26 March 2026
EMADOC-1700519818-2802677
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sotyktu

International non-proprietary name: Deucravacitinib

Procedure No. EMA/VR/0000282554

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
AE(s)	adverse event(s)
ANCOVA	analysis of covariance
APR	apremilast
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score with CRP
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD(s)	biologic disease-modifying anti-rheumatic drugs
BID	twice daily
BMS	Bristol Myers Squibb
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID	Coronavirus disease
CPK	creatine phosphokinase
CRF	Case Report Form
CRP	C-reactive protein
csDMARD(s)	conventional synthetic disease-modifying antirheumatic drug(s)
CSR(s)	Clinical Study Report(s)
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAS	Disease Activity Score
DAS28	Disease Activity Score in 28 Joints
DAS28-CRP	Disease Activity Score 28 with C-reactive protein
DBL	database lock
DDI	drug-drug interaction
DEUC	deucravacitinib
DMARD(s)	disease-modifying anti-rheumatic drug(s)
EQ-5D-5L	5-level EuroQol 5-dimension
E-R	exposure-response
FACIT	Functional Assessment of Chronic Illness Therapy
FPFV	first subject, first visit
HAQ-DI	Health Assessment Questionnaire - Disability Index
HI	hepatic impairment
hsCRP	high-sensitivity C-reactive protein
HV	Healthy volunteer
ICE	intercurrent events
IR	inadequate response
IRT	Interactive Response Technologies

Abbreviation	Definition
ITT	intent-to-treat
LDA	Low Disease Activity
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
MACE	major adverse cardiovascular events
MAX	maximum
MDA	minimal disease activity
MNAR	missing not at random
MTX	methotrexate
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
OLE	Open-label Long-term Extension
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PBO	Placebo
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PGA-F	Physician Global Assessment-Fingernails
PI(s)	prediction interval(s)
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
PROMIS	Patient-Reported Outcomes Measurement Information System
PsA	psoriatic arthritis
PsAID 12	12-Item Psoriatic Arthritis Impact of Disease Questionnaire
PsARC	Psoriatic Arthritis Response Criteria
PsO	psoriasis
P-value	probability (value between zero and one)
QD	once daily
RI	renal impairment
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36	Short Form (36) Health Survey
SPARCC	Spondyloarthritis Research Consortium of Canada
sPGA	Static Physician's Global Assessment
TNFi	tumor necrosis factor inhibitor
TNFα	tumor necrosis factor alpha
UST	ustekinumab

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 01 July 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include, for Sotyktu, alone or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to a prior DMARD therapy, based on results from the following phase 3 studies: Study IM011-054 (POETYK PsA-1); this is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of deucravacitinib in participants with active psoriatic arthritis who are naïve to biologic disease-modifying anti-rheumatic drugs, and Study IM011-055 (POETYK PsA-2); this is a multi-center, randomized, double-blind, placebo-controlled phase 3 study to evaluate the efficacy and safety of BMS-986165 in participants with active psoriatic arthritis (PsA) who are naïve to biologic disease modifying anti-rheumatic drugs or had previously received TNFα inhibitor treatment. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, as well as introduce administrative changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0262/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP in July 2018 (EMEA/H/SA/3783/2/2018/II). The scientific advice pertained to clinical aspects.

The applicant received Scientific Advice from the CHMP in January 2021 (EMA/SA/0000046847). The scientific advice pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Nicolas Beix Co-Rapporteur: Margareta Bego

Timetable	Actual dates
Submission date	1 July 2025
Start of procedure:	19 July 2025
CHMP Rapporteur Assessment Report	18 September 2025
PRAC Rapporteur Assessment Report	19 September 2025
CHMP Co-Rapporteur Assessment	23 September 2025
PRAC Outcome	2 October 2025
CHMP members comments	6 October 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2025
Request for supplementary information (RSI)	16 October 2025
MAH's responses submitted to the CHMP on	25 November 2025
CHMP Rapporteur Assessment Report	7 January 2026
PRAC Rapporteur Assessment Report	7 January 2026
PRAC members comments	n/a
PRAC Outcome	15 January 2026
CHMP members comments	19 January 2026
Updated CHMP Rapporteur Assessment Report	22 January 2026
Request for supplementary information (RSI)	29 January 2026
MAH's responses submitted to the CHMP on	2 February 2026
PRAC Rapporteur Assessment Report	2 March 2026
PRAC members comments	4 March 2026
CHMP Rapporteur Assessment Report	11 March 2026
PRAC Outcome	12 March 2026
CHMP members comments	16 March 2026
Updated CHMP Rapporteur Assessment Report	19 March 2026
CHMP Opinion	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Psoriatic Arthritis (PsA) is a chronic, heterogeneous disorder characterised by progressive inflammatory arthritis that can develops in patients with psoriasis (PsO) and may result in permanent joint damage and disability as well as health consequences beyond joint function, such as cardiovascular diseases. The PsA affects multiple tissues, including peripheral joints, skin and nails, axial joints (spondylitis), entheses (enthesitis), and digits (dactylitis). At initial presentation, oligoarticular disease is the most common subtype but as the disease evolves, the polyarticular variant becomes more prevalent. Human leukocyte antigen (HLA) alleles have also been associated with disease expression and prognosis of PsA. Pathogenesis involves dysregulation of the innate and adaptive immune systems. Activation of dendritic cells leads to the release of pro-inflammatory cytokines, particularly tumour necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23), driving synovial inflammation and enthesitis. This results in pannus formation, cartilage degradation, and pathological new bone formation.

State the claimed therapeutic indication

The initially proposed indication by the MAH was:

Sotyktu, alone or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Epidemiology

PsA is estimated to affect 0.1% to 1% of the general population worldwide. In the United States, the prevalence is reported between 0.06% and 0.25%. The global incidence has been estimated at approximately 133 per 100,000 persons, with continent-specific estimates of 207 (Europe), 64 (North America) and 37 (Asia) per 100 000. and with typical disease onset between 40 and 50 years of age and an equal distribution between sexes. Among patients with psoriasis, around 20% develop active PsA, and in 10% to 15% of cases, arthritis precedes the onset of skin manifestations.

The burden of PsA extends beyond joint and skin with significant psychosocial and functional consequences. The psychological impact is substantial, with moderate to severe depressive symptoms reported in 21.7% of patients overall and up to 36.7% among those with polyarthritis. PsA is also associated with impaired physical function, reduced quality of life, and considerable work-related disability, including absenteeism and loss of productivity, all of which correlate strongly with disease activity and physical limitations.

Biologic features and aetiology and pathogenesis

PsA is a chronic inflammatory arthropathy associated with psoriasis, resulting from a multifactorial interplay of genetic, immunological, and environmental influences. Genetically, susceptibility is

mostly linked to HLA-B27, with familial clustering supporting a heritable component. Additional genes implicated in PsA are located near or within the major histocompatibility complex region, including MICA-TM, HLA-E, and SEEK1. Other genetic associations involve pathways related to interferon (IFN) and IL-23 signalling (IL28RA, TYK2), T-cell regulation (RUNX3, IL13, TAGAP, ETS1, and MBD2), glycosaminoglycan metabolism (B3GNT2), and antiviral responses (IFIH1, DDX58, and RNF114). Environmental triggers, such as infection, psychological stress, mechanical trauma (Koebner phenomenon), obesity, and gut microbiome alterations, may precipitate disease in genetically predisposed individuals.

The pathogenesis of PsA reflects dysregulation of both the innate and adaptive immune systems. Activation of dendritic cells stimulates the production of pro-inflammatory cytokines, notably TNF-α, IL-17, and IL-23, which drive synovial inflammation, enthesitis, and subsequent structural joint damage.

The immunopathological process can be conceptualised in three functional stages: inducers, enhancers, and effectors.

- Inducers include metabolic dysregulation, obesity, intestinal dysbiosis, and psoriatic skin inflammation. These factors promote the release of mediators such as IL-23, adiponectin, IL-1α, IL-36, and S100A7.
- Enhancers comprise type 17 immune cells, including both adaptive and innate subsets, which secrete IL-17, TNF, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-γ, amplifying the inflammatory cascade.
- Effectors include macrophages and neutrophils that release TNF, prostaglandins, and other inflammatory mediators, contributing directly to tissue damage and aberrant bone remodelling.

Clinical presentation, diagnosis

PsA is a form of spondyloarthritis (SpA), a group of related inflammatory arthropathies that also includes ankylosing spondylitis (the most common and severe form), reactive arthritis, inflammatory bowel disease-associated arthritis, and undifferentiated spondyloarthritis. Multiple initiatives have sought to establish robust classification and diagnostic criteria for PsA. Diagnosis is guided by characteristic patterns of joint inflammation, the absence of rheumatoid factor in approximately 91–94% of cases, and the presence of psoriatic skin or nail lesions.

