# Rademikibart monotherapy for moderate-to-severe atopic dermatitis in a 1-year, randomized, phase II trial (S*EASI*DE CHINA): initial two-week dosing, followed by two-week or four-week dosing

**Running head:** Rademikibart therapy for atopic dermatitis: a Chinese randomized trial

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**Data availability:** The data underlying this article are available in the article.

**Ethics statement:** Study protocol was approved by institutional review boards and ethics committees.

**Patient consent:** Written patient consent for publication was obtained.


# Abstract

***Background:*** Rademikibart (CBP-201) is a potent, next-generation, optimized IL-4Rα-targeting antibody.

***Objectives:*** To evaluate rademikibart efficacy and safety, initially dosed every other week (Q2W), and Q2W or every fourth week (Q4W) from Week 16, in Chinese adults/adolescents with moderate-to-severe atopic dermatitis (AD).

***Methods:*** S*EASI*DE CHINA (NCT05017480) was a phase II trial: Stage 1 (16-week treatment period), Stage 2 (36-week treatment and 8-week follow-up periods). The primary endpoint was the proportion of patients with a vIGA score 0/1 and ≥2-point reduction from baseline at Week 16. Overall, 330 patients were randomized (2:1) double-blind to receive subcutaneous rademikibart, 600 mg on Day 1 and 300 mg Q2W from Week 2–14, or placebo. Pre-dose at Week 16, patients were assessed for minimally important change (≥50% Eczema Area and Severity Index score reduction, EASI-50) and re-randomized (1:1) double-blind to rademikibart 300 mg Q2W or Q4W.

***Results:*** In Stage 1, 29.0% of patients attained vIGA0/1 and ≥2-point reduction with rademikibart Q2W ($p<0.001$; 5.9% with placebo) at Week 16, without plateauing. Rapid, significant improvements were also observed with all other rating scales in Stage 1, including EASI-75 (58.6% vs 22.6%) and PP-NRS ≥4-point reduction (36.3% vs 10.5%) with rademikibart Q2W vs placebo, respectively, at Week 16. In Stage 2, Week 16 EASI-50 responders from Stage 1 continued to improve through Week 52 when treated with rademikibart Q2W or Q4W,

including vIGA0/1 (59.1%, 62.6%), EASI-75 (84.6%, 84.8%), and PP-NRS ≥4-point reduction (60.4%, 70.3%). Most patients with improvements during rademikibart Q2W therapy at Week 16 maintained these responses through Week 52 in both rademikibart Q2W and Q4W groups: vIGA0/1 (78.0%, 87.1%), EASI-75 (90.1%, 92.3%), PP-NRS ≥4-point reduction (85.3%, 94.8%). Injection site reactions were Grade 1 (mild). No serious TEAEs were treatment related. Three patients discontinued rademikibart due to TEAEs (AD flare, vitiligo, pregnancy).

***Conclusions:*** Rademikibart Q2W induced rapid improvements in AD lesions and pruritus during the initial 16 weeks, which were maintained/improved further with rademikibart Q2W or Q4W across an additional 36 weeks. Rademikibart Q2W and Q4W were similarly efficacious and well tolerated. These findings are compatible with those from the published WW001 international phase II rademikibart trial.

# Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects a large proportion of the global population. One-year prevalence estimates for countries around the world range from 1–18% for adults, without clear geographical patterns, including ~6% in Chinese populations.[1-5] In China, an estimated 11.6 million adults and adolescents had AD in 2010.[6]

Moderate-to-severe AD manifests as recurrent eczematous lesions and intense, unrelenting pruritus,[7] associated with sleep disturbance and depression.[8-12] Three systemic biologics, either targeting IL-4 receptor alpha (IL-4Rα; dupilumab) or IL-13 (tralokinumab and lebrikizumab), are approved treatments in the US and Europe for moderate-to-severe AD when dosed every other week (Q2W) through 16 weeks, with tralokinumab and lebrikizumab maintenance therapy potentially administered every fourth week (Q4W).[13-26] Dupilumab is not approved for Q4W dosing.[25,26] In China, the only systemic biologic approved for moderate-to-severe AD is dupilumab, when dosed Q2W.[27] Heterogeneous efficacy outcomes have been reported for AD medications, such as long-term loss of response, including when continuing with dupilumab once-weekly (QW) or Q2W or after switching to Q4W or Q8W dosing (33%–54% of patients maintained response).[20,28] If patients fail biologic therapy, oral Janus kinase inhibitors are approved second-line treatments, although potential safety warnings include herpes, serious

infections, malignancy, and cardiovascular events.[29-34] Thus, there is a need for medications with efficacy and safety demonstrated with particularly convenient dosing regimens for long-term AD management.

Rademikibart (formerly CBP-201) is a next-generation human IgG4 kappa monoclonal antibody targeting IL-4Rα. In preclinical experiments, rademikibart is optimized to bind to distinct IL-4Rα epitopes with higher affinity than dupilumab, resulting in potent downregulation of Th2-driven inflammatory responses *in vitro*, *in vivo* and *ex vivo*.[35] Structural and molecular dynamics suggest that rademikibart is more stable when connected to the IL-4Rα, demonstrating superior binding energy than dupilumab, thus rademikibart is expected to be efficacious at longer dosing intervals.[36] During the WW001 international phase II study, in adults with moderate-to-severe AD, rademikibart achieved rapid improvements in dermatitis and pruritus across 16 weeks of treatment.[37] Notably, improvements in eczematous lesions were similar with Q2W and Q4W dosing, and the lack of plateauing at Week 16 indicated further room for improvement with longer treatment durations.[37] The clinical safety profile of rademikibart was generally comparable to placebo.[37,38]

Here we report key findings from S*EASI*DE CHINA, a phase II trial assessing short-term (16 weeks) and long-term (52 weeks) rademikibart monotherapy in adults and adolescents with moderate-to-severe AD.

# Methods

## Study design

The S*EASI*DE CHINA phase II, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov, NCT05017480) was conducted across 45 centers in China. This 64-week trial comprised of screening (4 weeks), Stage 1 (16-week treatment period), and Stage 2 (36-week treatment and 8-week follow-up periods) (Figure S1).

Patients were randomized (2:1) double-blind to receive subcutaneous rademikibart (600 mg) or matching placebo on Day 1 and rademikibart (300 mg Q2W) or placebo from Week 2–14.

Pre-dose at Week 16, patients were assessed for minimally important change (MIC), defined as ≥50% reduction from baseline in Eczema Area and Severity Index score (EASI-50).[39] Week 16 EASI-50 responders were randomized (1:1) double-blind to receive rademikibart 300 mg Q2W or Q4W, with final doses administered at Weeks 50 and 48, respectively.

