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Proof-of-Concept Phase-2a Clinical Trial of ANB020 (Anti-IL-33 Antibody) in the Treatment of Moderate-to-Severe Adult Atopic Dermatitis

Professor Graham Ogg

University of Oxford

United Kingdom

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Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

Type	Company
Employment full time	University of Oxford and Oxford University Hospitals
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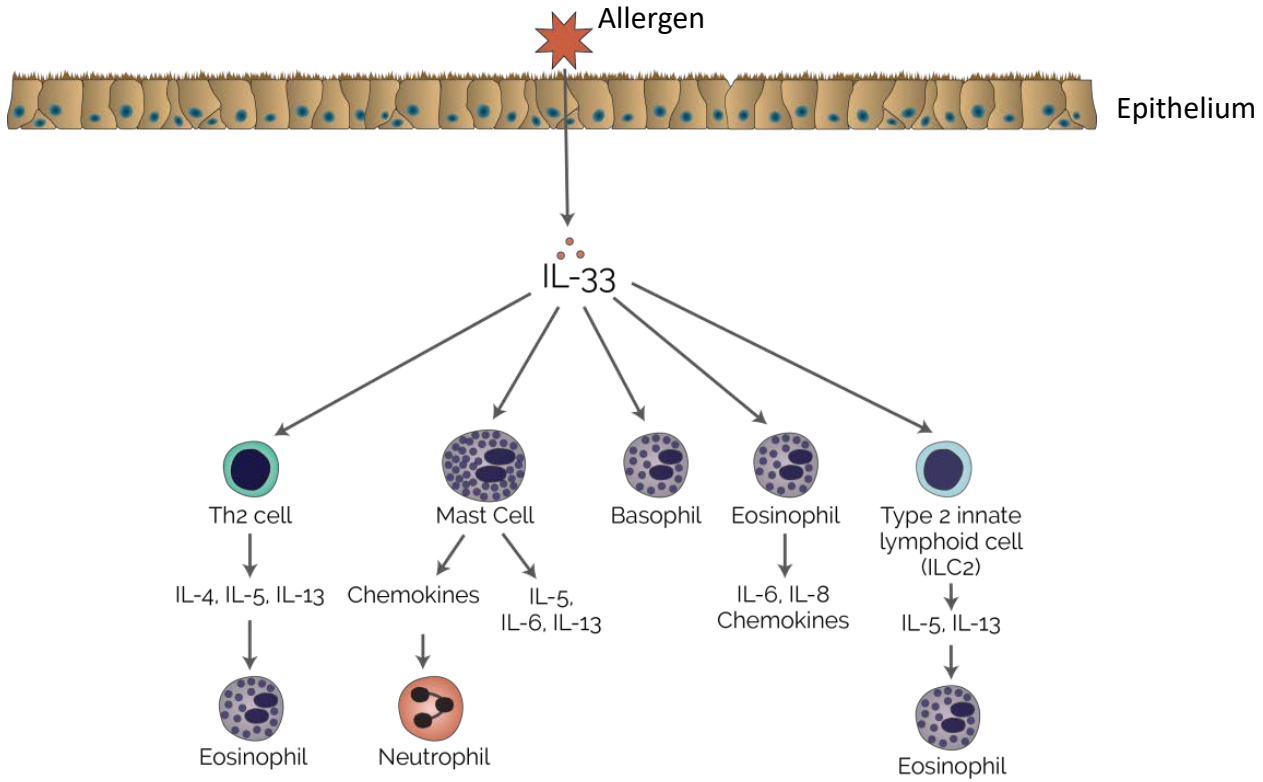
Speakers Bureau	Sanofi/Genzyme, La Roche Posay
Ownership interest (stock, stock-options, patent or intellectual property	Orbit Discovery
Consultant / advisory board	Novartis, UCB, Grunenthal, Evelo, Eli Lilly, Leo

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (eg. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.