For the purposes of clinical trials, and in accordance with the guideline on clinical investigation of medicinal products for the treatment of PsA (CHMP/EWP/438/04), three primary clinical patterns are recognised:

1. Pure peripheral polyarticular PsA, resembling rheumatoid arthritis.
2. Predominantly peripheral polyarticular PsA with coexistent axial involvement.
3. Pure axial PsA, closely resembling ankylosing spondylitis.

Management

Initial treatment of musculoskeletal symptoms consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections. Topical therapies are used for the initial treatment of psoriasis. In patients with polyarthritis or those with monoarthritis/ oligoarthritis and poor prognostic factors (e.g., structural damage, elevated acute phase reactants, dactylitis or nail

involvement), a conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARD) should be initiated. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a biologic (b) DMARD should be commenced (EULAR recommendation 2023).

Drugs licensed for PsA in the EU so far:

- csDMARDs, such as methotrexate (MTX), sulfasalazine and leflunomide;
- bDMARDs such as TNF-inhibitors (golimumab, adalimumab, certolizumab, etanercept, infliximab), the IL-12/23 (ustekinumab) or IL-23 pathway (guselkumab, risankizumab), and the IL-17A and IL-17A/F pathway (secukinumab, ixekizumab, bimekizumab);
- inhibitors of co-stimulation of T cells (abatacept),
- targeted synthetic (ts) DMARDs that inhibit Janus kinases (JAKs) or phosphodiesterase 4 (PDE4).

However, it is acknowledged that newer, more effective and safer treatments, or treatments with a different mechanism of action compared to approved biological therapies would be desirable to improve the quality of life of PsA patients.

2.1.2. About the product

DEUC (deucravacitinib) is a selective, oral small-molecule inhibitor of TYK2 that binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream functions in cells. TYK2 mediates signalling of interleukin-23 (IL-23), interleukin-12 (IL-12), and type I interferons (IFN), which are naturally occurring cytokines involved in inflammatory and immune responses. Deucravacitinib inhibits the release of proinflammatory cytokines and chemokines.

Marketing authorisation in the EU was granted on 24-Mar-2023 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The approved dose for the treatment of moderate to severe plaque psoriasis is 6 mg QD.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. However, since the systemic exposure in patient with psoriatic arthritis during the clinical trials was higher than those of patients with psoriasis, the MAH submitted a summary of the animal-to-human exposure (AUC or Cmax) multiples generated from a comparison of the pivotal non-clinical studies to the steady-state mean human exposures at the recommended human dose (RHD) in subjects with PsA. calculations were based on comparison between AUC values corresponding with the NOAELs in non-clinical studies relative to the RHD. This was endorsed by the CHMP, and section 5.3 was adequately updated.

In addition, the environmental risk assessment has been aligned with the requirements of 2024 EMA guideline. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of deucravacitinib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Treated	Study Population	Study Status; Type of Report
Safety/ PK	Study Identifier: IM011053Report location: Module 5.3.3.1	To evaluate the safety, tolerability, and to assess DEUC plasma PK following single and multiple oral doses of DEUC in healthy Chinese subjects	Phase 1, single center, randomized, double blind, placebo-controlled, single- and multiple-dose study	Single dose portion (Day 1): DEUC 6 mg PO DEUC 12 mg PO PBO PO Multiple-dose portion (Day 5-19): DEUC 6 mg QD PO DEUC 12 mg QD PO PBO QD PO	Total: 40 DEUC 6 mg: 16 (15 in multiple dose) DEUC 12 mg: 16 PBO: 8	Healthy males and females	Study Status: Complete Type of Report: Final CSR
Drug-drug interactions	Study Identifier: IM011159 Report location: Module 5.3.3.1	To evaluate the effect of multiple doses of BMS-986165 on the plasma PK of metformin in healthy subjects	Phase 1, open-label, two-arm crossover study	Arm 1: metformin IR 850 mg Day 1; DEUC 6 mg QD Days 2-7; DEUC 6 mg QD + metformin IR 850 mg Day 8 Arm 2: metformin IR 850 mg Day 1; DEUC 12 mg QD Days 2-7; DEUC 12 mg QD + metformin IR 850 mg Day 8	Total: 36 Arm 1: 18 Arm 2: 18	Healthy males and females	Study Status: Complete Type of Report: Final CSR

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Treated	Study Population	Study Status; Type of Report
Phase 2	Study Identifier: IM011084 Report location: Module 5.3.5.1	To assess the dose-response relationship of DEUC (6 or 12 mg QD) at Week 16 in the treatment of subjects with active PsA	Part A: 16-week randomized, double-blind, placebo-controlled study 1:1:1 randomization to the DEUC (6 mg QD or 12 mg QD) and placebo groups Part B: optional 36 weeks of double-blind, double-dummy controlled treatment with ustekinumab or DEUC after completing Part A	Part A: DEUC: 6 mg QD PO, 12 mg QD PO Placebo: QD PO Part B: DEUC: 6 mg QD PO, 12 mg QD PO Ustekinumab: 45 mg SQ, 90 mg SQ	Total: 203 DEUC 6 mg QD: 70 DEUC 12 mg QD: 67 Placebo: 66	Subjects with active PsA	Study Status: Complete Type of Report: Primary CSR (Part A) CSR Erratum (Part A) CSR Addendum (Part B)
Phase 3	Study Identifier: IM011054Report location: Module 5.3.5.1	To compare the efficacy of deucravacitinib to placebo in the treatment of participants with active PsA	52-week randomized, double-blind, placebo-controlled study followed by 104-week OLE period. 1:1 randomization to the DEUC and PBO groups	DEUC: 6 mg QD PO PBO: QD PO	Total: 665 DEUC: 332 PBO: 333	Adult subjects with active PsA who are naive to bDMARDs	Study Status: Ongoing Type of Report: Primary CSR
Phase 3	Study Identifier: IM011055Report location: Module 5.3.5.1	To compare the efficacy of deucravacitinib to placebo in the treatment of participants with active PsA	52-week randomized, double-blind, placebo-controlled study followed by 104-week OLE period. 3:3:1 randomization to the DEUC, PBO, and APR groups	DEUC: 6 mg QD PO PBO: QD PO APR: 30 mg BID PO (with initial titration per label)	Total: 728 DEUC: 312 PBO: 311 APR: 105	Adult subjects with active PsA who are naive to bDMARDs or previously exposed to TNFi	Study Status: Ongoing Type of Report: Primary CSR

Abbreviations: APR, apremilast; BID, twice daily; DEUC, deucravacitinib; bDMARD, biologic disease-modifying antirheumatic drug; IR, immediate release; PBO, placebo; PK, pharmacokinetics; PO, by mouth; PsA, psoriatic arthritis; QD, once daily; SQ, subcutaneous; TNFi, tumor necrosis factor inhibitor

The pharmacokinetic (PK) properties of deucravacitinib were sufficiently characterised in the initial MAA.

The PK data provided in support of this submission includes, a Phase 2 study **IM011084** and two pivotal Phase 3 studies **IM011054** and **IM011055**. A new population PK (PPK) analysis and exposure-response analysis have been performed.

2.3.2. Pharmacokinetics

Across the clinical development program, several methods were developed and validated to quantify DEUC, its main active metabolite BMT-153261 and another major metabolite BMT-158170 (refer to the initial MAA).

DEUC and BMT-153261

For studies IM011054, IM011055 and IM011084 the same method to quantify DEUC and BMT-153261 in human plasma, with K_2EDTA as anticoagulant was used. For studies IM011054, IM011055, another method DCN930154085 was developed at another site and cross validated to the previous one.

BMT-158170

For studies IM011054, IM011055 and IM011084 the same method to quantify BMT-158170 in human plasma, with K_2EDTA as anticoagulant, was used. For studies IM011054, IM011055, another method DCN930141442 was developed at another site and cross validated to the previous one.