## Patients

Eligibility criteria are shown in Table S1. Patients were 12–75 years old, with moderate-to-severe AD (validated Investigator Global Assessment Scale for AD [vIGA-AD™] ≥3, EASI ≥16, body surface area [BSA] involvement of AD ≥10%) inadequately controlled/not suitable for topical treatments. Patients were required to have an average Peak Pruritus Numerical Rating Scale (PP-NRS) score ≥4, based on ≥4 daily assessments for 7 days before randomization.

## Procedures, assessments, and endpoints

The trial complied with Good Clinical Practice guidelines and the Declaration of Helsinki. Patients provided written informed consent before participating. Informed consent forms and the study protocol were approved by institutional review boards and ethics committees.

Patients were randomly assigned to rademikibart or placebo using a central randomization scheme and interactive voice response system. Patients, site personnel, the sponsor, and designees conducting/monitoring the study were unaware of treatment assignment. Patients were stratified according to baseline severity (moderate [vIGA=3], severe [vIGA=4]).

Rademikibart was provided in 2 mL (150 mg/mL) SC injections. In the rademikibart and placebo arms, injection frequency was identical, and patients applied mild emollient twice daily from ≥7 days before baseline (ceasing 4 hours before evaluations). No other concomitant topical AD treatment was allowed, except for permitted rescue medications (including topical corticosteroids, calcineurin inhibitors and, for patients without adequate response after ≥7 days, systemic medication). If a patient received systemic corticosteroid or non-steroid immunosuppressive/immunomodulatory rescue therapy, study treatment was to be stopped immediately. If possible, the investigator was to assess efficacy and safety before administering rescue therapy. AD requiring rescue therapy was recorded as an adverse event (AE).

Investigator assessments of AD severity/extent (vIGA, EASI, BSA) were conducted at screening and on prespecified days (±3 days) during Stage 1 (pre-dose Day 1 and Days 15, 29, 57, 85, and

113) and Stage 2 (28-day intervals). Patients assessed peak pruritus severity during 24-hour periods using the PP-NRS, with potential scores ranging from 0 (none) to 10 (worst imaginable). PP-NRS scores were recorded in daily diaries, commencing 7 days before baseline. Using the Patient Oriented Eczema Measure (POEM), patients assessed various aspects of AD in the past week (dryness, itching, flaking, cracking, sleeplessness, bleeding and weeping/oozing), with potential scores ranging from 0 (none) to 28 (severe). The 10-item Dermatology Life Quality Index (DLQI) questionnaire was used to assess the impact of AD on quality of life (QoL) in the past week, with potential scores ranging from 0 (none) to 30 (severe).

Primary and secondary efficacy endpoints were assessed in Stage 1, followed by additional assessments during Stage 2. The primary endpoint was the proportion of patients with a vIGA score 0 or 1, and ≥2-point reduction from baseline, at Week 16 (Figure S1). Secondary endpoints at Week 16 included: proportions of patients achieving EASI-75, EASI-90, and weekly average PP-NRS score decrease of ≥3 and ≥4 points from baseline; percentage change from baseline in EASI, BSA, and PP-NRS scores (and at Week 2 for PP-NRS); change in POEM and DLQI. AEs were MedDRA coded (Version 26.0).

## Statistical analysis

The sample size, assuming 15% dropout by Week 16, would provide 90% power to detect a therapeutic effect on the primary endpoint for rademikibart versus placebo. Power was calculated based on the assumption that the proportion of patients reaching the primary endpoint was 27% in the rademikibart group and versus 9% in the placebo group. The two-sided significance level was 0.05.

In Stage 1, efficacy analyses were conducted with all randomized patients who received rademikibart or placebo. In Stage 2, efficacy analyses were conducted in all patients who received rademikibart in Stage 1 and achieved MIC (EASI-50) at Week 16. Patients without EASI-50 in Stage 1 were assessed for EASI-50 in Stage 2.

In Stage 1, binary responder endpoints were analysed by stratified Cochran-Mantel-Haenszel test, and score changes by Mixed-Effect Model for Repeated Measures (MMRM). The MMRM model included baseline value, treatment, visit, treatment by visit interaction, and baseline AD severity (IGA 3 or 4). Data after intercurrent events were imputed based on the type of events (Table S2). If the target variable was still missing after application of the strategies for managing

intercurrent events, missing data through Week 16 in the rademikibart and placebo arms were imputed using Jump to Reference (J2R) and Multiple Imputation (MI), respectively. Non-Responder Imputation (NRI) sensitivity analyses were also conducted through Week 16. In Stage 2, for patients who achieved MIC (EASI-50 in Stage 1), binary responses were analysed similar to Stage 1 using NRI and MI for intercurrent events and missing data, while score changes were analysed by Analysis of Covariance (ANCOVA) and MI for intercurrent events and missing data. The ANCOVA model included baseline value, treatment, and baseline severity (IGA 3 or 4).

# Results

## Baseline characteristics in Stages 1 and 2

From August 2021, 330 patients with moderate-to-severe AD were randomly assigned 2:1 to receive rademikibart 300 mg Q2W or placebo. The trial completed in September 2023. Disease characteristics and demographics were well balanced per treatment arm at baseline in Stages 1 and 2 (Tables S3 and S4).

In Stage 1, 80.2% of patients achieved MIC (i.e. EASI-50) in the rademikibart 300 mg Q2W arm ($p<0.001$ vs placebo, 38.8%) at Week 16. All Week 16 MIC responders were re-randomized 1:1 to receive rademikibart 300 mg Q2W or Q4W for 36 weeks in Stage 2 (Figure S1). Patients without MIC at Week 16 were eligible for rademikibart 300 mg Q2W therapy in Stage 2, and most of these patients subsequently achieved EASI-50 through Week 52 (by 68.7% and 88.1% who, in Stage 1, received rademikibart Q2W or placebo, respectively).

Most patients completed Stage 1 (95.4% rademikibart Q2W; 91.9% placebo) (Figure S2). Of the Week 16 MIC responders to rademikibart Q2W in Stage 1 who continued with 300 mg Q2W or switched to 300 mg Q4W dosing during Stage 2, 94.5% and 93.4% respectively completed the 36-week period (Figure S3).

Rescue medication rates in Stage 1 were 10.0% (rademikibart Q2W) and 16.2% (placebo), including 7.3% and 10.8% for topical corticosteroids, respectively. In Stage 2, rescue medication

rates for Week 16 MIC responders were 14.2% (rademikibart Q2W) and 21.4% (rademikibart Q4W), including 11.5% and 15.2% for topical corticosteroids, respectively.