IL-33: Central Mediator of Type 2 Diseases

Key Role in Pathogenesis of Atopic Dermatitis

- IL-33 is a key cytokine in type 2 inflammatory responses to allergen
  - Responsible for activation of Th2 and ILC2
  - Functions upstream of IL-4, IL-5 and IL-13
  - Modulates mast cell degranulation
- IL-33 is rapidly released by epithelium upon allergen exposure
- Genetic association of IL-33 pathway mutations with type 2 diseases[1]
- IL-33 is highly expressed in skin of atopic dermatitis patients with active disease[2]

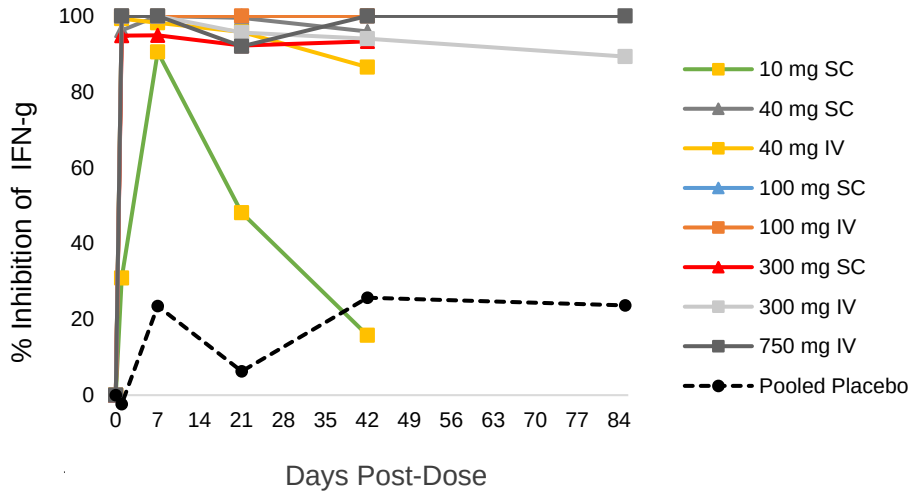


1. Ramirez-Carrozzi et al. 2014
2. Savinko et al. 2012

ANB020: Anti-Human IL-33 Antibody

- ANB020 is humanized anti-human IL-33 monoclonal antibody
  - High affinity binding to human IL-33 with K_d of approximately 1 pM
  - Potent neutralizing activity with an IC_{50} of approximately 1.5 nM

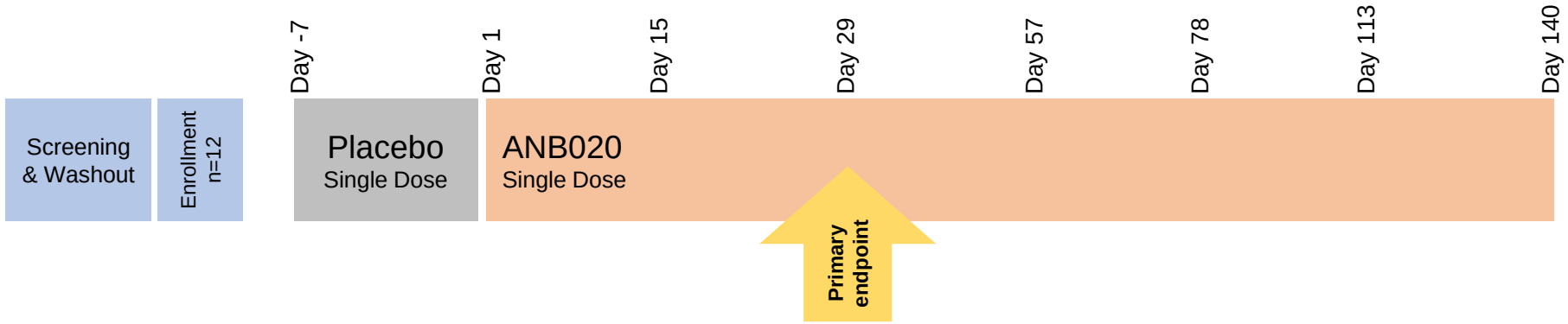
- Healthy volunteer Phase 1 trial (n=96) reported safety, pharmacokinetics and pharmacodynamics
  - Subjects dosed with 10mg to 750mg of ANB020 in single dose cohorts (n=48), 40mg to 300mg of ANB020 weekly for 4 weeks in multiple dose cohorts (n=24) and placebo (n=24)
  - *In vivo* half-life of approximately 16 days for both intravenous and subcutaneous administration
  - Pharmacodynamic effect persisted for 85 days at certain single dose levels of ANB020
  - ANB020 was generally well tolerated and no dose-limiting toxicities were observed



