

A Potent and Selective CRTh2 Antagonist is Efficacious in a Model of Atopic Dermatitis

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Abstract

Prostaglandin D₂ (PGD₂) is a potent prostanoid released from activated mast cells during atopic responses. CRTh2 (Chemoattractant Receptor-homologous molecule expressed on Th₂ lymphocytes; a.k.a. DP2), a PGD₂ receptor, mediates chemotaxis and mast cell-dependent activation of basophils, eosinophils and Th₂ lymphocytes. Preclinical data and emerging clinical results suggest CRTh2 antagonists may have utility in allergic diseases. ARRY-005 is a potent, selective, orally bioavailable competitive antagonist of CRTh2 (binding IC₅₀ = 1 nM). ARRY-005 inhibits i) PGD₂-mediated chemotaxis of isolated human basophils, ii) PGD₂-induced eosinophil shape change in human whole blood and iii) PGD₂-induced CRTh2 receptor internalization in human whole blood. In a model of atopic dermatitis (AD) utilizing NC/Nga mice that spontaneously develop symptoms of AD, oral administration of ARRY-005 at 30mg/kg (QD) inhibited ear edema, erythema, oozing, crust formation, hemorrhaging and pruritus and showed trends in improved skin histopathology. The selective CRTh2 antagonist, ARRY-005, is a potent inhibitor of basophils and eosinophils *in vitro* and exhibited significant protective activity in a model of dermatitis.

[Acknowledgement: Dr. Wenbin Ying, MD (Bio-Quant, San Diego, CA)]

Background

- Local antigen challenge stimulates PGD₂ production in the skin of atopic dermatitis patients

- Corticosteroids have no inhibitory effect on this event¹

- Increased levels of circulating CRTh2-positive lymphocytes have been detected in blood from AD patients²

- CRTh2 KO mice have diminished responses to allergic challenge with decreased IL-4, IL-13, IgE, mucus production, eosinophil migration & airway hyperresponsiveness

- CRTh2 is expressed on eosinophils, basophils & Th₂ T cells
 - CRTh2 activation results in chemotaxis
 - CRTh2 stimulation yields IL-4, 5 & 13 from Th₂ T cells

- There are reports of CRTh2 involvement in dermatitis models³

- A weak, non-selective CRTh2 antagonist with modest efficacy, is approved for allergic rhinitis in Japan (Ramatroban[®])

- Selective CRTh2 antagonists are in clinical development⁴

1. J. Immunol. 148 (2): 671-6, 1991.
 2. J. Invest. Derm. 119(3): 609-16, 2002.
 3. J. Immunol. 177: 2521-9, 2006; Int. Immunol. 21(1): 1-17 (and 81-93), 2008; Int. Immunol 16(7): 947-59.
 4. Abstract #3267, Eur. Resp. Soc. Ann. Meeting, Sept. 2009.
 5. Int. Immunol. 9: 461-6, 1997.

Unmet Medical Needs in Atopic Dermatitis

- Topical corticosteroids are typically effective but there are concerns with side effects particularly among pediatric patients
- Topical immunosuppressants are effective but have a black box warning

We hypothesize that an oral agent possessing efficacy similar to topical steroids and immunosuppressants but with a superior safety profile would provide benefit to patients

Profile of ARRY-005

	ARRY-005
Human CRTh2 Binding IC ₅₀	1 nM
Human CRTh2 Binding IC ₅₀ (4% HSA)	35 nM
Selectivity vs. 30 GPCR's, Ion Channels and Transporters	No significant activity @500 nM
CRTh2 FLIPR Calcium Mobilization IC ₅₀	5 nM
Human Isolated Basophil Chemotaxis IC ₅₀	1 nM
Human Whole Blood Eosinophil Shape Change IC ₅₀	33 nM
Human Whole Blood Receptor Internalization IC ₅₀	22 nM

Murine Model of Atopic Dermatitis

- NC/Nga mice: inbred mouse strain that develops a spontaneous AD-like pathology in non-sterile housing conditions⁵

- Dosing started at ~4 weeks of age; microscopic disease present

- Groups:

Vehicle (Labrafac, BID, po) x 30 days
 ARRY-005 (30 mg/kg, QD, po) x 30 days in CMC/SDS
 Protopic[®] (0.03% Tacrolimus) cream (10 mg/cm², BID, topical) x 30 days
 40 mg total dose daily of cream: 0.5 mg/kg of active drug

- Assessments:

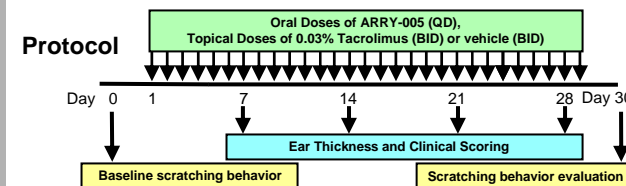
Twice weekly ear thickness measure

Weekly clinical scoring

Scores are summed erythema, edema/papulation and oozing/crusts/hemorrhage on a scale 0-3

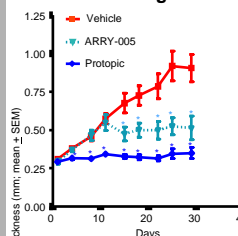
Scratching measures at Day 0 (baseline) & Day 30 (1 hr post-dose)

- Skin samples taken for histopathology at conclusion of study

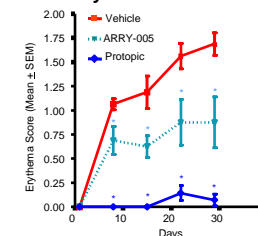


Results

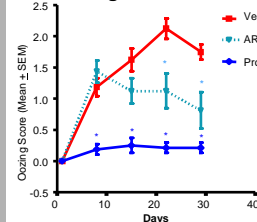
Ear Swelling



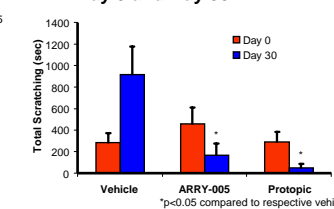
Erythema



Oozing/crusts/hemorrhage



Total Scratching: Day 0 and Day 30



Histopathology

	Vehicle treated skin section Marked epidermal hyperplasia (E) Moderate dermal inflammation (D) Excessive keratin (arrow) Moderate parakeratosis Marked orthokeratotic hyperkeratosis Panniculus muscle (P)
	ARRY-005 treated skin section Mild epidermal hyperplasia (E) Mild dermal inflammation (D) Excessive keratin (arrow) Minimal orthokeratotic hyperkeratosis Minimal epithelial necrosis Minimal epithelial inflammation

Summary

A potent, selective CRTh2 antagonist ameliorates several aspects of disease severity including pruritus via oral dosing in a mouse model of atopic dermatitis