including patients (n [%]) with thyroid disorders (39 [24.8]), juvenile diabetes mellitus (2 [1.3]), and pernicious anemia (1 [0.6]).
Primary Efficacy Endpoint: F-VASI50 Response

- At Week 24, the highest F-VASI50 response was achieved with the 1.5% QD and BID regimens.
F-VASI75 Response

- At Week 24, the highest F-VASI75 response was achieved with the 1.5% BID regimen
Treatment-Emergent Adverse Events Through 24 Weeks

- Ruxolitinib cream was not associated with clinically significant application site reactions or serious treatment-related adverse events

<table>
<thead>
<tr>
<th>Vehicle (n=32)</th>
<th>Ruxolitinib Cream</th>
<th>Total (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.15% QD (n=31)</td>
<td>0.5% QD (n=31)</td>
</tr>
<tr>
<td>Patients with TEAE, n (%)</td>
<td>20 (62.5)</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>Most common TEAEs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>1 (3.1)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>3 (9.4)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (9.4)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>5 (15.6)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (9.4)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Treatment-related TEAE, n (%)</td>
<td>12 (37.5)</td>
<td>11 (35.5)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation, n (%)</td>
<td>1 (3.1)</td>
<td>1 (3.2)*</td>
</tr>
<tr>
<td>Serious TEAE, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event. * Occurring in ≥5% of the total patient population; † Headache related to treatment; ‡ Subdural hematoma not related to treatment.
Conclusions

• Significantly more patients achieved F-VASI50 after 24 weeks of treatment with ruxolitinib cream (all regimens) vs vehicle
  - F-VASI50 was most notably achieved with ruxolitinib cream 1.5% BID (45.5%) and 1.5% QD (50.0%); both P<0.001 vs vehicle

• F-VASI75 was achieved by 30.3% and 16.7% of patients in the 1.5% BID and 1.5% QD groups, respectively

• All doses of ruxolitinib cream were well tolerated
Next Steps in Ruxolitinib Cream Development

Vitiligo

Phase 3 initiation

Phase 3 results

Atopic dermatitis

Phase 3 results

2020

2021
Building Value through Innovative Medicines