Single dose ANB020 healthy volunteer Phase 1 pharmacodynamic *ex vivo* assay measuring inhibition of IL-33 induced Interferon-gamma (IFN-g) relative to pre-dose levels

ANB020 Phase 2a Atopic Dermatitis

Proof-of-Concept Trial



- Study design:
  - Enrolled 12 moderate-to-severe adult atopic dermatitis patients inadequately controlled with topical corticosteroids
  - Single intravenous dose of placebo (Day -7) followed by a single 300 mg intravenous dose of ANB020 (Day 1)
  - EASI, 5-D pruritus, SCORAD, DLQI and IGA clinical scores determined at specific time points
- Study objective:
  - Demonstrate EASI-50 response in at least 50% of patients at Day 29 (primary endpoint)

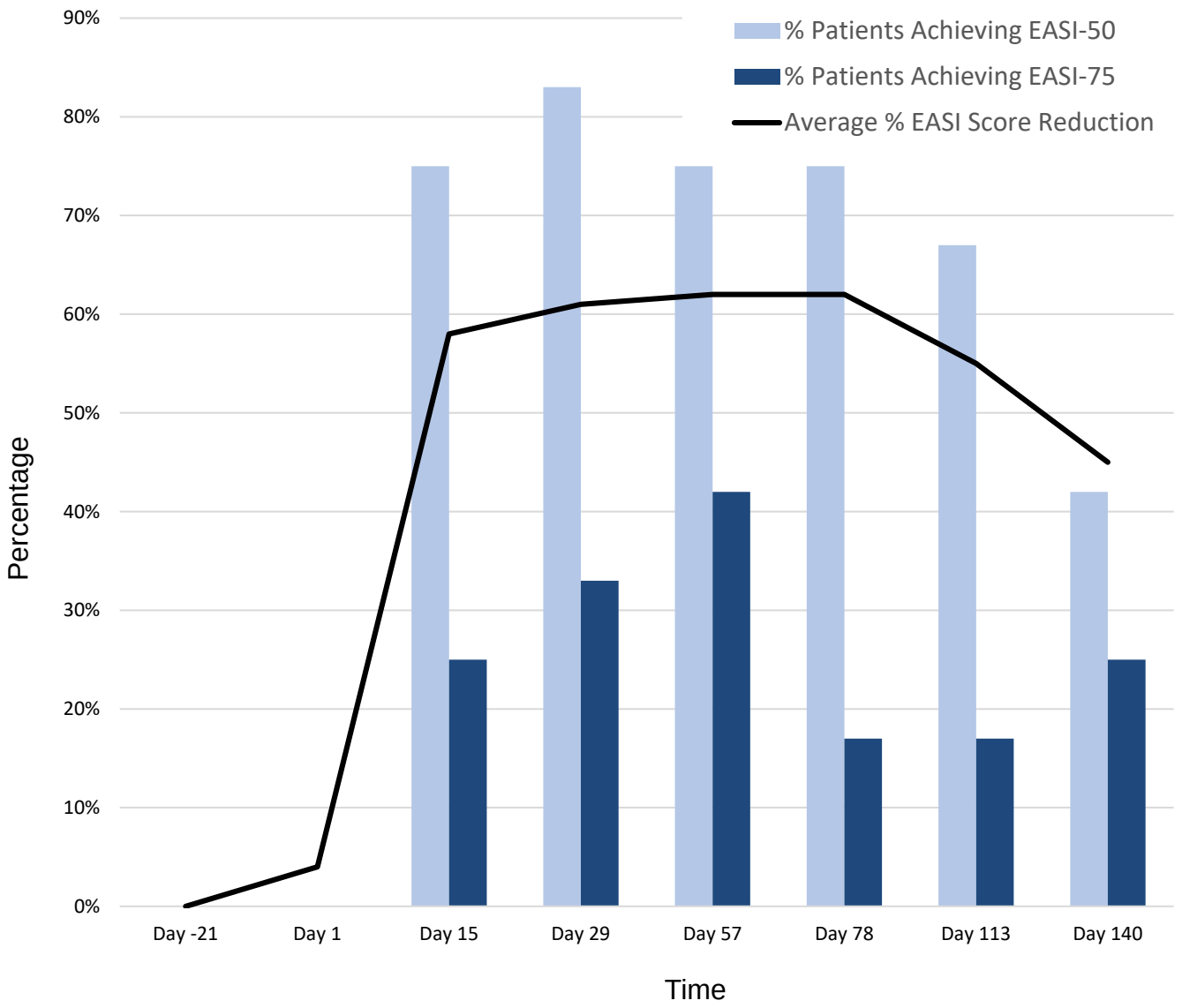
Baseline Characteristics

Characteristic	Average (n=12)
Age (years)	40.4 ± 13.5
Male, number (%)	11 (91.7%)
Caucasian race, number (%)	12 (100%)
Body-Mass Index	26.14 ± 4.145
EASI, score	32.25 ± 10.89
IGA, 0-5 scale	4 ± 0.74
SCORAD, score	64.79 ± 12.02
Pruritus, 5-D score	19.1 ± 4.85
DLQI, score	12.92 ± 6.54
Eosinophils, per microliter blood	588 ± 468

All 12 patients were inadequately controlled on corticosteroids pre-study
7 of 12 enrolled patients were treated with systemic immuno-modulators pre-study and presented with a baseline EASI score of 36
5 of 12 patients were not treated with systemic immuno-modulators pre-study and presented with a baseline EASI score of 27