Population PK analysis

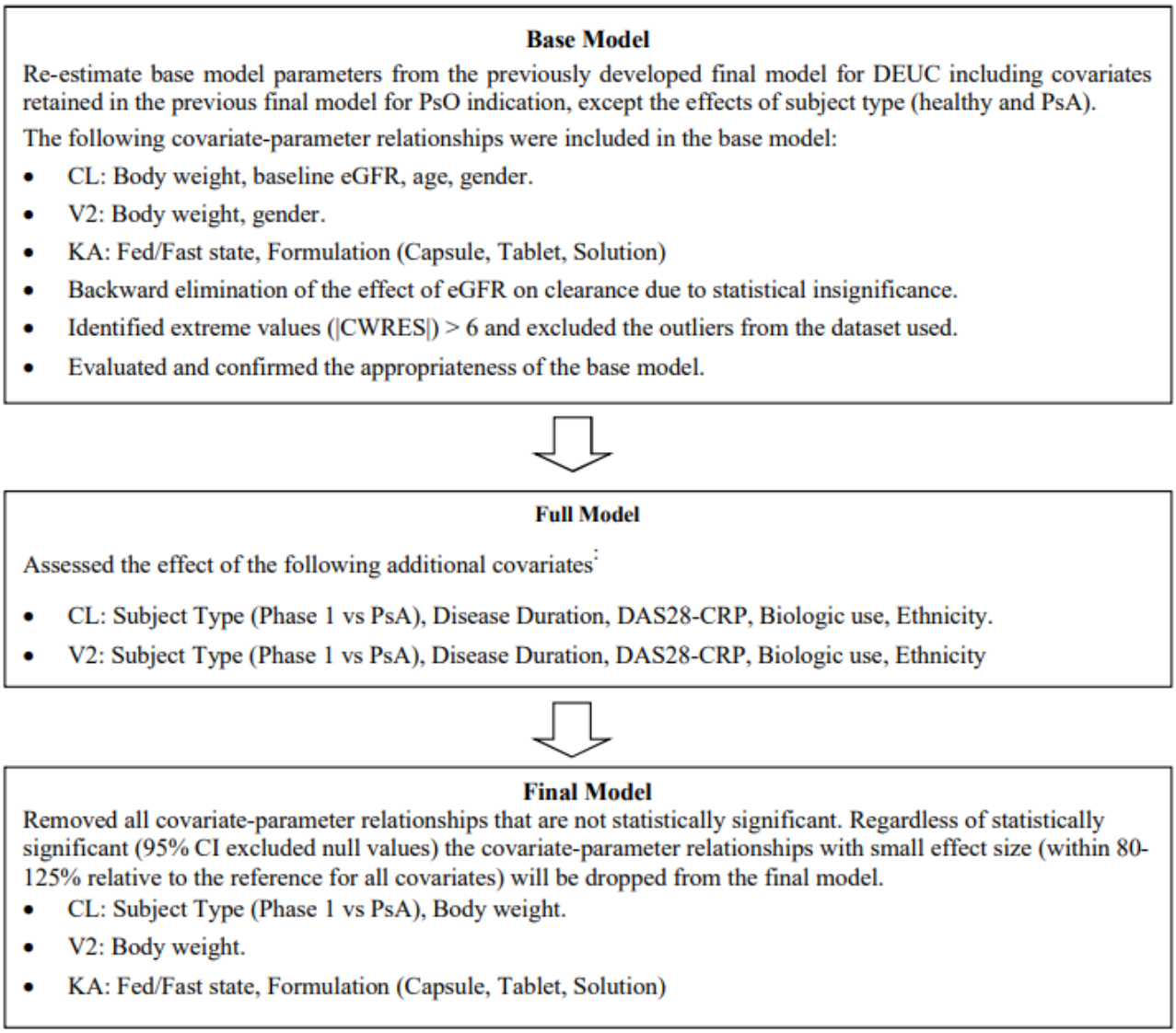
In this analysis, the same Phase 1 studies were used in addition to study IM011053. The Phase 2 and 3 studies for PsO indication were discarded and replaced by studies IM011084, IM011054 and IM011055.

The objectives of the analysis were to:

- Characterise the PPK of DEUC in subjects with active PsA and
- quantify the effects of intrinsic and extrinsic factors that may contribute significantly to PPK variability of DEUC

The DEUC PPK model was developed in three key steps: base model, full model, and final model (Figure 1).

Figure 1. Schematic overview of the PPK model development for DEUC



The results from the full model were used to infer the covariate effects on the PK parameters. The final model was developed by removing covariate effects in the full model that either were not statistically significant or had low effect size, and the remaining parameters were re-estimated. The covariates that were not found statistically significant during the full model development and were not retained in the final PsO model were not evaluated in the PsA population pharmacokinetic model development including but not limited to race, region, hepatic function, and smoking status.

The EBE of individual PK parameters derived from the final DEUC population pharmacokinetic model for each subject were used to simulate steady state exposure (e.g., C_{minss}, C_{maxss} and C_{avgss}) of the dosing regimens of interest (e.g., 6 mg QD), and for further assessment of the impact of the intrinsic and extrinsic factors on PK of DEUC.

PK dataset

A total of 1748 subjects were considered from which 1685 subjects were included. Among the 1685 participants, 78.6% of the participants had PsA.

Of the 21516 PK observations available, 16645 were included in the analysis. For the PK data excluded for the healthy volunteer subjects, this has already been discussed as part of the initial

MAA. For studies in PsA participants, predose sample BQL were excluded flagged (Day 1 predose). The "Other" exclusion consisted of missing dose or sample information, post first dose BQL, outlier absCWRES>6 or other reasons. However more than 90% of the PK data Phase 3 studies were used.

Dose normalised concentration vs time after dose profiles by dosing regimen. Phase 2/3 subjects with PsA generally had between 5 and 12 plasma samples (sparse sampling) per subject in the DEUC, while the Phase 1 studies' range extended higher with a large percentage having 20 to 30 samples.

Final PPK model

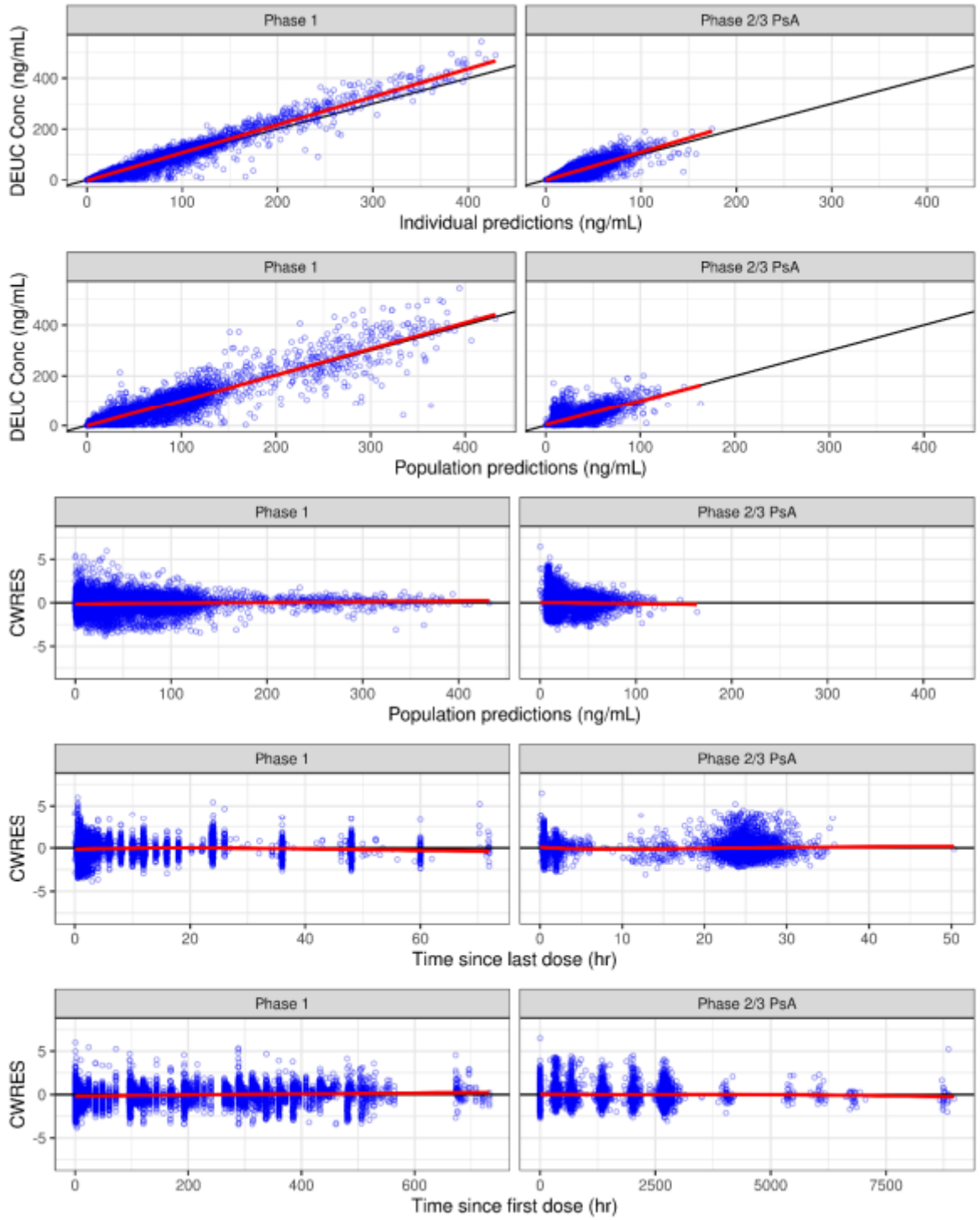
The final PPK model parameter estimates are provided in Table 1, associated GOF plots in Figure 2 and pcVPC plots in Figure 3 and Figure 4 for PsA subjects. The final model is stable (condition number 165, which is less than 1,000) and the covariate effect parameters are estimated with high precision. The covariate relationships in the final model included an effect of BW and disease status on CL/F, BW on V2/F and food effect/formulation effect on ka. Eta-shrinkage was 20.6%, 41.4%, 14.7% and 60.5% for CL/F, V2/F, ka and LF respectively. RUV was modelled using a combined error model with a high proportional term of 45% and an additional term of 0.516 ng/mL.

