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The Oral JAK/SYK Inhibitor ASN002 Demonstrates Efficacy and Improves Associated Systemic Inflammation in Patients with Moderate-to-Severe Atopic Dermatitis: Results from a Randomised, Double-Blind, Placebo-Controlled Study

Short title: ASN002 Demonstrates Efficacy and Improves Inflammation in Atopic Dermatitis

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Keywords:

Atopic dermatitis, ASN002, SYK, JAK, tyrosine kinases, SYK inhibitor, JAK inhibitor, treatment outcome, immune response, systemic inflammation, randomised controlled trial.

Abstract

Background: ASN002 is an oral dual inhibitor of JAK and SYK which are involved in the pathogenesis of atopic dermatitis (AD) through their regulatory role on Th1, Th2, and Th17/Th22 pathways.

Objectives: The objectives were to evaluate the efficacy, safety, pharmacokinetics, and effects on systemic biomarkers of ASN002 in patients with moderate-to-severe AD.

Methods: Thirty-six patients with moderate-to-severe AD were randomised (3:1) to ASN002 or placebo in the phase 1b study. Three dose cohorts were studied over a 28- day period: 20-mg, 40-mg, and 80-mg once a day.

Results: ASN002 was superior to placebo for the proportion of patients achieving EASI-50 (20-mg: 20.0%, $p=0.93$; 40-mg: 100.0%, $p=0.003$; 80-mg: 83.3%; $p=0.03$; placebo: 22.2%), EASI-75 (20-mg: 0%, $p=0.27$; 40-mg: 71.4%, $p=0.06$; 80-mg: 33.3%, $p=0.65$; placebo: 22.2%), and in change from baseline in pruritus (20-mg: -1.3 ± 2.1 , $p=0.81$; 40- mg: -3.1 ± 2.7 , $p=0.27$; 80-mg: -4.7 ± 2.1 , $p=0.01$; placebo: -1.6 ± 1.8). Adverse events were generally mild and similar across all groups. ASN002 showed dose-dependent plasma exposure with low inter-subject variability, significantly downregulated several serum biomarkers involved in Th1, Th2, and Th17/Th22 immunity, and decreased the atherosclerosis-associated biomarker E selectin/SELE.

Limitations: Small sample size and short treatment duration.

Conclusions: In patients with moderate-to-severe atopic dermatitis, ASN002 showed strong efficacy with rapid onset of action and associated improvements in systemic inflammation.

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Bulleted statements

- Currently available therapeutic options for atopic dermatitis (AD) include topical corticosteroids, calcineurin inhibitors, crisaborole, dupilumab, cyclosporine, and phototherapy. However, only few oral treatments are available and those are associated with safety concerns.
- ASN002, an oral, dual JAK and SYK inhibitor, was well tolerated and showed promising efficacy and rapid onset of action in patients with moderate-to-severe AD at daily doses of 40-mg and 80-mg.
- The encouraging efficacy, safety, and tolerability profile of ASN002 warrant further investigation of ASN002 in patients with moderate-to-severe AD.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a lifetime prevalence as high as 20%.¹ Moderate-to-severe AD is characterised by the presence of eczematous lesions over large surface areas associated with intense pruritus, which can significantly impair quality of life.¹⁻³ Currently available treatments include topical corticosteroids, calcineurin inhibitors, and phototherapy which often have more limited efficacy in patients with extensive disease.^{4, 5} Systemic immune-modulators, including cyclosporine, methotrexate, azathioprine, and corticosteroids (the only Food and Drug Administration (FDA)-approved oral medication for moderate-to-severe AD in the United States), can improve AD but their use is limited by long-term toxicity.^{6, 7} Dupilumab, a monoclonal antibody against the interleukin (IL)-4 receptor has recently been approved by the FDA and

European Medicines Agency (EMA) for the treatment of adult patients with moderate-to-severe AD who are candidate for systemic therapies.⁸⁻¹⁰ However, only approximately 50% of patients with moderate-to-severe AD achieve a reduction of 75% or more in Eczema Area and Severity Index (EASI-75) after 16 weeks of treatment.¹¹ Thus, a high unmet need remains for novel oral treatments with improved efficacy for moderate-to-severe AD.

Spleen tyrosine kinase (SYK) and Janus kinase (JAK) are tyrosine kinases (TYK) that play important roles in inflammatory processes.^{12, 13} SYK is involved in the release of cytokines during the proinflammatory process, including IL-1 β , IL-10, and IL-17,¹⁴ and regulates dendritic cells, B lymphocytes, and keratinocyte differentiation, suggesting that SYK inhibitors could improve inflammatory skin diseases with aberrant differentiation, such as AD.¹⁵ The JAK kinases family (JAK1, JAK2, JAK3, and TYK2) is also involved in signalling pathways of several cytokines involved in AD such as IL-4, IL-13, IL-31, and IL-33¹⁶⁻¹⁸. In addition, JAK inhibitors, targeting mostly JAK1, have been shown to be effective for the treatment of AD.¹⁹⁻²¹ ASN002 is a potent, dual inhibitor of JAK and SYK kinases with inhibitory concentration (IC₅₀) values of 5 nM (SYK), 46 nM (JAK1), 4 nM (JAK2), 11 nM (JAK3), and 8 nM (TYK2) in biochemical assays.²² The goal of this study was to evaluate its efficacy and safety in patients with moderate-to-severe AD.

Materials and Methods

This randomised, double-blind, placebo-controlled study was conducted at ten centres in Canada and United States, from April 2017 to November 2017, and included patients 18 to 75 years of age with moderate-to-severe AD. Eligible patients were required to have an EASI score of at least 16, an Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe), a Body Surface Area (BSA) involved with AD of at least 10%, and a body mass index (BMI) less than or equal to 35 kg/m² at Day 1. Washout periods were 1 week for hydroxyzine, diphenhydramine, topical products containing urea, and topical antibiotics, 2

weeks for systemic antibiotics and topical medicated treatment for AD, 4 weeks for systemic treatments and 12 weeks or 5 half-lives (whichever was longer) for biological agents. This study was approved by a research ethics board on 17 March 2017 and written informed consent was obtained from each patient before any study procedure was performed.