## Rapid improvements in dermatitis and pruritus with rademikibart Q2W through Stage 1 (Week 16)

In Stage 1, 29.0% of patients gained vIGA0/1 response (clear/almost clear skin, and ≥2-point decrease from baseline) with rademikibart Q2W ($p<0.001$ vs 5.9% with placebo) at Week 16, without plateauing (Figure 1). This analysis of the primary endpoint, using J2R and MI methodology for the rademikibart and placebo arms, respectively, was supported by NRI sensitivity analysis (28.9% vs 5.5% of patients achieved vIGA 0/1 response with rademikibart Q2W vs placebo, respectively, at Week 16; $p<0.001$).

EASI, PP-NRS, POEM, and DLQI outcomes improved rapidly, with continuous improvement across 16 weeks of treatment (Figures 2–4, Figure S4 and Table S5). In the rademikibart Q2W group, 58.6% of patients gained EASI-75 response at Week 16 ($p<0.001$ vs 22.6% with placebo) (Figure 2). Percent change in PP-NRS at Week 2 (a secondary endpoint) was significant in the rademikibart Q2W group, compared with placebo (LS mean -14.3% vs -6.9%; $p<0.01$) and sustained through Week 16 (-40.0% vs -13.5%; $p<0.001$) (Figure 3).

## Further improvements through Stage 2 (Week 52) were similar with Q2W and Q4W dosing

In Stage 2, when assessed in Week 16 MIC EASI-50 responders to rademikibart Q2W from Stage 1, the proportion of patients with clear/almost clear skin continued to increase across the 36-week treatment period and was comparable with Q2W and Q4W dosing (59.1% and 62.6%, respectively, at Week 52) (Figure 1). Further AD improvements in Stage 2 were also obtained with the other AD rating scales, and were similar with Q2W and Q4W dosing, including the proportions of patients with EASI-75 (84.6% and 84.8%, respectively, at Week 52) (Figures 2–4, Figure S4 and Table S5).

## Responders in Stage 1 (Week 16) maintained efficacy through Stage 2 (Week 52) with both Q2W and Q4W dosing

In Stage 2, most patients who achieved response criteria during treatment with rademikibart Q2W at Week 16 in Stage 1 maintained these responses through Week 52, with similar efficacy

in the Q2W and Q4W groups (78–95% of patients for vIGA0/1, EASI-75, or PP-NRS ≥4-point reduction) (Figures 5 and 6).

## Safety

Treatment-emergent adverse events (TEAEs) are summarized across Stages 1 and 2 in Tables 1, 2, S6, and S7. In the rademikibart Q2W versus placebo groups at Week 16, incidence of Grade 3 TEAEs (1.8% vs 4.5%) and serious TEAEs (0.5% vs 2.7%) was lower with rademikibart, while the incidence of any TEAE was comparable (73.1% vs 69.4%, respectively). No TEAEs were Grade ≥4, and no serious TEAEs were related to study treatment.

Four patients discontinued treatment due to TEAEs, three in the rademikbart arms across Stages 1 and 2 and one in the placebo arm in Stage 1 (Table 1 and 2). Two patients discontinued due to AD flares, one each in the rademikibart Q2W (Grade 2) and placebo (Grade 3) arms during Stage 1. Two patients reported TEAEs that led to discontinuation of rademikibart in Stage 2; one patient was pregnant (classified as a TEAE) and the other developed Grade 2 vitiligo in Stage 1 (rademikibart 300 mg Q2W arm) and the patient discontinued in Stage 2.

Injection site reactions (ISRs), all Grade 1 (mild) in severity, were experienced in Stage 1 by 9.1% of patients (rademikibart Q2W) vs 2.7% (placebo) and in Stage 2 by 5.3% (Q2W) and 7.1% (Q4W) (Table 1 and 2). Other TEAEs of particular interest in the rademikibart Q2W and placebo groups, respectively, included ophthalmic TEAEs (conjunctivitis,[a] 5.5% vs 2.7%; keratitis,[b] 0.9% vs 0%) and herpes infections[c] (1.8% vs 1.8%) in Stage 1, with similar/lower incidence reported in Stage 2. One TEAE of anaphylaxis was reported (non-serious, Grade 1, unrelated to study treatment, and the patient continued treatment with rademikibart).

[a]'Conjunctivitis' includes the MedDRA Preferred Terms 'conjunctivitis' (2.7% vs 2.7%) and 'conjunctivitis allergic' (3.2% vs 0%) in the rademikibart Q2W versus placebo arms, respectively. There were no reports of bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, or eye inflammation.

[b]'Keratitis' includes the Preferred Term 'keratitis' (0.9% vs 0%) in the rademikibart Q2W versus placebo arms, respectively. There were no reports of ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, or ocular herpes simplex.

[c]'Herpes infections' includes the Preferred Terms 'herpes virus infection' (0.5% vs 0.9%), 'herpes zoster' (0% vs 0.9%), 'herpes simplex' (0.5% vs 0%), 'herpes simplex reactivation' (0.5% vs 0%), and 'oral herpes' (0.5% vs 0%) in the rademikibart Q2W versus placebo arms, respectively.

# Discussion

In the S*EASI*DE CHINA phase II trial, most patients with moderate-to-severe AD experienced clinically meaningful reductions in the severity and extent of eczematous lesions, in burdensome pruritus, and substantially better health-related QoL. These improvements occurred rapidly, during the first 16 weeks of rademikibart 300 mg Q2W monotherapy (Stage 1), and continued during the subsequent 36-week treatment period (Stage 2) when, importantly, they were comparable for patients who remained on rademikibart Q2W or switched to Q4W monotherapy. Large proportions of patients with vIGA0/1, EASI-75, and PP-NRS ≥4-point reduction at Week 16 maintained these responses through Week 52 with rademikibart Q2W or Q4W (78–95% of patients), and response maintenance was comparable with both dosing regimens. Although caution should be exercised when indirectly comparing studies (given that outcomes may be affected by various study design/conduct variables), the improvements through Weeks 16 and 52 were similar/greater than those obtained with Q2W or Q4W lebrikizumab, tralokinumab, and dupilumab.[14-20,28,40-42] Treatment completion rates were also high across the 1-year of rademikibart therapy (generally more than 90% in Stages 1 and 2). Based on these findings, after an initial 16 weeks of treatment with Q2W dosing, we would expect most patients to benefit greatly from rademikibart when administered at convenient once-monthly (Q4W) dosing frequencies for 1 year.