Table 1. Final PPK model parameter estimates

Name [Units][a,ball]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL [L/h]	θ_1	8.15	0.194 (2.37%)	[7.77, 8.53]
V2 [L]	θ_2	90.5	2.19 (2.42%)	[86.2, 94.8]
V3 [L]	θ_3	39.1	1.55 (3.96%)	[36.1, 42.1]
Q [L/h]	θ_4	2.53	0.164 (6.48%)	[2.21, 2.85]
KA [1/h]	θ_5	2.57	0.145 (5.64%)	[2.28, 2.85]
Logit of F1	θ_6	2.21	0.195 (8.83%)	[1.82, 2.59]
ED50 on F1	θ_7	0.585	0.111 (19%)	[0.367, 0.803]
ALAG1 [h]	θ_8	0.182	0.0175 (9.61%)	[0.148, 0.217]

Name [Units][a,ball]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
D1 [h]	θ_9	0.407	0.0327 (8.04%)	[0.343, 0.471]
CLBBWT: Baseline body weight on CL	θ_{14}	0.546	0.0562 (10.3%)	[0.435, 0.656]
V2BBWT: Baseline body weight on V2	θ_{15}	0.988	0.0373 (3.77%)	[0.915, 1.06]
KAFED: Food on KA (High-fat Meal vs Fasted)	θ_{16}	-1.49	0.157 (10.6%)	[-1.8, -1.18]
KAFORMN1: Formulation on KA (Solution vs Tablet)	θ_{17}	0.982	0.0509 (5.19%)	[0.882, 1.08]
KAFORMN2: Formulation on KA (Capsule vs Tablet)	θ_{18}	0.344	0.148 (43%)	[0.0539, 0.634]
CLPOP: Subject type on CL (Phase 1 vs Phase 2/3 PsA)	θ_{23}	0.328	0.0205 (6.25%)	[0.287, 0.368]
Random Effects				
CL	ω^2_{CL}	0.136	0.0073 (5.38%)	[0.121, 0.15]
CL-V2	$\omega_{CL}:\omega_{V2}$	0.0358	0.00436 (12.2%)	[0.0273, 0.0444]
V2	ω^2_{V2}	0.0177	0.00272 (15.4%)	[0.0124, 0.023]
KA	ω^2_{KA}	1.4	0.105 (7.48%)	[1.2, 1.61]
LF	ω^2_{LF}	0.913	0.147 (16.1%)	[0.626, 1.2]
Residual Error				
Proportional Error (Phase 1) [%]	θ_{10}	0.259	0.00782 (3.01%)	[0.244, 0.275]
Additive Error (Phase 1) [ng/mL]	θ_{11}	0.242	0.0283 (11.7%)	[0.186, 0.297]
Proportional Error (Phases 2 and 3) [%]	θ_{12}	0.455	0.00766 (1.69%)	[0.44, 0.47]
Additive Error (Phases 2 and 3) [ng/mL]	θ_{13}	0.516	0.109 (21.1%)	[0.302, 0.729]

Figure 2. GOF plots for DEUC PPK (HV+PsA)



The final PPK model of DEUC was evaluated using pcVPC with 1,000 simulations by subject type and specifically examining the subjects with PsA who received 6 mg QD. The 5th, 50th, and 95th percentiles of the observed concentration data at each time point were generally contained within the respective 95% CI of the simulated data. There was an overall good agreement in the time course and central tendency between distribution of observed and simulated data.

Figure 3. pcVPC of DEUC concentrations vs actual TApD by Populations

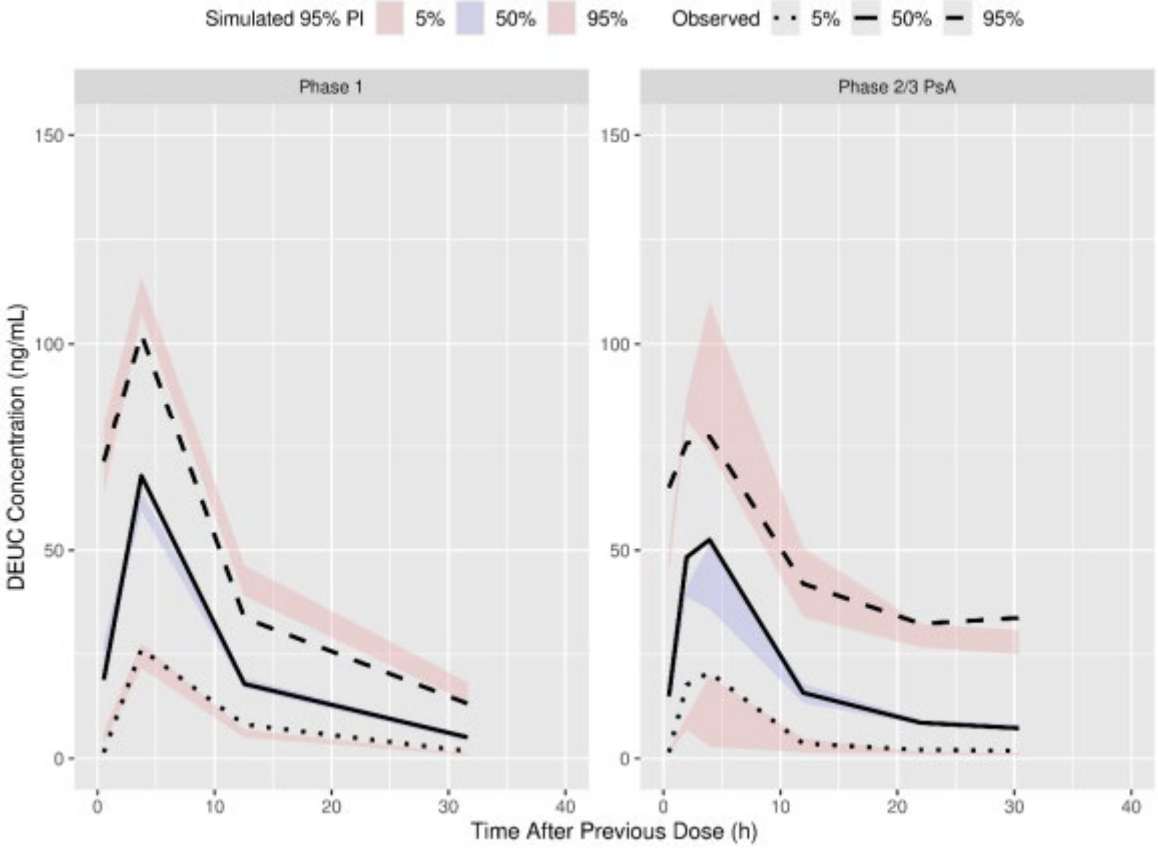
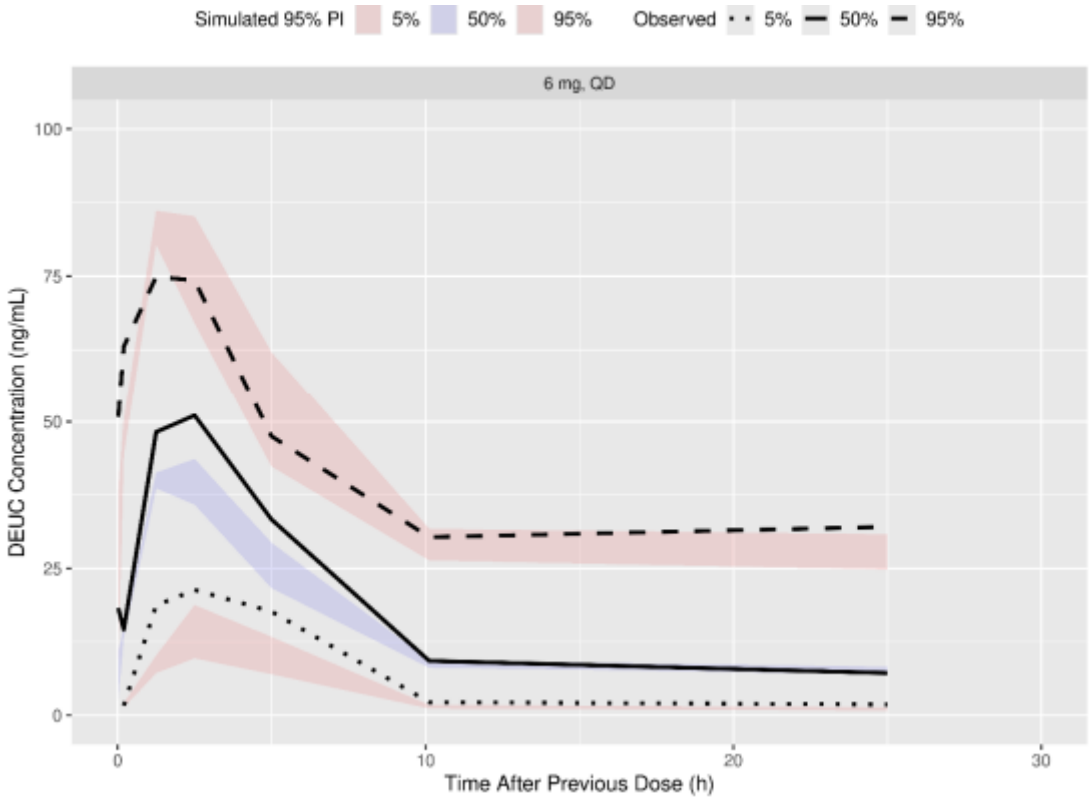


Figure 4. pcVPC of DEUC concentrations vs actual TApD – 6mg for PsA



The EBE of PK parameters were estimated from the final PPK model for each subjects and are presented in Table 2 below.