Three sequential cohorts were enrolled, with doses of 20, 40, and 80-mg orally administered once daily for 28 Days. In each dosing cohort, 12 patients were randomised in a 3:1 ratio to receive ASN002 or placebo according to a central randomisation scheme provided by an interactive web response system (IWRS). Investigators, patients, and study site personnel were blinded for treatment assignment. Patients were evaluated at baseline, Days 15 and 29, and follow-up for safety, efficacy, and serum biomarkers. Safety and pruritus were also evaluated at Days 2, 8, 16, and 22.

The primary objective was to evaluate the safety of ASN002 by evaluation of treatment-emergent adverse events (TEAEs). Secondary efficacy endpoints included the proportion of patients achieving EASI-50, EASI-75, and IGA of 0/1 with at least a 2-grade reduction from baseline, and change from baseline in BSA, EASI, and single weekly pruritus Numeric Rating Scale (NRS) over time. Change from baseline in weekly average pruritus NRS for patients with a baseline score of at least 4 was evaluated over time as a post-hoc analysis. The pharmacokinetic (PK) endpoint included evaluations of ASN002 plasma concentrations and PK parameters at Days 1 and 15. Inflammatory markers in serum were evaluated at Days 15 and 29 as an exploratory objective to determine the effect of ASN002 on the disease process.

No formal sample size calculations were performed given the exploratory nature of this study. A design including 12 patients randomised (3:1) to active treatment or placebo was deemed sufficient to explore safety and efficacy of ASN002. Demographics and baseline characteristics, as well as safety and PK data are presented using descriptive statistics. The proportion of patients achieving EASI-50, EASI-75, and IGA of 0/1 with at least a 2-grade reduction from baseline were analysed using a Cochran-Mantel-Haenszel (CMH), in the per-

protocol population using non-responder imputation (NRI) for missing data. This was the primary analysis planned in the statistical analysis plan. Change from baseline in EASI, BSA, and pruritus NRS were analysed with a mixed-effect model for repeated measures (MMRM) with treatment, visit, and treatment by visit as fixed effects and baseline as a covariate. For the change from baseline endpoints a per-protocol analysis with last observation carried forward (LOCF) was used for missing data. Analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC) with a significance level of 0.05. Similar data were obtained when analyzing the intent-to-treat population (data not shown).

Plasma concentration of ASN002 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Pharmacokinetic parameters were determined via non-compartmental analysis.

Serum biomarkers were analysed using OLINK Proseek Multiplex Assay, based on proximity extension assay technology,²³⁻²⁶ and quantified using Fluidigm BioMark HDTM real-time polymerase chain reaction platform.^{24, 27} Biomarkers were analysed using 4 multiplex panels including Inflammation I, cardiovascular disease (CVD) II, CVD III, and neuroinflammation, containing a broad array of established and exploratory biomarkers.²³ Statistical analysis was performed using R-language Version 3.3.2 (R-project.org). The treatment groups were compared using a linear mixed effect model with time and treatment as fixed factors, and a random intercept for each patient. T-test was used for the comparisons, and $p < 0.05$ was considered for significance. The biomarkers that changed significantly in any treatment groups were combined and compared to placebo group to increase power. Biomarkers with significant changes between treatment and placebo group were considered for pathway enrichment analysis with XGR software,²⁸ using pathway databases including KEGG, PID, MSigDB, BioCarta, and REACTOME.²⁹⁻³³ The significance cutoff for enriched pathways was the Benjamini-Hochberg fixed discovery rate (FDR) < 0.05 .

Results

A total of 36 patients were randomised. Patient disposition is presented in Figure 1, and baseline demographics and clinical characteristics are presented in Table 1. The proportion of patients achieving EASI-50 at Day 29 was significantly higher for patients receiving ASN002 40-mg (100.0%; $p=0.003$) and 80-mg (83.3%; $p=0.03$) but not 20-mg (20.0%; $p=0.93$) as compared to placebo (22.2%) (Fig. 2a). The proportion of patients achieving EASI-75 at Day 29 was higher for patients receiving ASN002 40-mg (71.4%; $p=0.06$) and ASN002 80-mg (33.3%; $p=0.65$) versus placebo (22.2%). None of the patients randomised to ASN002 20-mg achieved EASI-75. At Day 15, a significant difference versus placebo in EASI-75 was observed for patients receiving ASN002 40-mg (42.9%; $p=0.04$), but not for those receiving ASN002 20-mg (20.0%; $p=0.18$) or ASN002 80-mg (16.7%; $p=0.65$) (Fig. 2b). There was also a significant decrease in change from baseline in EASI at Day 29 for patients randomised to ASN002 40-mg (-17.5 ± 5.9 ; $p=0.02$) and a similar, but not statistically significant, decrease for patients receiving ASN002 80-mg (-16.5 ± 6.8 ; $p=0.17$) as compared to placebo (-7.6 ± 4.6). ASN002 20-mg (-9.6 ± 16.2 ; $p=0.64$) did not show a relevant difference from placebo. The proportion of patients achieving an IGA of 0/1 with at least a 2-grade reduction from baseline at Day 29 was 42.9% ($p=0.16$) for patients receiving ASN002 40-mg, 16.7% ($p=0.77$) for patients receiving ASN002 80-mg, 0.0% ($p=0.46$) for patients receiving ASN002 20-mg, and 11.1% for patients receiving placebo. There was a significant decrease in change from baseline in BSA at Day 29 for patients receiving ASN002 40-mg (-21.6 ± 19.3 ; $p=0.03$) and a similar, but not statistically significant, decrease for patients receiving ASN002 80-mg (-22.1 ± 14.9 ; $p=0.08$) as compared to placebo (-3.2 ± 10.9). ASN002 20-mg (-9.0 ± 16.9 ; $p=0.98$) did not show a relevant difference from placebo. There was a significant difference in change from baseline in weekly average pruritus NRS for patients with a baseline score of at least 4 at Day 29 for patients receiving ASN002 80-mg (-4.7 ± 2.1 , $p=0.01$) versus placebo (-1.6 ± 1.8), but the difference was not statistically significant for patients receiving ASN002 40-mg (-3.1 ± 2.7 , $p=0.27$) and ASN002 20-mg (-1.3 ± 2.1 , $p=0.81$).