S*EASI*DE CHINA efficacy findings are compatible with those from the WW001 international phase II trial of rademikibart.[37] However, efficacy responses were often larger than in WW001, even though all patients had moderate-to-severe AD in both trials. In S*EASI*DE CHINA, approximately half of patients had severe AD at baseline, compared with around a third in WW001. *Post hoc* analyses of multiple clinical trials suggest that placebo responses are larger in populations with less severe AD,[43-45] and it may be the case that baseline severity does not equally affect responses in active and placebo arms.[44,45] Baseline AD severity ratings in S*EASI*DE CHINA were similar, and AD improvements were greater/similar in magnitude, when indirectly compared with trials of other biologics.[14-20,28,40-42] However, it is notable that in phase II and III trials of dupilumab, EASI responses appeared to plateau by Week 16.[14-16] In both S*EASI*DE CHINA and WW001, the rapid reductions in AD extent and severity did not plateau at Week 16, suggesting further room for improvement which, in S*EASI*DE CHINA, was demonstrated across 1 year of rademikibart treatment.

Rescue medication usage was numerically lower/comparable versus other AD biologic treatments.[17,18,20,28,40-42] The rescue medication rate at Week 16 was 10.0% with rademikibart Q2W, whereas rates for dupilumab were 21.6% (QW) and 17.1% (Q2W) when pooled for two phase III international studies and 19.5% (Q2W) in a Chinese clinical trial.[17,18] Rescue medication rates for Week 16 MIC (EASI-50) responders across the subsequent 36-week period were 14.2% (Q2W) and 21.4% (Q4W), compared with 19.5% (QW or Q2W dosing) and 30.2% (Q4W) for IGA 0/1 or EASI-75 responders treated with dupilumab.[28]

No treatment-related serious safety concerns were identified, three patients discontinued rademikibart due to TEAEs (AD flare, vitiligo, pregnancy), and most TEAEs were mild or moderate in severity. Across all AD trials of rademikibart, every ISR was mild in severity.[37,38] In S*EASI*DE CHINA, the incidence of ISRs with rademikibart 300 mg Q2W (9.1%) versus placebo (2.7%) at Week 16 was comparable to other biologics, including dupilumab 300 mg Q2W in international (12.3%)[17] and Chinese (8.5%) trials.[18] The incidence of ISRs was higher than in the WW001 international phase II trial (1.8% across the treatment arms) at Week 16,[37] which we speculate may be related to the quantity of solution per injection (1 mL versus 2 mL) in the WW001 and S*EASI*DE CHINA trials, respectively. It is also notable that, in S*EASI*DE CHINA, ISR incidence with rademikibart was lower during the 36-week treatment period (5.3% [Q2W] and 7.1% [Q4W]) than during the initial 16 weeks (9.1% [Q2W]). The incidence of conjunctivitis with rademikibart was generally comparable/lower than reported for other AD biologics across 52 weeks.[14-20,28,40-42] However, these indirect comparisons are hampered by a lack of standardized and clear reporting of the AE MedDRA Preferred Terms included under the umbrella term 'conjunctivitis'.

The S*EASI*DE CHINA trial has several strengths and limitations. First, the analyses were conducted in a sizable population (330 adult and adolescent patients in Stage 1), which to the best of our knowledge constitutes the largest AD clinical trial in China to date. Second, all patients were Chinese. It appears unlikely that efficacy varies according to ethnicity with IL-4Rα targeting medications; in *post hoc* analyses of three phase III trials of dupilumab, slightly greater responses in Asian patients versus White and Black/African American patients were likely related to baseline differences in AD severity.[46] However, AD is heterogeneous, and the phenotype may vary according to ethnic background.[47] Third, a strength of our study is that improvements in AD and QoL were assessed with several instruments by investigators (IGA,

EASI, BSA) and patients (PP-NRS, POEM, DLQI). Other recently developed self-assessment instruments that were not used in the current study – Recap of Atopic Eczema (RECAP) and Atopic Dermatitis Control Test (ADCT) – are recommended by experts, to investigate long-term AD control.[48] Since the study was conducted, both RECAP and ADCT have been validated in Chinese patients and strongly correlated with POEM and DLQI.[48-50] Fourth, MIC was defined as EASI-50;[39] alternative definitions of EASI MIC are available.[51] Finally, another notable strength is that outcomes were investigated across a longer duration of treatment (1 year) than in the WW001 international trial of rademikibart and Chinese trial of dupilumab (16 weeks).[18,37]

In summary, the S*EASI*DE CHINA phase II AD trial of rademikibart achieved all prespecified efficacy endpoints. Rapid improvements in AD signs and pruritus with rademikibart Q2W did not plateau through Week 16, and were sustained through Week 52 with comparable efficacy by Q2W and Q4W dosing. The efficacy findings of S*EASI*DE CHINA are greater/similar in magnitude to those obtained with lebrikizumab, tralokinumab, and dupilumab.[14-20,28,40-42] Rademikibart was also well tolerated (>90% of patients completed each treatment period). Taken together, these findings indicate that most patients with moderate-to-severe AD benefitted from rapid improvements during initial treatment with rademikibart, and that these improvements were highly maintained during 1 year of treatment with a convenient once-monthly (Q4W) dosing regimen.

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# Figure legends

**Figure 1** vIGA0/1 response in the overall population and in Week 16 MIC (EASI-50) responders. ***, **, * for P<0.001, <0.01, <0.05, respectively, vs placebo. Each n represents the number of patients in the analysis, which remained constant at each time point due to the use of statistical methodology to impute missing values. Up to Week 16, binary response data were analysed by Cochran-Mantel-Haenszel. Through Week 16, data after intercurrent events were imputed based on the type of events (Table S2). If the target variable was still missing after application of the strategies for managing intercurrent events, missing data through Week 16 in the rademikibart and placebo arms were imputed using Jump to Reference and Multiple Imputation methodology, respectively. From Week 16, binary response data were analysed by Non-Responder Imputation and Multiple Imputation. EASI, Eczema Area and Severity Index; EASI-50, at least 50% decrease from baseline; MIC, minimal important change; vIGA0/1, validated Investigator Global Assessment of 0 (clear skin) or 1 (almost clear) and a decrease of ≥2 points from baseline; Q2/4W, every 2/4 weeks.

**Figure 2** EASI-75 and EASI-90 response in the overall population and in Week 16 MIC (EASI-50) responders. ***, **, * for P<0.001, <0.01, <0.05, respectively, vs placebo. Each n represents the number of patients in the analysis, which remained constant at each time point due to the use of statistical methodology to impute missing values. Up to Week 16, binary response data were analysed by Cochran-Mantel-Haenszel. Through Week 16, data after intercurrent events were imputed based on the type of events (Table S2). If the target variable was still missing after application of the strategies for managing intercurrent events, missing data through Week 16 in the rademikibart and placebo arms were imputed using Jump to Reference and Multiple Imputation methodology, respectively. From Week 16, binary response data were analysed by Non-Responder Imputation and Multiple Imputation. EASI, Eczema Area and Severity Index; EASI-50/75/90, at least 50/75/90% decrease from baseline; LSM, least squares mean; MIC, minimal important change; Q2/4W, every 2/4 weeks.

