JAK Inhibitors for Chronic Itch: What’s the Future?

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Disclosures

- Consultant
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- Founder and Chief Scientific Officer
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- Patents
  - Patent pending for JAK inhibitors in chronic itch
What is chronic pruritus or itch?

Itch

1. an uncomfortable sensation on the skin that causes a desire to scratch

Chronic itch

1. itch that lasts for longer than six weeks
The problem and unmet need

1. Chronic itch affects >15% of the population
2. Negative impact on quality of life comparable to chronic pain
3. Incidence is increasing
4. No FDA-approved medications
Itch may be the most common medical symptom

- Dermatologic
  - Atopic dermatitis (AD), contact dermatitis, lichen planus, prurigo nodularis, psoriasis
- Infection
  - HIV, mites/parasites
- Malignancy
  - Polycytemia vera, leukemia, lymphoma

- Medication-induced
  - Opioids, checkpoint inhibitors
- Neurologic
  - Shingles, disc herniation, multiple sclerosis
- Systemic
  - Thyroid, kidney, and liver disease
- Idiopathic
  - Chronic pruritus of unknown origin (CPUO)
The opportunity in chronic itch

1. Accessible population of 19 million in U.S.

2. $5.4 billion market in U.S.

3. Large population of discouraged patients

4. Recent discovery of itch-specific pathways
JAK inhibitors are rapidly emerging for the treatment of atopic dermatitis
The immunologic paradigm of JAK-STAT signaling
Menlo Therapeutics Inc. is a late stage biopharmaceutical company focused on the development of selopititant for the treatment of pruritus (itch) associated with dermatologic conditions such as atopic dermatitis, psoriasis and prurigo nodularis, and for refractory chronic cough.
Itch-sensory neurons employ JAKs
The sensory paradigm of JAK-STAT signaling

Immune Cell

Sensory Neuron

JAK

STAT

TRP Channel

STAT
Oral JAK inhibitors have itch-selective effects

- Upadacitinib demonstrated reduction in pruritus (itch) within the first week and improvement in skin within the first two weeks for all doses[1]

- Study shows positive results for upadacitinib and no new safety signals detected[1]
- All doses achieved the primary endpoint of greater mean percentage change from baseline in Eczema Area andSeverity Index (EASI) score versus placebo at 16 weeks[1]
- Clear or almost clear skin was achieved by 50 percent of patients receiving 30 mg once-daily dose of upadacitinib[1]
- Upadacitinib demonstrated reduction in pruritus (itch) within the first week and improvement in skin within the first two weeks for all doses[1]
- Upadacitinib, an oral agent engineered by AbbVie to selectively inhibit JAK1, is being studied as a once-a-day therapy in atopic dermatitis and across multiple immune-mediated diseases[2][3][4-9]
Oral JAK inhibitors have itch-selective effects

Atopic Dermatitis

Chronic Pruritus of Unknown Origin (CPUO)

Chronic Pruritus of Unknown Origin (CPUO)

Oetjen et al. Cell 2017
Topical JAK inhibitors demonstrate anti-itch effects by 24-36 hours

A Phase 2, Randomized, Dose-Ranging, Vehicle- and Active-Controlled Study to Evaluate the Safety and Efficacy of Ruxolitinib Cream in Adult Patients With Atopic Dermatitis

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The intranasal route can directly access the cerebrospinal fluid

Djupesland et al. *Therapeutic Delivery* 2014
Intranasal JAK inhibition suppresses itch

JAK1-selective Inhibitors:
PF – PF-04965842
INCB – itacitinib

WT
Low Dose JAKi (i.n.)

Behavior & Sac.

Day 0 1 2 3 4 5 6 7
AD-like disease

Scratching bouts / 30 min

Control PF INCB

*P value = 0.0417
Ordinary one-way ANOVA

Unpublished Data
Chronic itch beyond atopic dermatitis

Chronic Pruritus of Unknown Origin
- Idiopathic
- Elderly pruritus

Neuropathic Pruritus
- Brachioradial pruritus
- Notalgia paresthetica
- Scalp pruritus
- Genital pruritus

Medication-Associated Pruritus
- Opioids
- Checkpoint inhibitors

Systemic Pruritus
- Chronic kidney disease
- Hepatobiliary disease

Malignancy-Associated Pruritus
- Leukemia/lymphoma
- Polycythemia vera

Idiopathic
Elderly pruritus
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