The difference was also statistically significant at all other days starting from Day 8 for patients receiving ASN002 80-mg (Fig. 3). In addition, changes in single weekly pruritus NRS for patients receiving ASN002 were higher versus placebo as early as Day 2 (20-mg: -1.0 ± 0.82 , $p=0.41$; 40-mg: -0.3 ± 1.03 , $p=0.24$; 80-mg: -1.0 ± 2.74 ; $p=0.16$; placebo: 0.4 ± 0.79).

Mean plasma ASN002 concentration at Days 1 and 15 are presented in Supplemental Figure 1. Systemic ASN002 exposure was generally measurable up to the 24-hour time point at all dose levels. A rapid oral absorption and a moderate elimination rate were observed with T_{max} (time to reach peak plasma concentrations) ranging from 2 to 4 hours, and mean terminal half-life ($t_{1/2}$) ranging from 7.3 to 14.1 at steady state. Maximum observed concentration (C_{max}) and area under the plasma concentration (AUC) parameters showed dose-dependent exposure, and AUC approximately proportional to the increase of dose (Supplemental Table 1). Inter-subject variability in C_{max} and AUC was low to moderate, and minimal drug accumulation was measured at steady state.

A summary of TEAEs occurring in at least two patients per treatment group and events meeting the stopping rules is presented in Table 2. Overall, TEAEs were similar across all groups, including placebo. There were two events meeting the stopping rule—mild hypertension and low lymphocyte counts. The event of mild hypertension was reported in a subject receiving ASN002 80-mg, and was classified as a possibly related TEAE. The event of lymphopenia was reported in a subject who had pre-dose lymphocytes levels of $0.67 \times 10^3/\mu\text{L}$ at Day 1 and $0.56 \times 10^3/\mu\text{L}$ at Day 8. There was one serious adverse event of anxiety attack reported in a patient from the ASN002 80-mg group. This event occurred after the treatment period and was evaluated by the investigator as not related to the treatment. No clinically significant changes in lipid profile and vital signs were observed.

ASN002 induced significant, and progressive reductions in the AD inflammatory serum signature,^{26, 34} which was particularly evident in the higher doses (Fig. 4a; Supplemental Fig. 2, Supplemental Table 2). Among the highly and/or significantly downregulated markers,

are products of general inflammation (MMP12, TRAIL), innate immunity (CD300/CLM6, MARCO/macrophage receptor with collagenous structure, CD163/macrophage scavenger receptor), T-cell/B-cell (CD5, CD38), T-cell activation (CD6, IL-16, IL-2RA, CD355/CRTAM, AXL, CCL19, CD137/TNFRSF9), Th1 (CXCL10/CXCL11/CXCL9, CCL4, IL-18, IL-12B/IL12/23p40), Th2 (IL-13, CCL13, CCL17), Th17 (IL-27, KYNU/kynureninase, CD318/CDCP1), and related markers. ASN002 also induced significant increases in negative regulator products (SOD2, PON3) (Fig. 4a, *o*; Supplemental Fig. 2, *m*). At Day 15, many markers already showed significant treatment-effects with ASN002 versus placebo, predominantly at 40-mg and 80-mg (CD5, CD300/CLM6, CXCL10, CCL4, IL-18, IL-12B/IL-12/23p40, CCL13, IL-27, KYNU, SOD2, and others). Similar or more significant modulations were observed at Day 29. Among the downregulated markers with ASN002 were atherosclerosis mediators, such as E selectin/SELE, recently shown to be upregulated in AD (Supplemental Table 2).²⁶ An enrichment analysis based on several well-established databases was also conducted to identify the pathways most significantly modulated in ASN002-treated patients, as compared to baseline (Supplemental Table 3) and to placebo-treated patients at Day 29 (Fig. 4b). All doses were grouped together due to small sample size. The most significantly enriched pathways impacted by JAK/SYK were cytokine-cytokine-receptor interaction, cytokine, Th1-Th2, inflammatory, chemokine receptor binding, chemokine signalling, JAK-STAT signalling, and IL-23 pathways.

Discussion

This proof of concept study showed that ASN002, at oral doses of 40-mg and 80-mg, once daily was effective at improving signs and symptoms of AD and was well tolerated. At both doses, the efficacy was consistently higher than placebo and most of the efficacy endpoints achieved statistical significance. However, ASN002 20-mg did not show significant differences in efficacy compared to placebo. The small effect size observed with 20 mg suggests that this dose may be lower than the minimum effective dose. In general, improved

efficacy outcomes were observed with the 40- mg compared with the 80-mg dose. Further studies are needed to see if this is related to the small sample size and baseline differences between groups observed in the current study. Noteworthy, a rapid-onset of action on pruritus was observed as early as Day 2 with a statistically significant decrease on Day 8 for ASN002 80-mg. Early and rapid decrease in pruritus has been reported with topical and systemic JAK inhibitors and could be related to the inhibition of the IL-31 signalling pathway.³⁵ After only 4 weeks of treatment with ASN002 at 40-mg, 100% of patients achieved EASI-50 and 71% achieved EASI-75.