EASI Scores Following Single ANB020 Dose

Rapid response and all patients achieved EASI-50 on or before Day 57

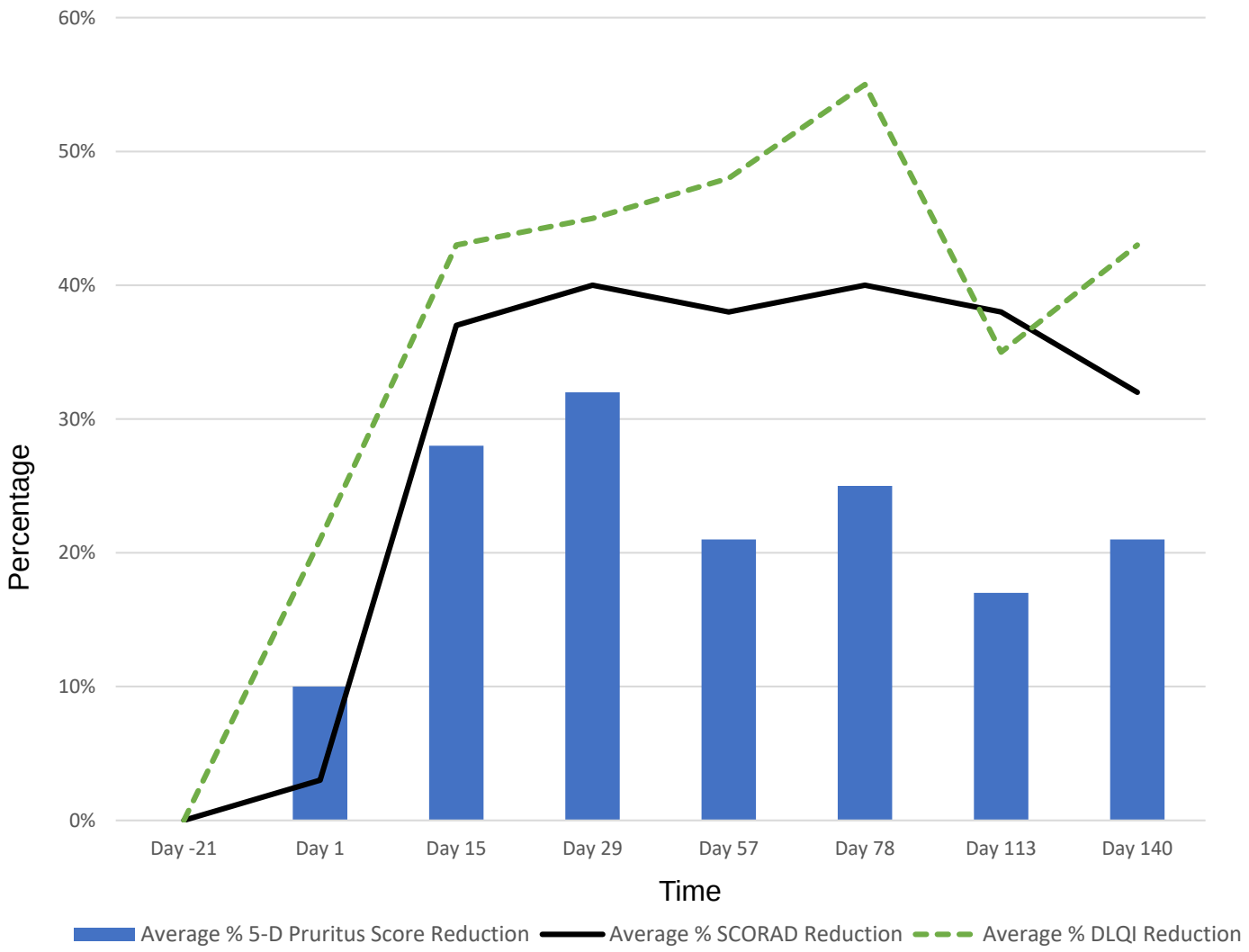


Timepoint	Average % EASI Score Reduction*	% Patients Achieving EASI-50*	% Patients Achieving EASI-75*
Day -21 (Baseline)	0%	0	0
Day 1 (ANB020 Dosing)	4%	0	0
Day 15	58%	9 of 12 (75%)	3 of 12 (25%)
Day 29	61%	10 of 12 (83%)	4 of 12 (33%)
Day 57	62%	9 of 12 (75%)	5 of 12 (42%)
Day 78	62%	9 of 12 (75%)	2 of 12 (17%)
Day 113	55%	8 of 12 (67%)	2 of 12 (17%)