Table 2. Summary of primary PK parameters in subjects with PsA from Phase 3 studies vs HV

Parameter (Units)	Phase 1 Healthy Subjects (N = 332)	Phase 2/3 PsA Subjects (N = 1325)
KA (1/h)		
Geo. Mean (Geo. CV%)	1.64 (144.8%)	2.36 (138.7%)
Median [Min, Max]	1.62 [0.0451, 31.8]	2.32 [0.0838, 274]
F1 (6 mg dose)	0.781 (12.4%)	0.820 (2.4%)
Geo. Mean (Geo. CV%)		
Median [Min, Max]	0.816 [0.305, 0.878]	0.820 [0.601, 0.876]
CL (L/h)		
Geo. Mean (Geo. CV%)	10.9 (33.6%)	8.24 (32.2%)
Median [Min, Max]	11.3 [3.69, 22.2]	8.36 [2.11, 22.0]
Q (L/h)		
Geo. Mean (Geo. CV%)	2.44 (10.6%)	2.57 (12.2%)
Median [Min, Max]	2.44 [1.96, 3.20]	2.58 [1.70, 3.84]
VC (L)		
Geo. Mean (Geo. CV%)	84.3 (22.5%)	92.9 (23.3%)
Median [Min, Max]	85.3 [47.9, 136]	93.3 [37.7, 191]
VP (L)		
Geo. Mean (Geo. CV%)	36.7 (19.3%)	40.4 (22.2%)
Median [Min, Max]	36.8 [24.6, 60.0]	40.5 [19.0, 83.5]
Alpha half-life (h)		
Geo. Mean (Geo. CV%)	3.89 (14.7%)	4.90 (13.3%)
Median [Min, Max]	3.92 [2.45, 5.88]	4.90 [2.98, 7.05]
Beta half-life (h)		
Geo. Mean (Geo. CV%)	14.4 (13.4%)	17.3 (17.8%)
Median [Min, Max]	14.1 [10.7, 25.4]	17.1 [11.7, 52.3]

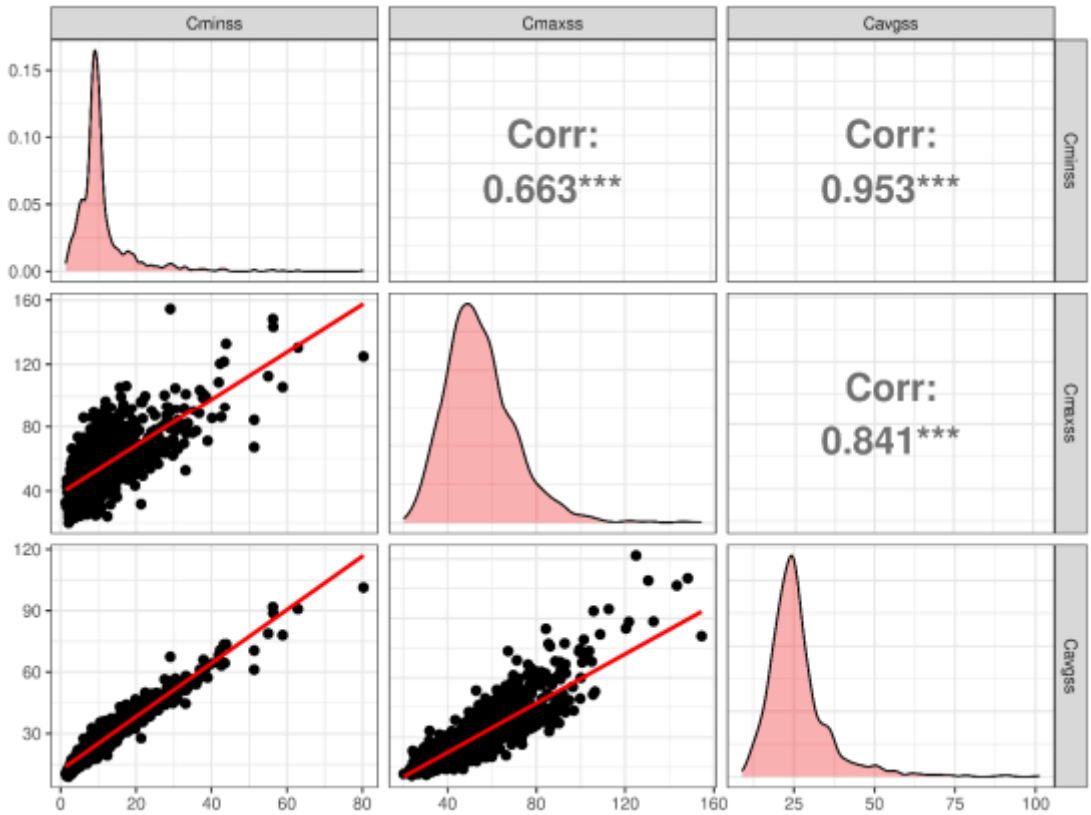
The 6 mg QD DEUC exposures (C_{max}, C_{min} and C_{avg}) after the first dose and at steady-state are summarised in Table 3. An accumulation ratio of 1.3 was predicted and an effective half-life of 11.42h.

Table 3. Summary of model predicted DEUC exposures after the first dose and at steady-state in subjects with PsA (6mg)

Exposure Measure (unit)	After First Dose (N = 1325)	Steady-state (N = 1325)
Cmax (ng/mL)		
Median [Min, Max]	43.9 [16.3, 127]	52.5 [20.2, 154]
Geo. Mean (Geo. CV%)	43.4 (28.1%)	52.7 (28.9%)
5th Percentile	27.2	32.7
95th Percentile	67.2	83.7
Cmin (ng/mL)		
Median [Min, Max]	6.37 [1.03, 28.4]	9.29 [1.27, 80.3]
Geo. Mean (Geo. CV%)	6.32 (47.3%)	9.36 (57.3%)
5th Percentile	2.84	3.81
95th Percentile	13.7	25.1
Cavg (ng/mL)		
Median [Min, Max]	19.0 [7.90, 51.3]	24.5 [8.89, 101]
Geo. Mean (Geo. CV%)	19.1 (26.3%)	24.9 (33.6%)
5th Percentile	12.3	14.8
95th Percentile	29.0	44.6

Figure 5 presents the correlation between the predicted exposure metrics.

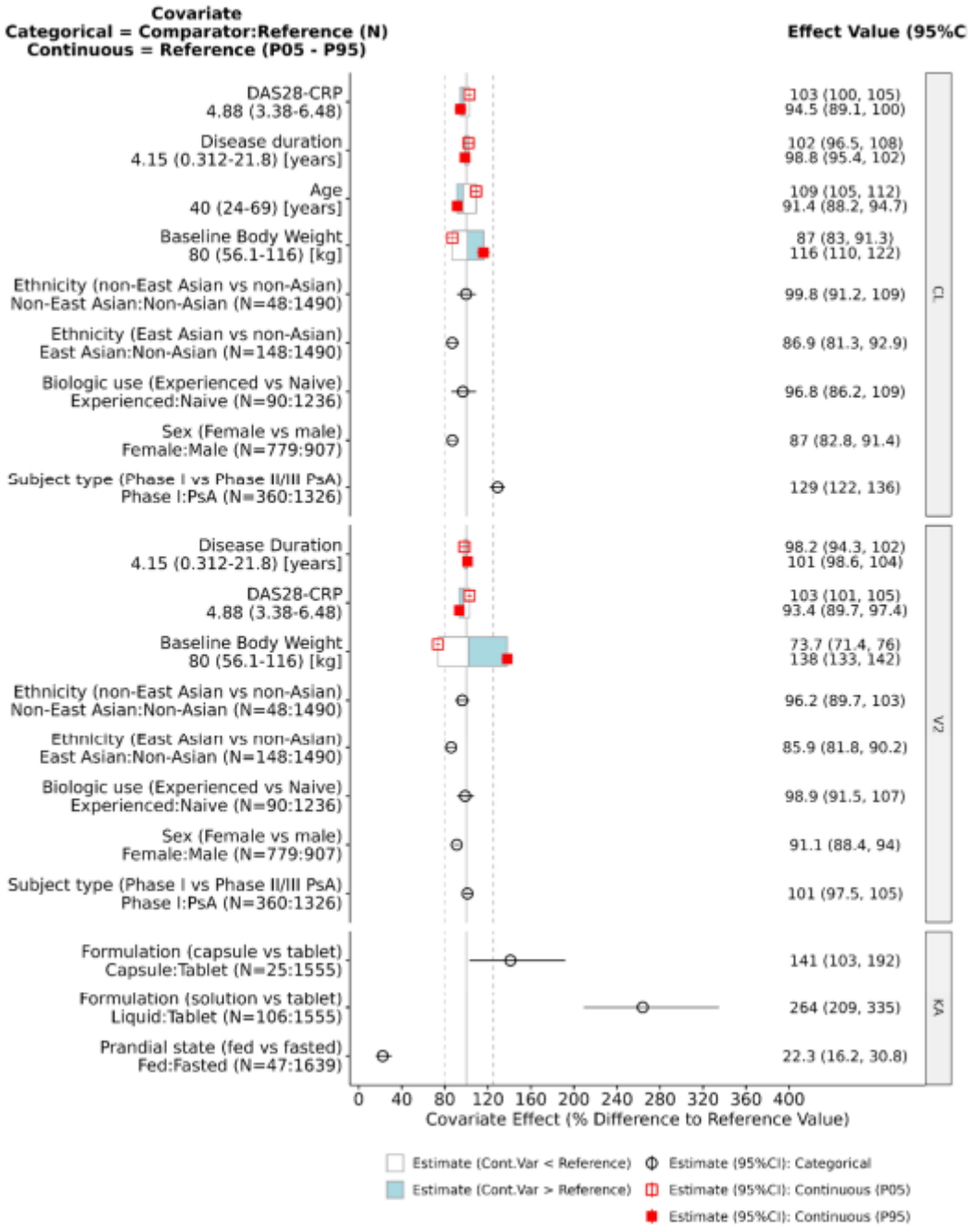
Figure 5. Pairwise comparison of DEUC steady-state exposure measures (PsA)