Several cytokines including Th1/interferon- γ , Th2/IL-4, IL-13, IL-31, IL-33, IL-5, Th17/Th22/IL-17, IL-22 have been shown to be increased in AD, suggesting that the possible involvement of Th1, Th2, and Th17 pathways in disease pathogenesis.¹⁶⁻¹⁸ Moreover, the relative role of these pathways varies with age and ethnicity.^{3, 36-39} For example, Th17 activation has been shown to be higher in children and Asians.^{36, 39} SYK is involved in several cytokines signalling pathways, including the Th17 pathway.¹⁴ It induces the production of CCL20, which attracts Th17-cells to the skin.¹⁵ SYK also acts as a negative regulator of keratinocyte differentiation, and gradually decreases during the terminal differentiation process due to a cross-regulation with epidermal growth factor receptor (EGFR).¹⁵ In addition SYK is involved in B lymphocytes survival, proliferation, and activation and in differentiation of dendritic cells.^{40, 41} Therefore, combining SYK with JAK inhibition could provide additional clinical benefits in the treatment of AD.

Based on serum biomarker analyses, our study showed that ASN002 provided greater and more significant modulation of many key AD circulatory biomarkers as compared to placebo, particularly at high doses.⁴² Many established AD biomarkers, including inflammatory measures (MMP12, TRAIL), or Th1/CXCL10, Th2/CCL17, CCL13 related products, were significantly downregulated only with ASN002, and the negative regulators SOD2 and PON3, which have possible protective anti-inflammatory and anti-oxidant properties,^{43, 44} were upregulated. Interestingly serum markers associated with atherosclerosis were

downregulated by ASN002, including E-selectin/SELE,^{24, 26} possibly suggesting that effective AD therapy may have the potential to reduce cardiovascular risk in AD patients. There was also a significant difference in expression of B-cell-associated products (CD5, CD38, CD137, IL-16, CD300) suggesting that ASN002 also has effects on B lymphocytes. While these analyses were intended to compare the effects of ASN002 on serum biomarkers to the placebo, it is important to note that the measured changes may not be associated with clinical response to ASN002. Despite this limitation, the present study uncovered that ASN002 has a robust effect on multiple inflammatory pathways as compared with placebo, including those related to cytokine/chemokine, JAK-STAT, SYK, and Th1/Th2/Th17 signalling.

In the current trial, ASN002 at both 40-mg and 80-mg showed good evidence of activity, but efficacy was generally higher for ASN002 40-mg. The difference in response between 40-mg and 80-mg could be related to the small size of the current study or to differences in baseline characteristics between the groups. There were demographic differences between groups with higher baseline EASI, BSA, proportion of severe patients, and mean weight (13.1 kg) in the 80-mg group. The difference is probably not related to patient adherence as PK analysis showed clear dose-dependent increases in plasma levels after oral administration of ASN002.

Overall, ASN002 demonstrated statistically significant efficacy in treatment of AD, with a rapid improvement in key parameters of clinical efficacy and inflammation, despite the small sample size and short treatment duration. ASN002 was well tolerated at all tested doses, with no obvious relationship between dose and incidence of TEAEs. The safety profile of ASN002 was also consistent with that expected upon dual inhibition of JAK and SYK.^{45, 46} However, the conclusions on safety are limited by the small number of patients in each

treatment group. No serious infections, tuberculosis, opportunistic infections, thrombocytopenia, thromboembolic events, changes in cholesterol, or effect on blood pressure were observed. Collectively, these data support further development of ASN002 in AD and beyond.

Abbreviations

AD = atopic dermatitis;

AE = adverse events;

AUC = area under the plasma concentration;

BMI = body mass index;

BSA = body surface area;

C_{max} = observed maximum concentration;

CMH = Cochran-Mantel-Haenszel;

CVD = cardiovascular disease;

EASI = Eczema Area and Severity Index;

ECG = electrocardiogram;

EMA = European Medicines Agency;

FDA = Food and Drug Administration;

FDR = fixed discovery rate;

IC₅₀ = inhibitory concentration

IGA = Investigator's Global Assessment;

IL = interleukin;

IRB = Institutional Review Board;

IWRS = interactive web response system;

JAK = Janus kinase;

LOCF = last observation carried forward;

MMRM = mixed-effect model for repeated measures;

NRI = non-responder imputation;

NRS = Numeric Rating Scale;

PK = pharmacokinetic;

SRC = safety review committee;

SYK = spleen tyrosine kinase;

$T_{1/2}$ = terminal half-life;

TEAE = treatment-emergent adverse events;

T_{max} = time at which C_{max} is observed;

TYK = tyrosine kinase.

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Figure legends

Figure 1: Atopic dermatitis. CONSORT Diagram

Abbreviations: CONSORT = Consolidated Standards of Reporting Trials; PD = pharmacodynamic (population); PK = pharmacokinetic (population); PP = per-protocol (population).

Figure 2: Atopic dermatitis. Proportion of Patients Achieving EASI-50 and EASI-75 over time

- (a) Proportion of patients achieving Eczema Area and Severity Index (EASI) 50 over time.
- (b) Proportion of patients achieving EASI-75 over time. The proportion of patients achieving EASI-50 and EASI-75 were analysed using a Cochran-Mantel-Haenszel (CMH), in the per-protocol population using non-responder imputation (NRI) for missing data.

Figure 3: Atopic dermatitis. Change from Baseline in Weekly Average Pruritus NRS for Patients with a Baseline of at Least 4

Change from baseline in weekly average pruritus numeric rating scale (NRS) for patients with a baseline of at least 4 over time. Changes from baseline were analysed with a mixed effect model for repeated measures (MMRM) with treatment, visit, and treatment by visit as fixed effects and baseline as a covariate. A per-protocol analysis with last observation carried forward (LOCF) was used for missing data.

Figure 4: Atopic dermatitis. Changes in Serum Protein Levels with ASN002 Treatment and Placebo-Treated Patients.

- (a) Boxplots depict mean fold changes (FCHs) from baseline at Day 15 and Day 29. Significant reduction was seen in serum levels of markers of general Inflammation (a), T-cell/B-cell markers (b-c), T-cell activation (d-e), innate immunity (f), Th1 axis (g-i), Th2 axis (i-l), Th17 axis (m-n), and negative regulator (o). Red stars denote significance versus baseline in respective groups whereas black stars identify significant changes in respective

drug-groups compared to placebo group. The treatment groups were compared using a linear mixed effect model with time and treatment as fixed factors, and a random intercept for each patient. T-test was used for the comparisons. [†]p<0.1, *p<0.05, **p<0.01, ***p<0.001. AD: Atopic Dermatitis.