Day 140	45%	5 of 12 (42%)	3 of 12 (25%)

* Relative to baseline upon enrollment at Day -21

Additional Efficacy Data

5-D Pruritus, SCORAD, DLQI and IGA Scores



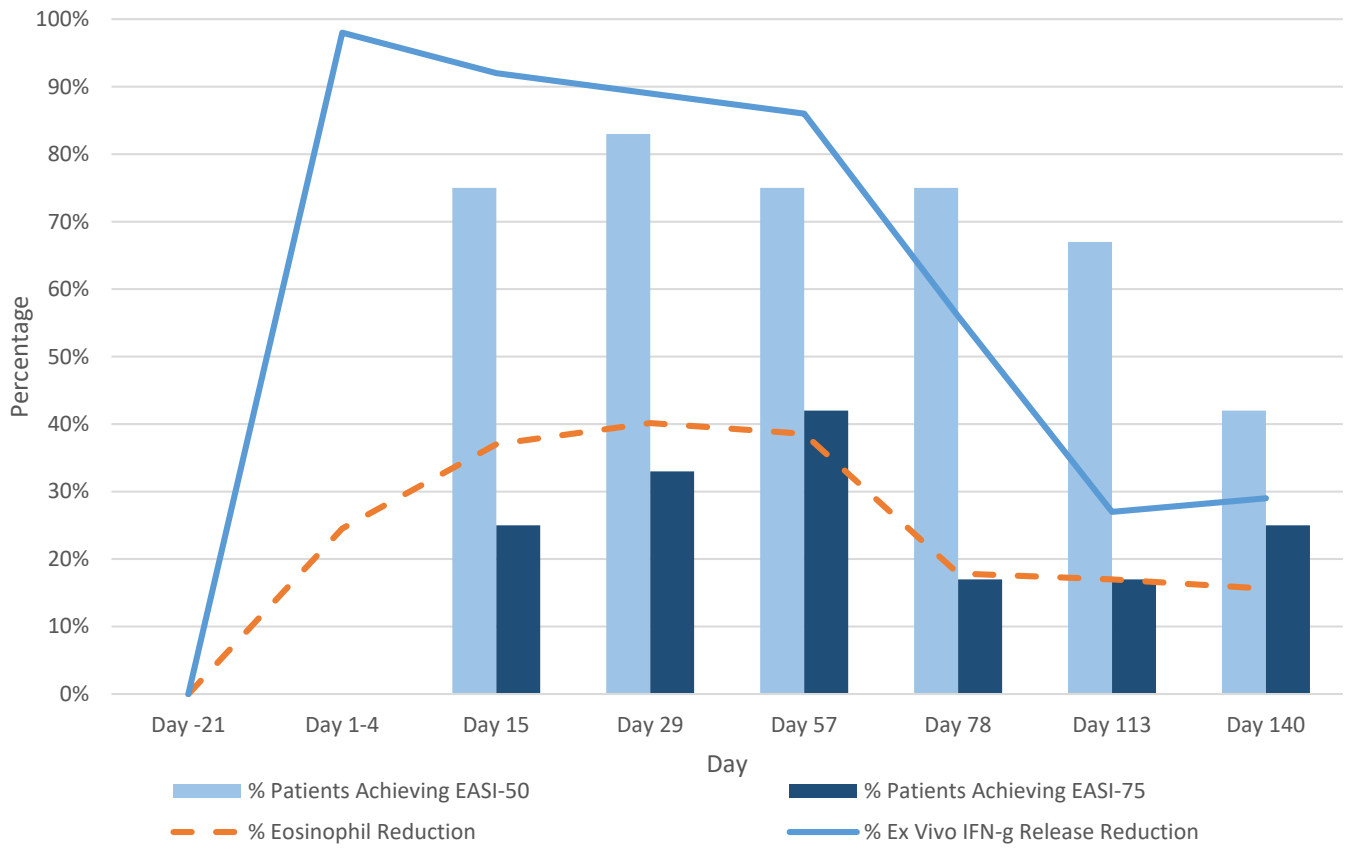
Timepoint	Average % 5-D Pruritus Score Reduction*	Average % SCORAD Reduction*	Average % DLQI Reduction*
Day -21 (Baseline)	0%	0%	0%
Day 1 (ANB020 Dosing)	10%	3%	21%
Day 15	28%	37%	43%
Day 29	32%	40%	45%
Day 57	21%	38%	48%
Day 78	25%	40%	55%
Day 113	17%	38%	35%
Day 140	21%	32%	43%