Special populations

For the full PPK model, Figure 6 present the covariate parameter relationship.

Figure 6. Covariate-Parameter relationship: Full DEUC PPK model

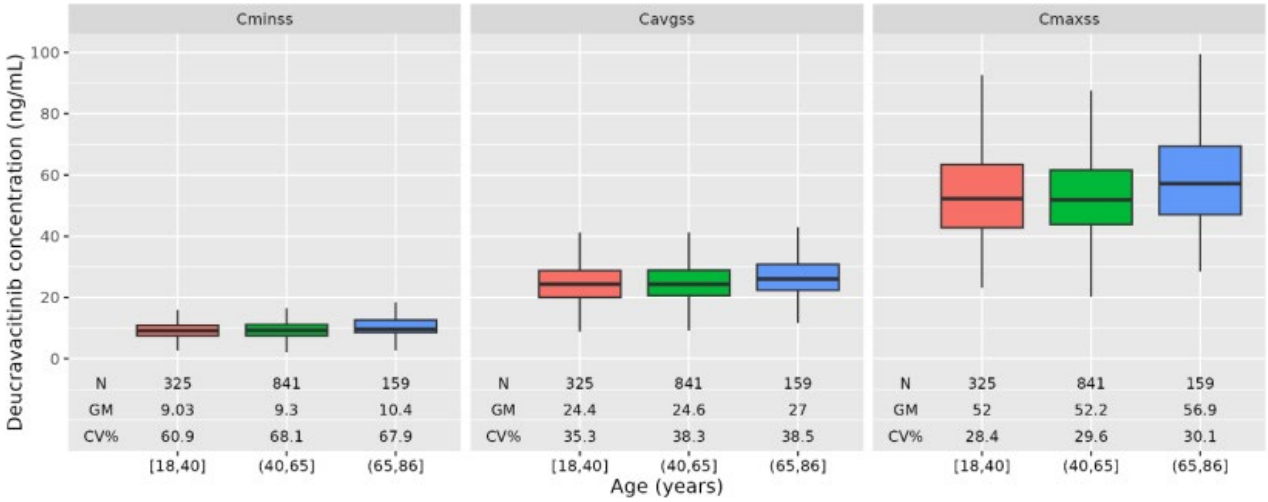


- Age/Elderly

No formal dedicated study investigating the effect of age on the DEUC PK has been performed. The effect of age on DEUC PK was investigated using the full PPK model. Out of 1685 participants included in the PPK model, median age (min-max) was 48 y (18-86 y). In the 1325 PsA subjects median age was 51 y (21-86 y).

Based on the full PK model, age was found to have a significant effect on DEUC CL/F. Geometric mean DEUC exposures (C_{maxss} and C_{avgss}) were not meaningfully changed in PsA patients > 65 years relative to patients aged ≤ 65 years (< 20% difference). Geometric mean DEUC exposures (C_{maxss} and C_{avgss}) were not meaningfully changed in PsA patients > 65 years relative to patients aged 40 to 65 years (<20% difference) as shown in Figure 7.

Figure 7. Distribution of DEUC individual prediction of C_{minss}, C_{avgss} and C_{maxss} by Age in subjects with PsA (6 mg QD)



- Gender

No formal dedicated study investigating the effect of gender on the DEUC PK has been performed. The effect of gender on DEUC PK was investigated using the full PPK model.

Out of 1685 participants included in the PPK model, male/female were 907/778. In the 1325 PsA subject's male/female proportion was similar 666/659.

Based on the full PK model, gender was found to have a significant effect on DEUC CL/F and V2/F. In addition, female subjects often have lower WT, which could further influence the PK between typical male and female subjects with PsA. Female subjects with PsA have a higher C_{maxss} (16.2%) and C_{avgss} (13.2%) compared to male subjects with PsA.

- Race/Ethnicity

The effect of race/Ethnicity has been investigated in two formal PK studies IM011002 Part C (Japanese vs non-Japanese, MAD of DEUC from 2 mg to 12 mg BID) and IM011053 (Chinese).

As part of the PPK model developed for PsO, race was not identified to have a significant effect on DEUC PK. As part of the full model, the covariate was not tested, however individual prediction based on the final PPK model for PsA was performed. East-Asian was tested as a categorical covariate in the full PPK model for DEUC and was found significant. Model prediction indicated that between East Asian (n=141), Non-East Asian (n=10) and Non-Asian (n=1200) PsA subjects, both C_{avgss} and C_{maxss} were generally similar.

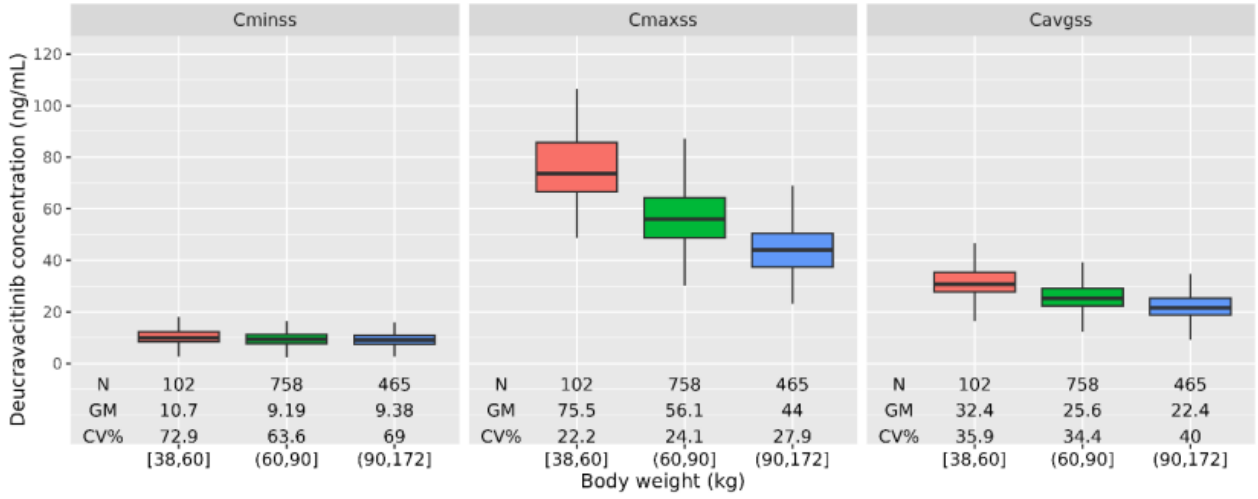
- BW

No formal dedicated study investigating the effect of BW on the DEUC PK has been performed. The effect of BW on DEUC PK was investigated using the final PPK model.

Out of 1685 participants included in the PPK model, male/female were 907/778. In the 1325 PsA subjects male/female proportion was similar 666/659. Body weight ranged from 38.5 to 172 kg (median 81.7 kg).

Based on the final PK model, BW was found to have a significant effect on DEUC CL/F and V2/F. Relative to a reference BW range from 60-90 kg, PsA subjects with BW above 90 kg had a lower C_{maxss} and C_{avgss} (21.6% and 12.5%). Conversely, PsA subjects with BW below 60 kg had a higher C_{maxss} and C_{avgss} (34.6% and 26.6%) as shown in Figure 8.