(b) Pathway analyses. Pathways significantly enriched in serum of drug-treated versus placebo-treated patients at Day 29 as compared to baseline. All drug-treated patients regardless of dose were grouped together due to the small patient number. The pathways are ordered by significance, with the black line representing false discovery rate (FDR) <0.05. The significance cutoff for enriched pathways was the Benjamini-Hochberg fixed discovery rate (FDR)<0.05.

Tables

Table 1: Atopic dermatitis. Baseline Demographics and Clinical Characteristics
(Safety Population)

	ASN002 20-mg	ASN002 40-mg	ASN002 80-mg	ASN002 Overall	Placebo
Baseline Demographics	N = 9	N = 9	N = 9	N = 27	N = 9
Age, mean(years)±SD	38.2±14.36	42.4±13.88	33.1±10.42	37.9±13.09	29.9±9.33
Gender, n (%)					
Male	5 (55.6)	5 (55.6)	5 (55.6)	15 (55.6)	3 (33.3)
Female	4 (44.4)	4 (44.4)	4 (44.4)	12 (44.4)	6 (66.7)
Race, n (%)					
Caucasian	6 (66.7)	7 (77.8)	7 (77.8)	20 (74.1)	8 (88.9)
Black	2 (22.2)	1 (11.1)	2 (22.2)	5 (18.5)	1 (11.1)
Asian	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.7)	0 (0.0)
Other	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
Weight at screening, mean(kg)±SD	76.3±11.65	72.3±11.46	85.4±16.23	78.0±13.94	72.3±15.11
Height at screening, mean(cm)±SD	169.1±5.57	165.0±8.45	174.0±6.22	169.4±7.59	165.0±9.82
BMI at screening, mean(kg/m ²)±SD	26.8±4.92	26.6±3.87	28.2±5.44	27.2±4.66	26.5±4.75
Clinical Characteristics	N = 9	N = 9	N = 9	N = 27	N = 9
EASI Score, mean±SD	29.0±13.49	21.8±6.21	28.2±11.67	26.3±10.97	21.6±6.24
IGA Score, n (%)					
3 = Moderate	5 (55.6)	8 (88.9)	4 (44.4)	17 (63.0)	8 (88.9)
4 = Severe	4 (44.4)	1 (11.1)	5 (55.6)	10 (37.0)	1 (11.1)
BSA, mean±SD	44.1±20.19	31.4±17.96	36.9±25.88	37.5±21.42	25.1±10.49
Pruritus NRS, mean±SD	5.4±2.26	6.1±2.47	6.0±2.55	5.8±2.36	5.9±2.57

BMI = body mass index; BSA = body surface area; EASI = Eczema Area and Severity Index;

IGA = Investigator's Global Assessment; NRS = Numeric Rating Scale; SD = standard deviation.

Table 2: Atopic dermatitis. Summary of Treatment-Emergent Adverse Events Occurring in at Least two Patients per Treatment Group and Events Meeting the Stopping Rules

Treatment-emergent-adverse-events	ASN002 20-mg (N = 9)	ASN002 40-mg (N = 9)	ASN002 80-mg (N = 9)	ASN002 Overall (N = 27)	Placebo (N = 9)
Headache, n (%)	1 (11.1)	4 (44.4)	2 (22.2)	7 (25.9)	3 (33.3)
Nausea, n (%)	0 (0.0)	1 (11.1)	4 (44.4)	5 (18.5)	2 (22.2)
Diarrhoea, n (%)	0 (0.0)	1 (11.1)	2 (22.2)	3 (11.1)	1 (11.1)
Nasopharyngitis, n (%)	2 (22.2)	1 (11.1)	0 (0.0)	3 (11.1)	1 (11.1)
Back pain, n (%)	0 (0.0)	2 (22.2)	0 (0.0)	2 (7.4)	0 (0.0)
Events meeting the stopping rules	ASN002 20-mg (N = 9)	ASN002 40-mg (N = 9)	ASN002 80-mg (N = 9)	ASN002 Overall (N = 27)	Placebo (N = 9)
Mild hypertension, n (%)	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)
Low lymphocytes levels. n (%)	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.7)	0 (0.0)

Supplementary Appendix

Supplemental Table 1:

Summary of pharmacokinetics parameters of ASN002 in atopic dermatitis (AD) patients following once daily oral administration.

Supplemental Table 2:

Olink data per gene with corresponding protein in each treatment group at specific time points with significance by p-values and fixed discovery rates (FDR) adjusted p-values.

Supplemental Table 3:

Pathway enrichment analysis based on databases including Kyoto Encyclopedia of Genes and Genomes/KEGG, Reactome Pathway Database, BioCarta, Pathway Interaction Database/PID, and MSigDB.

Supplemental Figure 1: Atopic dermatitis. Mean Plasma Concentration of ASN002 at Days 1 and 15