**Figure 3** PP-NRS and EASI score change in the overall population and in Week 16 MIC (EASI-50) responders. ***, **, * for P<0.001, <0.01, <0.05, respectively, vs placebo. Each n represents the number of patients in the analysis, which remained constant at each time point due to the use of statistical methodology to impute missing values. Up to Week 16, score change was analysed by Mixed-Effect Model Repeat Measurement (MMRM). The MMRM model included baseline value, treatment, visit, treatment by visit interaction, and baseline AD severity (IGA 3 or 4). Through Week 16, data after intercurrent events were imputed based on the type of events (Table S2). If the target variable was still missing after application of the strategies for managing intercurrent events, missing data through Week 16 in the rademikibart and placebo arms were imputed using Jump to Reference and Multiple Imputation methodology, respectively. From Week 16, score change was analysed by Analysis of Covariance (ANCOVA) and Multiple Imputation. The ANCOVA model included baseline value, treatment, and baseline severity (IGA 3 or 4). EASI, Eczema Area and Severity Index; EASI-50, at least 50% decrease from baseline; IGA, Investigator Global Assessment; LSM, least squares mean; MIC, minimal important change; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2/4W, every 2/4 weeks.

**Figure 4** PP-NRS ≥3-point and ≥4-point response in the overall population and in Week 16 MIC (EASI-50) responders. ***, **, * for P<0.001, <0.01, <0.05, respectively, vs placebo. Each n represents the number of patients in the analysis, which remained constant at each time point due to the use of statistical methodology to impute missing values. Up to Week 16, binary response data were analysed by Cochran-Mantel-Haenszel. Through Week 16, data after intercurrent events were imputed based on the type of events (Table S2). If the target variable was still missing after application of the strategies for managing intercurrent events, missing data through Week 16 in the rademikibart and placebo arms were imputed using Jump to Reference and Multiple Imputation methodology, respectively. From Week 16, binary response data were analysed by Non-Responder Imputation and Multiple Imputation. EASI, Eczema Area and Severity Index; EASI-50, at least 50% decrease from baseline; MIC, minimal important change; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2/4W, every 2/4 weeks.

**Figure 5** Maintenance of vIGA0/1 and EASI-75 responses from Week 16 through Week 52. Data were analysed by NRI-MI (Non-Responder Imputation for rescue medications and Multiple Imputation for remaining missing data). EASI, Eczema Area and Severity Index; EASI-50/75, at least 50%/75% decrease from baseline; vIGA0/1, validated Investigator Global Assessment of 0 (clear skin) or 1 (almost clear) and a decrease of ≥2 points from baseline.

**Figure 6** Maintenance of PP-NRS ≥4-point response from Week 16 through Week 52. Data were analysed by NRI-MI (Non-responder Imputation for rescue medications and Multiple Imputation for remaining missing data). EASI, Eczema Area and Severity Index; EASI-50, at least 50% decrease from baseline; PP-NRS, Peak Pruritus Numerical Rating Scale.

**Table 1.** Overview of treatment-emergent adverse events during Stage 1

| | **Rademikibart 300 mg Q2W (N=219) n (%)** | **Placebo Q2W (N=111) n (%)** | **Total (N=330) n (%)** |
|---|---|---|---|
| TEAEs | 160 (73.1) | 77 (69.4) | 237 (71.8) |
| Related to study drug | 67 (30.6) | 25 (22.5) | 92 (27.9) |
| Serious TEAEs | 1 (0.5) | 3 (2.7) | 4 (1.2) |
| Serious TEAEs related to study drug | 0 | 0 | 0 |
| Leading to death | 0 | 0 | 0 |
| Leading to study drug discontinuation | 2 (0.9)* | 1 (0.9) | 3 (0.9) |
| Severe (Grade 3) TEAEs | 4 (1.8) | 5 (4.5) | 9 (2.7) |
| Injection site reactions (all were Grade 1) | 20 (9.1) | 3 (2.7) | 23 (7.0) |
| Injection site erythema | 11 (5.0) | 1 (0.9) | 12 (3.6) |
| Injection site induration | 7 (3.2) | 1 (0.9) | 8 (2.4) |
| Injection site oedema | 5 (2.3) | 1 (0.9) | 6 (1.8) |
| Injection site hematoma | 1 (0.5) | 1 (0.9) | 2 (0.6) |
| Injection site reaction | 2 (0.9) | 0 | 2 (0.6) |
| Injection site inflammation | 1 (0.5) | 0 | 1 (0.3) |
| Injection site pain | 1 (0.5) | 0 | 1 (0.3) |
| Injection site pruritus | 1 (0.5) | 0 | 1 (0.3) |

| | Rademikibart 300 mg Q2W (N=219) n (%) | Placebo Q2W (N=111) n (%) | Total (N=330) n (%) |
|---|---|---|---|
| Injection site swelling | 1 (0.5) | 0 | 1 (0.3) |
| Conjunctivitis[†] | 12 (5.5) | 3 (2.7) | 15 (4.5) |
| Keratitis[‡] | 2 (0.9) | 0 | 2 (0.6) |
| Anaphylaxis[#] | 1 (0.5) | 0 | 1 (0.3) |
| Herpes infections[§] | 4 (1.8) | 2 (1.8) | 6 (1.8) |

*One patient discontinued in Stage 2 (36-week treatment period) after onset of the Grade 2 vitiligo in Stage 1 (16-week treatment period). [†]'Conjunctivitis' includes the MedDRA Preferred Terms 'conjunctivitis' (2.7% vs 2.7%) and 'conjunctivitis allergic' (3.2% vs 0%) in the rademikibart Q2W versus placebo arms, respectively. There were no reports of bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, or eye inflammation. [‡]'Keratitis' includes the Preferred Term 'keratitis' (0.9% vs 0%) in the rademikibart Q2W versus placebo arms, respectively. There were no reports of ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, or ocular herpes simplex. [#]The anaphylaxis TEAE was Grade 1 and unrelated to study drug. [§]'Herpes infections' includes the following Preferred Terms: herpes virus infection (0.5% vs 0.9%), herpes zoster (0% vs 0.9%), herpes simplex (0.5% vs 0%), herpes simplex reactivation (0.5% vs 0%), and oral herpes (0.5% vs 0%) in the rademikibart Q2W versus placebo arms, respectively.