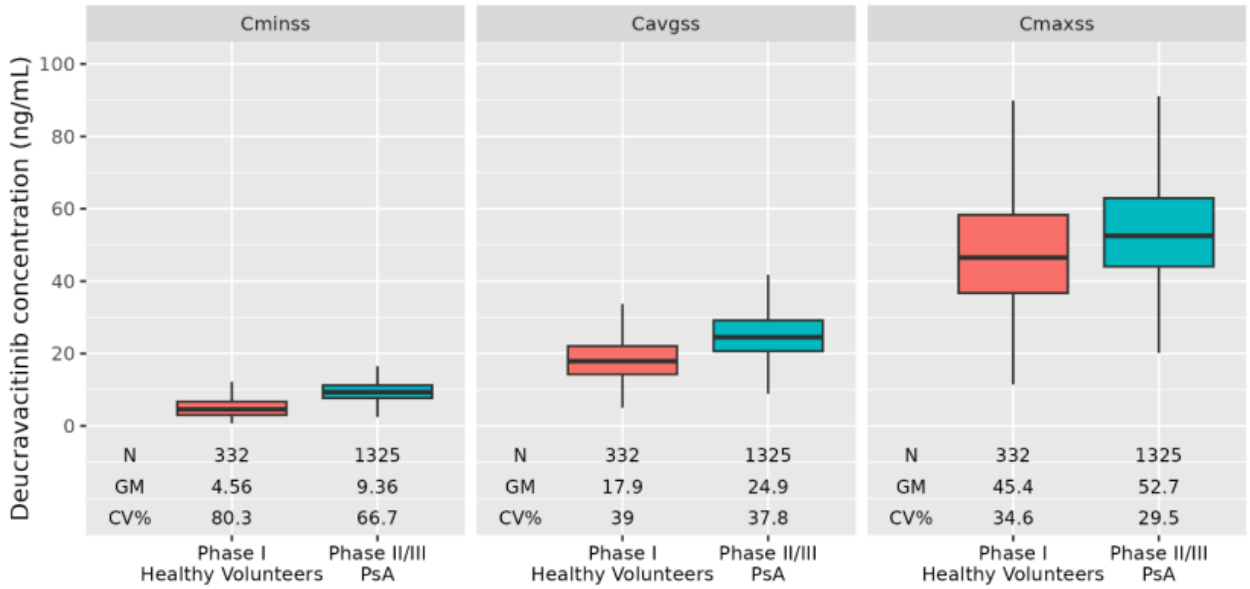
Figure 8. Distribution of DEUC individual prediction of C_{minss}, C_{avgss} and C_{maxss} by BW range in subjects with PsA (6 mg QD)



- Disease status

Among PsA disease relevant factors (subject type, disease status, disease duration, DAS28-CRP, prior biologic use), only subject type was evaluated as a categorical covariate and was found to be a significant covariate on DEUC clearance. Subject type had a modest effect on DEUC exposure (<50%). Compared to health volunteers (HV), PsA subjects have a higher C_{avgss} and C_{max} of 39.1 and 16.1% respectively.

Figure 9. Distribution of DEUC individual prediction of C_{minss}, C_{avgss} and C_{maxss} by subject type in subjects with PsA (6 mg QD)



Pharmacokinetic interaction studies

Pharmacokinetic interaction profile of deucravacitinib was well defined in the initial application.

A new DDI study (IM011159) was submitted with this application, which was an open-label, two-arm cross-over study to investigate the effect of BMS-986165 (DEUC) on the PK of metformin in healthy volunteers. The primary objective of the study was to evaluate the effect of multiple doses of BMS-986165 on the plasma PK of metformin in healthy subjects. The secondary objectives were to evaluate the safety and tolerability of metformin co-administered with multiple doses of DEUC in healthy subjects, to evaluate the effect of multiple doses of BMS-986165 on the urine PK of metformin in healthy subjects, to evaluate the effect of multiple doses of BMS-986165 on the secondary PK parameters of metformin in healthy subjects, to evaluate plasma PK of DEUC and its active metabolite BMT-153261 after BMS-986165 administration with metformin and to evaluate the PD effect of metformin alone or co-administered with 12 mg QD BMS-986165 using the OGTT (oral glucose tolerance test).

Following multiple dose administration of deucravacitinib at either 6 mg QD or 12 mg QD dose, co-administration with metformin did not change the plasma peak (C_{max}) or total exposures (AUC) of metformin in healthy subjects, compared with administration of metformin alone. DEUC (12 mg QD) in healthy subjects, when co-administered with metformin, did not alter the expected effect of OGTT on glucose levels.

2.3.3. Pharmacodynamics

In subjects with PsA, reduction in biomarkers including CRP, MMP3, MMP1, C1M, and TNF-α was observed.

In Phase 2 PsA Study IM011084, DEUC reduced levels of biomarkers such as IL-17A, IL-19, β defensin, CRP and MMP3. Mean levels of IL-17, IL-19 and β defensin were reduced 30%, -40%, -60%; mean levels of CRP, MMP1, MMP3, C4M were reduced 60%, 25%, 10% compared to placebo.

As IL-23 is an important mediator of psoriatic arthritis disease, PD of IL-23 inhibition were monitored in IM011054 by measuring IL-17A, IL-19 in plasma and beta-defensin in serum. These markers were measured over time in the placebo-controlled period up to the primary endpoint at Week 16. Adjusted mean percent decrease of circulated levels of IL-17A, IL-19 and beta-defensin were reduced by 9%, 32% and 48%, respectively, in DEUC-treated subjects, whereas, in placebo treated subjects, adjust mean percent increase of 2 and 3 for IL-17A and IL-19 was observed with percent decrease beta-defensin levels by 1%. IL-17A, IL-19 and beta-defensin levels were associated with PASI score at baseline and over time. Biomarkers including CRP and MMP3 were investigated.

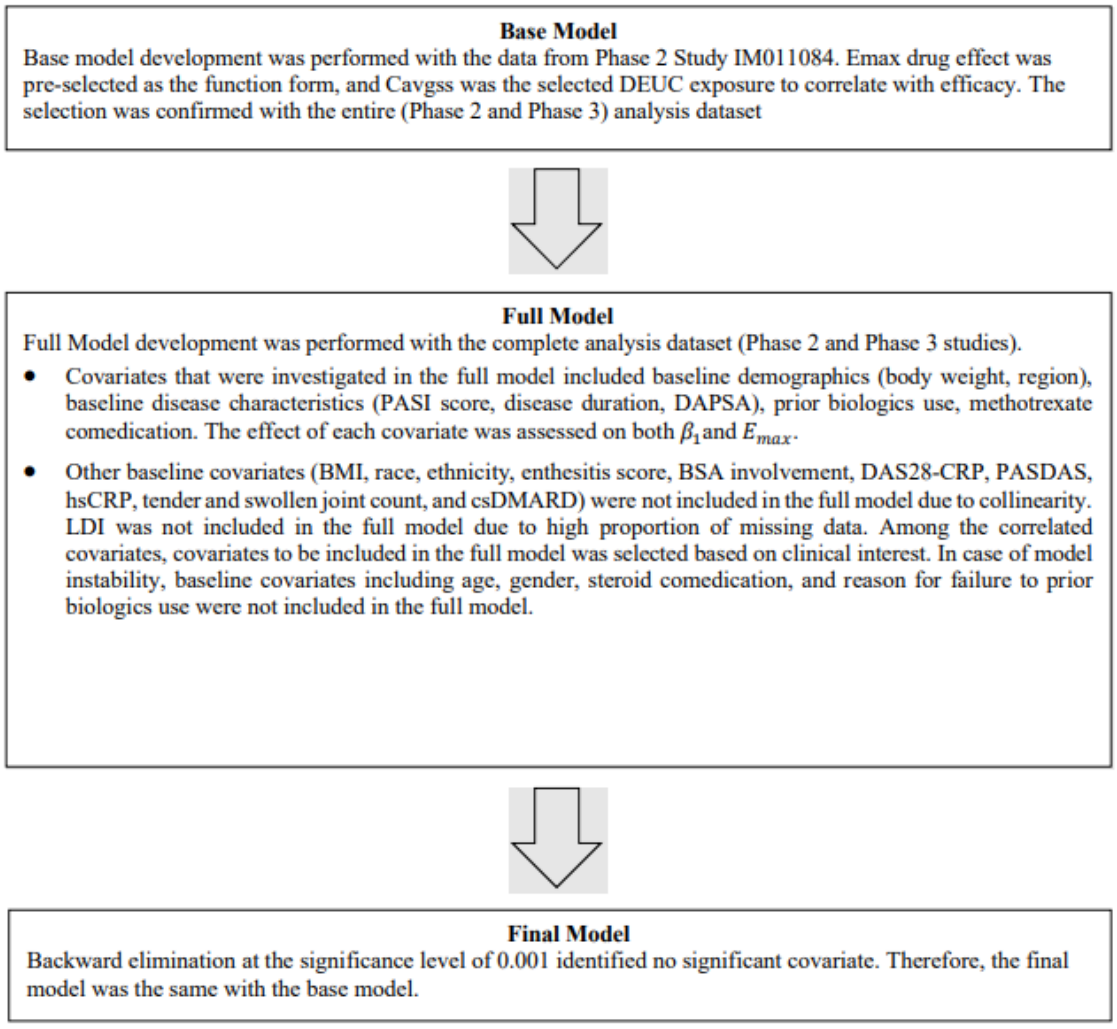
In Study IM011055, adjusted mean percent decrease of circulated IL-17A, IL-19 and beta-defensin were 11%, 33% and 43%, respectively, in DEUC-treated subjects, whereas, in placebo-treated subjects adjusted mean percent decrease of IL-17A, IL-19 and beta-defensin were 2%, 1% and 3%, respectively. Biomarkers including CRP and MMP3 were investigated.