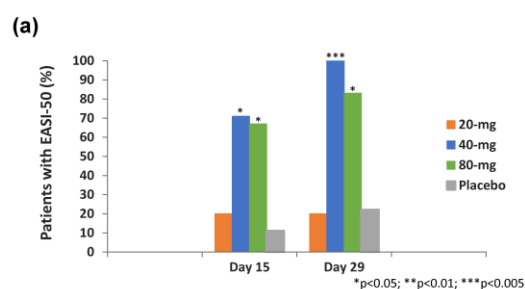
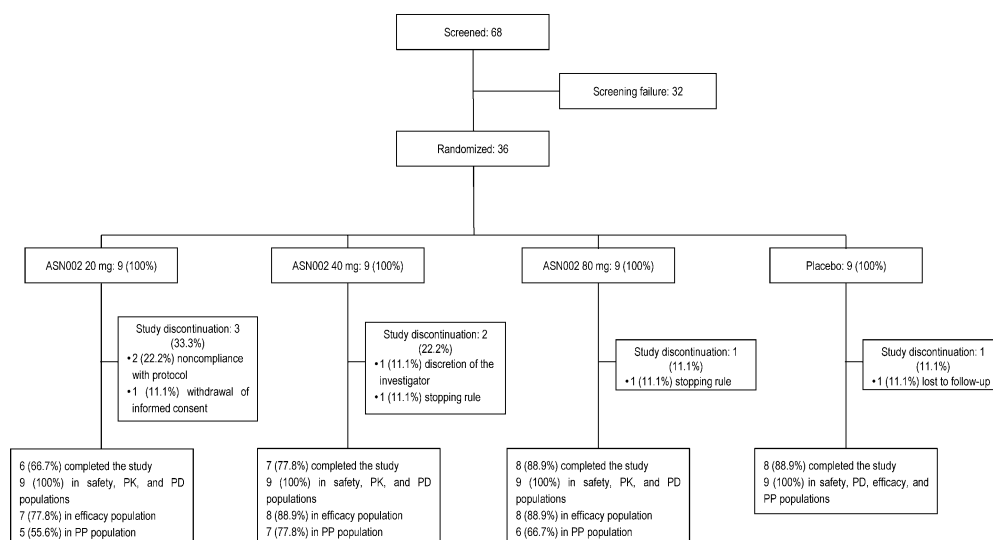
(a) Mean plasma concentration of ASN002 at Day 1. **(b)** Mean plasma concentration of ASN002 at Day 15.

Supplemental Figure 2:

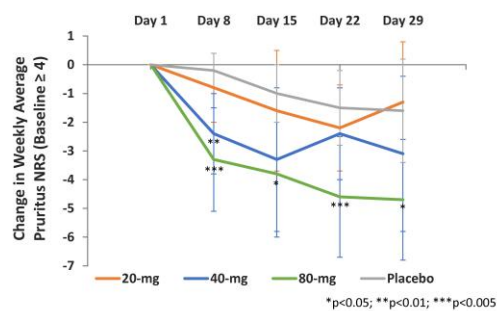
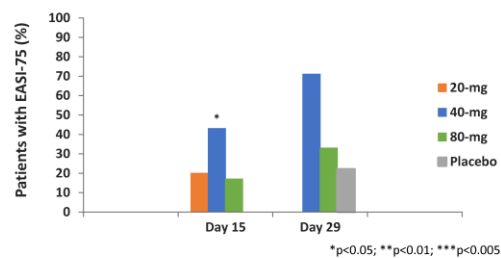
Boxplots depicting serum chemokine/cytokines mean fold change (FCH) from baseline in AD patients in treatment groups of 80mg, 40mg, 20mg, and placebo at two time points of Day 15 and Day 29. Serum markers significantly modulated were products of: general inflammation (a), innate immunity (b-c), T-cell/B-cell activation (d), T-cell Activation (e-h), Th1 (i-k), Th17 (l), and negative regulator (m). Red star of significance denotes significance in each group compared to baseline. Black stars denote significance compared to placebo in each drug group. The treatment groups were compared using a linear mixed effect model with time and

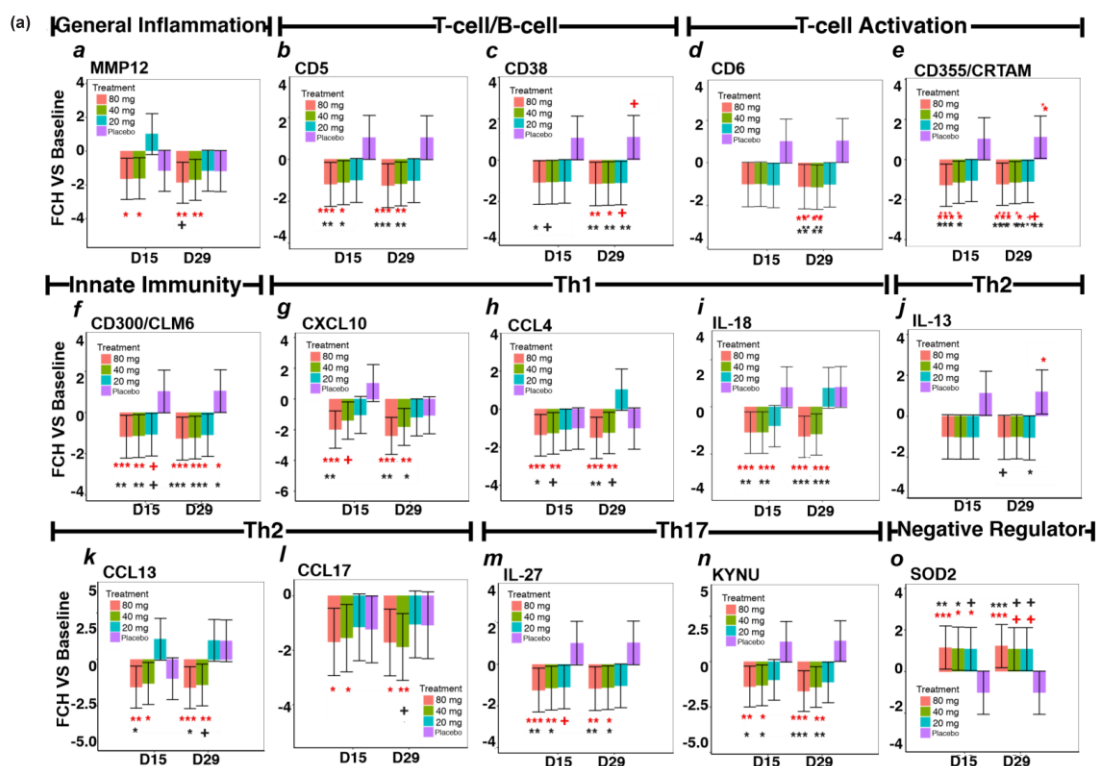
treatment as fixed factors, and a random intercept for each patient. T-test was used for the comparisons. [†]p<0.1, *p<0.05, **p<0.01, ***p<0.001.