TEAEs in Stage 1 were defined as adverse events occurring or worsening on or after the first study dose and prior to the Stage 2 dose or 70 days after the last dose in Stage 1, which occurred first.

EASI, Eczema Area and Severity Index; EASI-50, ≥50% reduction in EASI score from baseline; MedDRA, Medical Dictionary for Regulatory Activities; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

**Table 2.** Overview of treatment-emergent adverse events during Stage 2

| | Week 16 EASI-50 responders from Stage 1* | | Week 16 EASI-50 non-responders from Stage 1* | Total (N=310) n (%) |
|---|---|---|---|---|
| | Rademikibart 300 mg Q2W (N=113) n (%) | Rademikibart 300 mg Q4W (N=112) n (%) | Rademikibart 300 mg Q2W (N=85) n (%) | |
| TEAEs | 93 (82.3) | 95 (84.8) | 71 (83.5) | 259 (83.5) |
| Related to study drug | 28 (24.8) | 28 (25.0) | 25 (29.4) | 81 (26.1) |
| Serious TEAEs | 1 (0.9) | 3 (2.7) | 6 (7.1) | 10 (3.2) |
| Serious TEAEs related to study drug | 0 | 0 | 0 | 0 |
| Leading to death | 0 | 0 | 0 | 0 |
| Leading to study drug discontinuation† | 0 | 0 | 1 (1.2) | 1 (0.3) |
| Severe (Grade 3) TEAEs | 3 (2.7) | 5 (4.5) | 6 (7.1) | 14 (4.5) |
| Injection site reactions (all were Grade 1) | 6 (5.3) | 8 (7.1) | 6 (7.1) | 20 (6.5) |
| Injection site erythema | 3 (2.7) | 6 (5.4) | 3 (3.5) | 12 (3.9) |
| Injection site induration | 3 (2.7) | 3 (2.7) | 1 (1.2) | 7 (2.3) |
| Injection site oedema | 1 (0.9) | 1 (0.9) | 3 (3.5) | 5 (1.6) |
| Injection site inflammation | 1 (0.9) | 1 (0.9) | 1 (1.2) | 3 (1.0) |
| Conjunctivitis‡ | 6 (5.3) | 6 (5.4) | 7 (8.2) | 19 (6.1) |

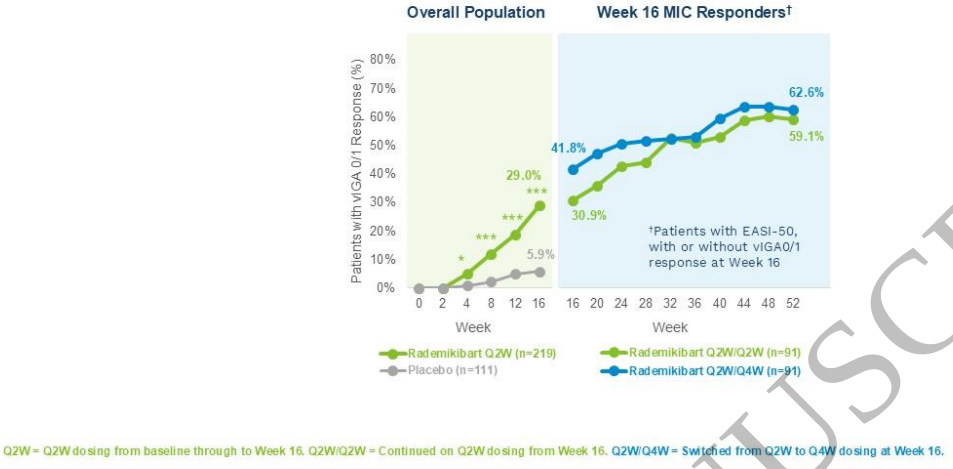
| | Week 16 EASI-50 responders from Stage 1* | | Week 16 EASI-50 non-responders from Stage 1* | Total (N=310) n (%) |
|---|---|---|---|---|
| | Rademikibart 300 mg Q2W (N=113) n (%) | Rademikibart 300 mg Q4W (N=112) n (%) | Rademikibart 300 mg Q2W (N=85) n (%) | |
| Keratitis[#] | 1 (0.9) | 0 | 0 | 1 (0.3) |
| AST/ALT elevated >5×ULN[§] | 0 | 1 (0.9) | 0 | 1 (0.3) |
| Parasitic and opportunistic infection** | 1 (0.9) | 0 | 0 | 1 (0.3) |
| Herpes infections[††] | 0 | 0 | 3 (3.5) | 3 (1.0) |

*Includes patients treated with rademikibart or placebo during Stage 1 (16-week treatment period). [†]The patient discontinued due to a TEAE of pregnancy; another patient discontinued due to a TEAE in Stage 2 (Grade 2 vitiligo), although the TEAE began in Stage 1, in the rademikibart 300 mg Q2W arm, thus the patient is reported in the Stage 1 discontinuations in Table 1. [‡]'Conjunctivitis' includes the MedDRA Preferred Terms 'conjunctivitis' (3.5% vs 2.7% vs 7.1%) and 'conjunctivitis allergic' (1.8% vs 3.6% vs 1.2%) in the respective treatment arms. There were no reports of bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, or eye inflammation. [#]'Keratitis' includes the Preferred Term 'keratitis'. There were no reports of ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, or ocular herpes simplex. [§]The hepatic enzyme TEAE was Grade 3 and unrelated to study drug. **The infection TEAE was Grade 2, with the Preferred Term 'otitis externa fungal'. [††]'Herpes infections' includes the following Preferred Terms: herpes zoster (1.2%) and herpes simplex (2.4%) in the Week 16 EASI-50 non-responder arm.

TEAEs in Stage 2 were defined as adverse events occurring or worsening on or after the first study dose in Stage 2 to the end of follow-up.