* Relative to baseline upon enrollment at Day -21

IGA scores of zero or 1 (clear/almost clear skin) observed in 25% (3/12) of patients

Biomarker Data

Clinical Efficacy Consistent With Reduction of Blood Eosinophil Levels and Ex Vivo Pharmacodynamic Assay



Timepoint	% Blood Eosinophil Reduction*	% Ex Vivo IL-33-Mediated IFN-g Release Reduction*	% Patients Achieving EASI-50*	% Patients Achieving EASI-75*
Day -21 (Baseline)	0%	0%	0%	0%
Day 1-4**	25%	98%	0%	0%
Day 15	37%	Not measured	75%	25%
Day 29	40%	Not measured	83%	33%
Day 57	39%	86%	75%	42%
Day 78	18%	Not measured	75%	17%
Day 113	Not measured	27%	67%	17%
Day 140	16%	29%	42%	25%

* Average relative to baseline upon enrollment
** 6 to 72 hours post-ANB020 dose

ANB020-mediated eosinophil reduction is aligned with genotypic data from prior human IL-33 loss-of-function studies[#]
Inhibition of ex vivo IL-33-mediated interferon-gamma (IFN-g) release consistent with Phase 1 pharmacodynamic results

[#] Smith et al. (2017) A rare *IL33* loss-of-function mutation reduces blood eosinophil counts and protects from asthma. PLoS Genet 13(3): e1006659.

Key Conclusions & Next Steps

- Rapid and persistent efficacy following single dose of ANB020
  - Rapid efficacy observed as early as Day 15
  - Efficacy was maximized between Day 29 and Day 57
  - All patients achieved at least EASI-50 response on or before Day 57
  - EASI responses consistent with 5-D pruritus, SCORAD, IGA and DLQI scores
- Disease severity does not limit ANB020 efficacy
  - ANB020 was similarly efficacious in patients with higher baseline EASI scores (treated with systemic immuno-modulators pre-study) versus lower baseline EASI score patients that did not require systemic therapy pre-study
- Biomarker data consistent with ANB020 clinical efficacy
  - ANB020-mediated eosinophil reduction is aligned with genotypic data from prior human IL-33 loss-of-function studies
  - Ex vivo IL-33-mediated IFN-g release consistent with Phase 1 pharmacodynamic assay results
- ANB020 was well-tolerated and no drug-related safety signals observed
  - Most frequent adverse event was dizziness in 17% of patients post-placebo versus headache in 25% of patients post-ANB020
  - A single serious adverse event of depression reported on Day 140 post-ANB020, which was consistent with the patient's pre-trial history of depression, and was deemed not drug-related
- Initiated multi-dose placebo-controlled, double-blind, randomized 300 adult moderate-to-severe atopic dermatitis Phase 2b trial
  - Assess different dose levels and dosing frequencies of subcutaneously-administered ANB020

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