AD: Atopic Dermatitis.

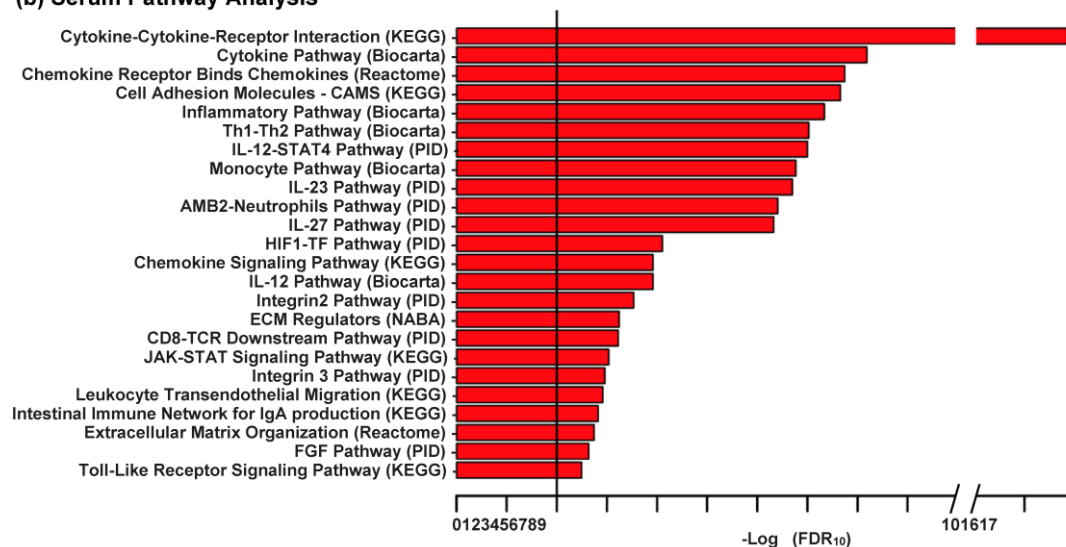


(b)

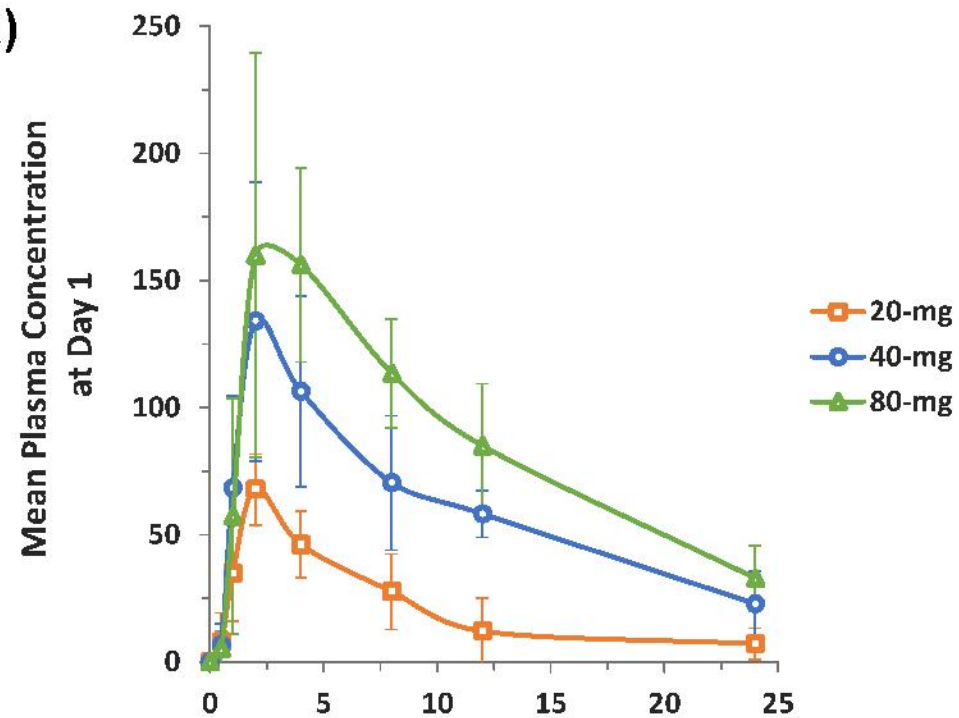




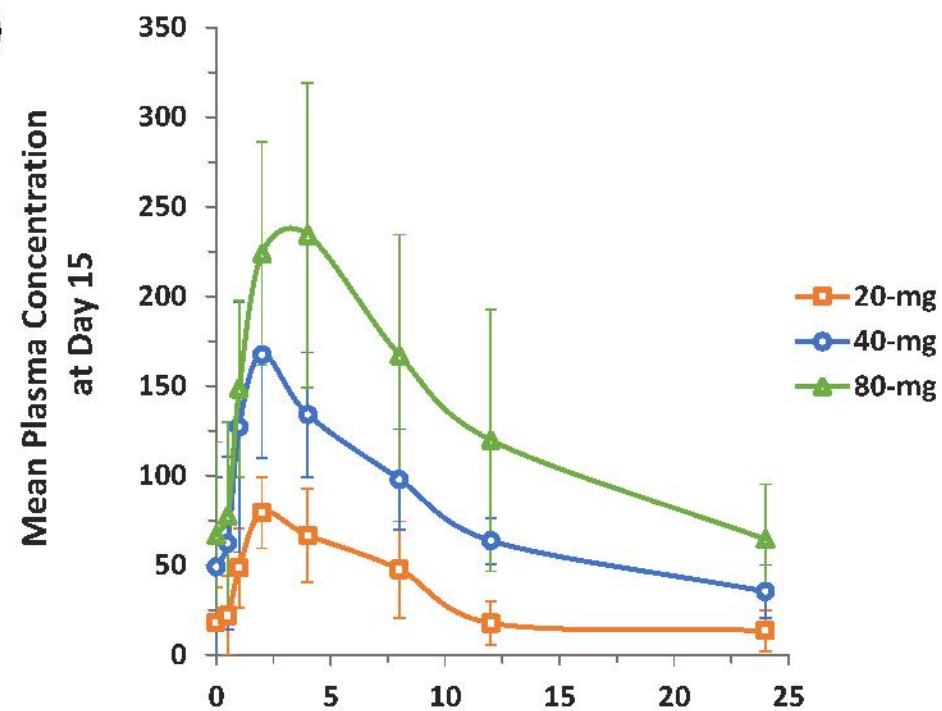
(b) Serum Pathway Analysis



(a)