EASI, Eczema Area and Severity Index; EASI-50, ≥50% reduction in EASI score from baseline; MedDRA, Medical Dictionary for Regulatory Activities; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

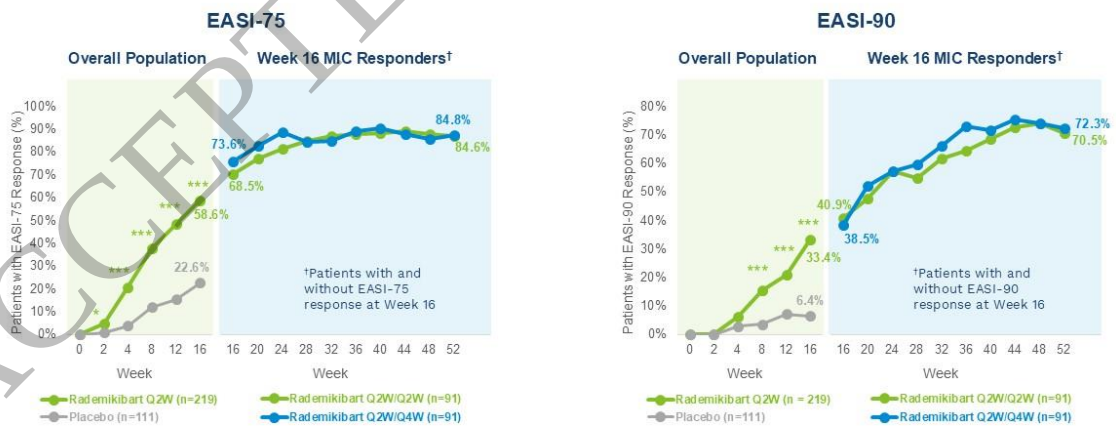
## Figure 1. vIGA0/1 response in the overall population and in Week 16 MIC (EASI-50) responders




Q2W = Q2W dosing from baseline through to Week 16. Q2W/Q2W = Continued on Q2W dosing from Week 16. Q2W/Q4W = Switched from Q2W to Q4W dosing at Week 16.

*Figure 1*
*236x133 mm (DPI)*

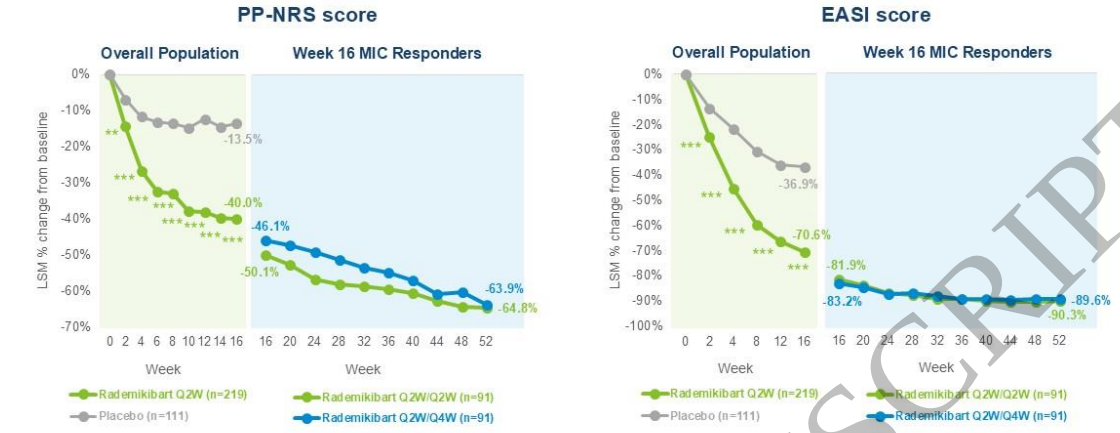
## Figure 2. EASI-75 and EASI-90 response in the overall population and in Week 16 MIC (EASI-50) responders




Q2W = Q2W dosing from baseline through to Week 16. Q2W/Q2W = Continued on Q2W dosing from Week 16. Q2W/Q4W = Switched from Q2W to Q4W dosing at Week 16.

*Figure 2*
*236x133 mm (DPI)*

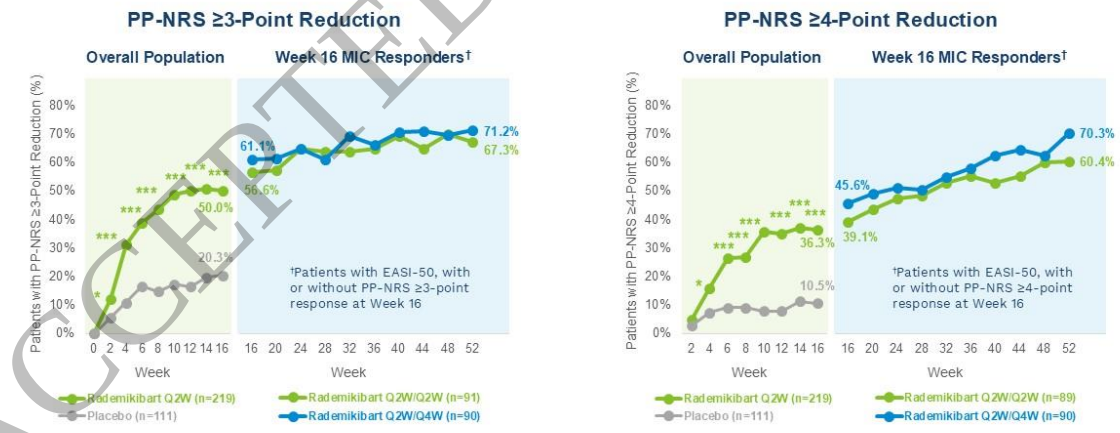
## Figure 3. PP-NRS and EASI score change in the overall population and in Week 16 MIC (EASI-50) responders




Q2W = Q2W dosing from baseline through to Week 16. Q2W/Q2W = Continued on Q2W dosing from Week 16. Q2W/Q4W = Switched from Q2W to Q4W dosing at Week 16.

*Figure 3*
*236x133 mm (DPI)*

## Figure 4. PP-NRS ≥3-point and ≥4-point response in the overall population and in Week 16 MIC (EASI-50) responders




Q2W = Q2W dosing from baseline through to Week 16. Q2W/Q2W = Continued on Q2W dosing from Week 16. Q2W/Q4W = Switched from Q2W to Q4W dosing at Week 16.