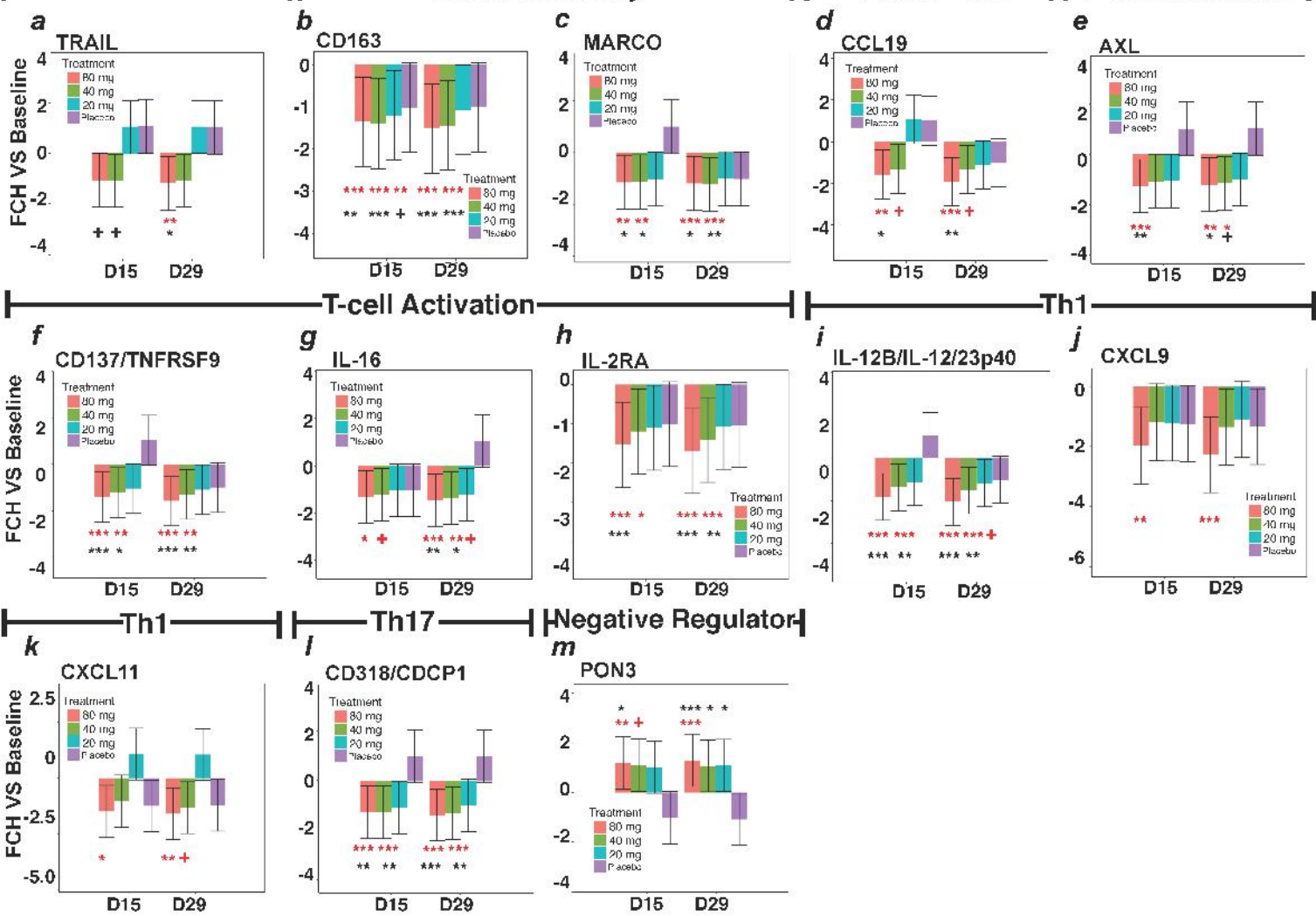


(b)



Supplemental Figure 2

[General Inflammation] [Innate Immunity] [T-cell/B-cell] [T-cell Activation]



Dose (mg)	Day	Parameters	$t_{\max}^a$ (hr)	$C_{\max}$ (ng/ml)	$AUC_{(0-24)}$ (ng*hr/ml)	$t_{1/2}$ (hr)
20-mg	1	Mean	2	67.8	580	6.62
		CV%	2-2	20.5	42.4	46.9
	15	Mean	2	82.9	850	7.33
		CV%	2-4	16.8	28.7	22.6
40-mg	1	Mean	2	136	1410	9.10
		CV%	2-4	39.9	37.4	26.9
	15	Mean	2	171	2097	10.7
		CV%	2-4	30.1	28.5	10.2
80-mg	1	Mean	2	186	2120	11.2
		CV%	2-4	28	20.8	45.5
	15	Mean	3	252	3281	14.1
		CV%	2-4	30.2	36.7	51.4

^a Median and range

$AUC_{(0-24)}$ = area under the concentration-time curve versus time curve from time 0 to 24 hours; $C_{\max}$ = maximum observed plasma concentration; CV% = coefficient of variation; $t_{\max}$ = time to reach peak plasma concentrations; $t_{1/2}$ = mean terminal half-life.