*Figure 4*
*236x133 mm (DPI)*

## Figure 5. Maintenance of vIGA0/1 and EASI-75 responses from Week 16 through Week 52

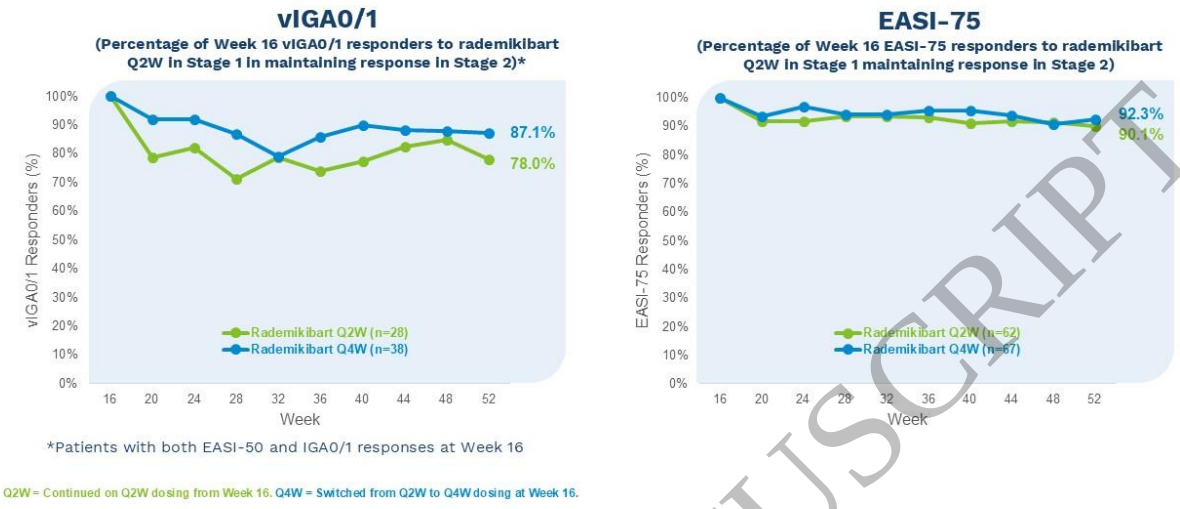



*Figure 5*
*236x133 mm (DPI)*

## Figure 6. Maintenance of PP-NRS ≥4-point response from Week 16 through Week 52

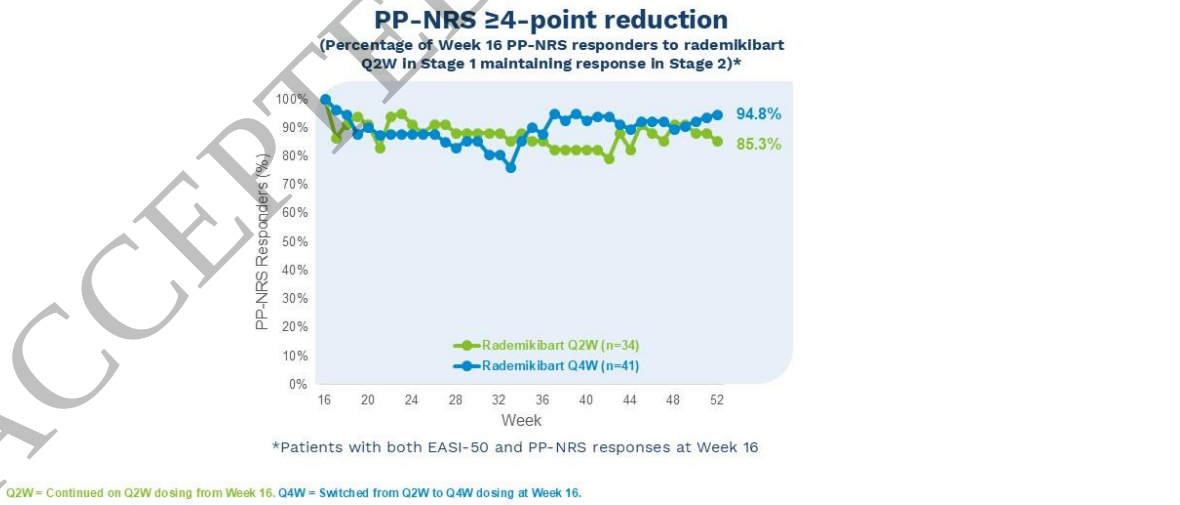
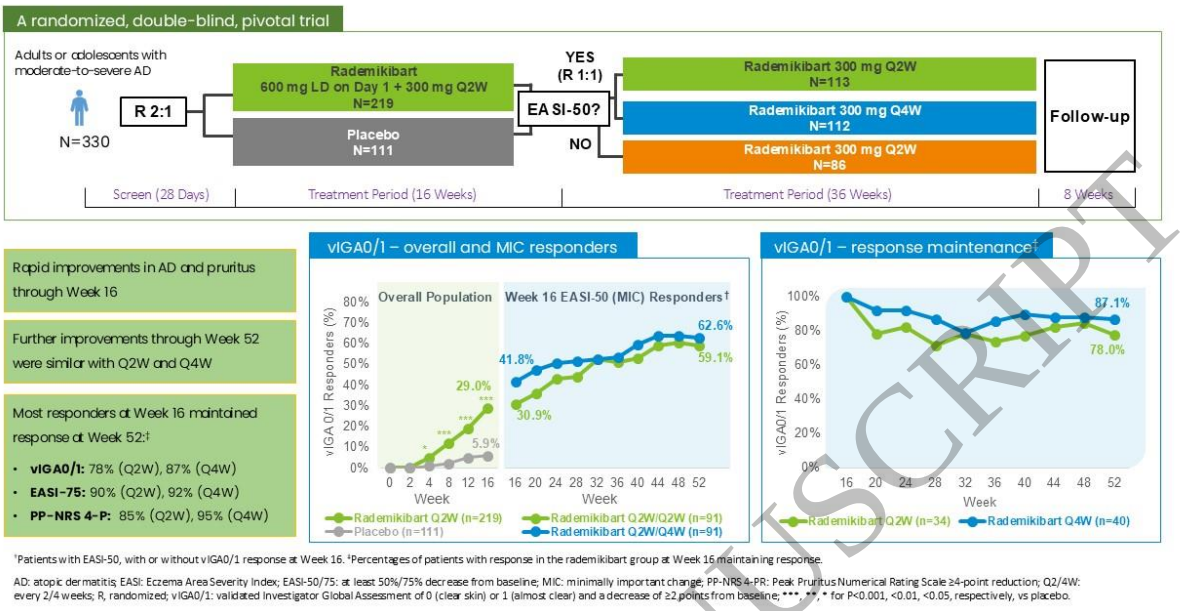



*Figure 6*
*236x133 mm (DPI)*

**Rademikibart monotherapy for moderate-to-severe atopic dermatitis in a 1-year, randomized, phase II trial (S*EASI*DE CHINA): initial two-week dosing, followed by two-week or four-week dosing**




†Patients with EASI-50, with or without vIGA0/1 response at Week 16. ‡Percentages of patients with response in the rademikibart group at Week 16 maintaining response.

AD: atopic dermatitis; EASI: Eczema Area Severity Index; EASI-50/75: at least 50%/75% decrease from baseline; MIC: minimally important change; PP-NRS 4-PR: Peak Pruritus Numerical Rating Scale ≥4-point reduction; Q2/4W: every 2/4 weeks; R, randomized; vIGA0/1: validated Investigator Global Assessment of 0 (clear skin) or 1 (almost clear) and a decrease of ≥2 points from baseline; ***, **, * for P<0.001, <0.01, <0.05, respectively, vs placebo.

*Graphical Abstract*
*236x133 mm DPI)*