2.3.4. PK/PD modelling

Exposure-response analysis

The same methodology as used for PsO participants was applied for PsA participants and consisted of three stages for model development: base, full and final model (Figure 10). The base model is the structure model incorporating the contribution of drug exposure without covariates contribution, then the full model investigates the covariates contribution and finally in the final model, influential covariates will be retained after a backward elimination.

Figure 10. Schematic overview of the ER ACR model development



The full model consisted of testing covariates. For the final model the BIC criteria was used for backward elimination. The final model was evaluated by VPCs. The main applications of this analysis was to perform simulations based either on the full or the final E-R model.

PD dataset

The E-R analysis of efficacy included data up to and including Week 16 from all subjects from the Phase 2 study (**IM011084**) and 2 Phase 3 studies (**IM011054** and **IM011055**).

Drug exposure metrics were imputed to be zero for participants who received placebo. Data from participants who received apremilast (IM011055) were not included in the analysis.

A total of 1485 subjects with 1485 ACR observations were available with 198, 664 and 623 observations in study **IM011084**, **IM011054** and **IM011055**, respectively. The percentage of patients with active PsA achieving ACR is presented in Figure 11 per treatment dose and the proportion of responders is presented in Figure 12.

Figure 11. Percentage of patients with active PsA achieving ACR20/50/70 over time

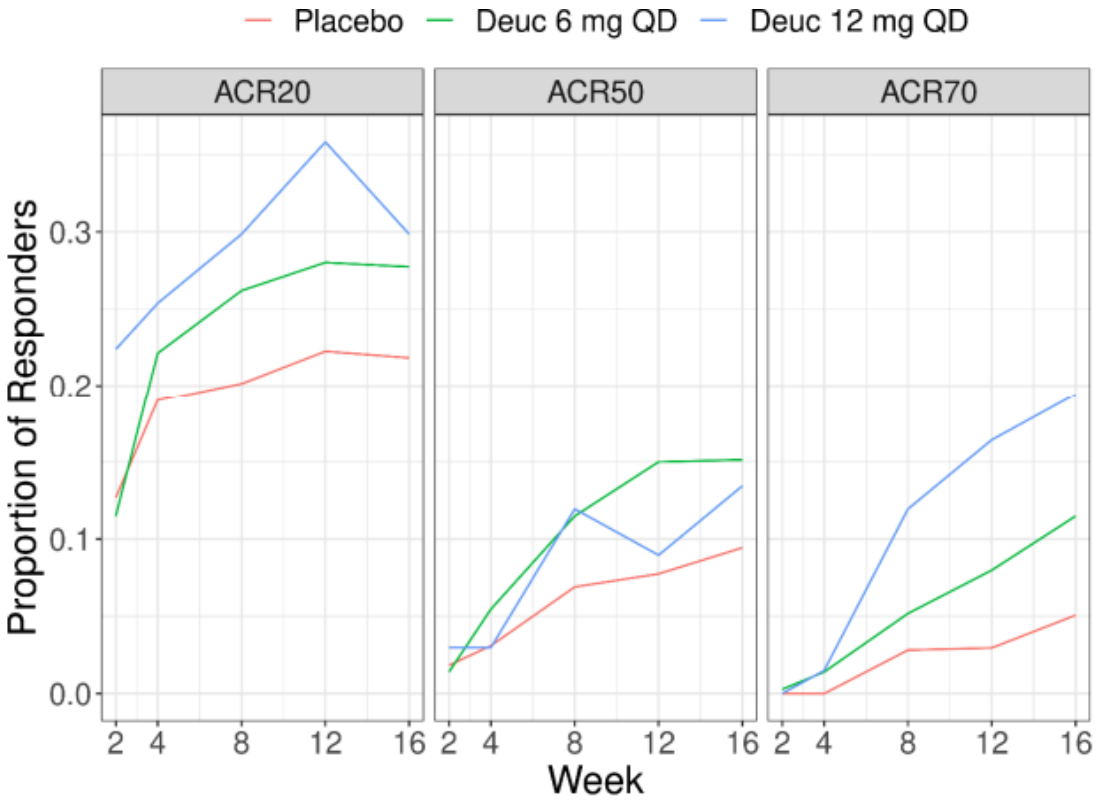
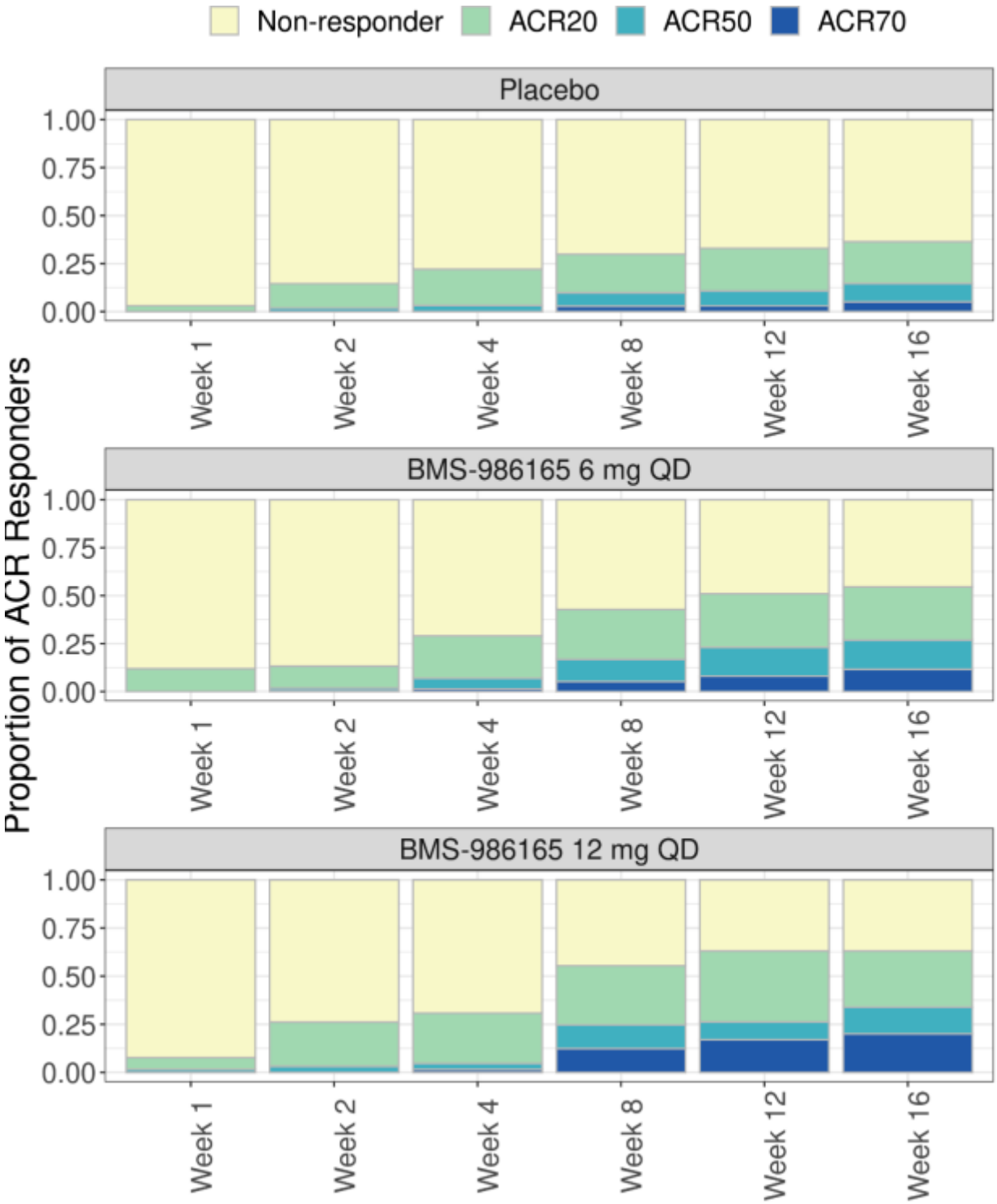


Figure 12. Proportion of responders-ACR



Summary statistics of continuous and categorical covariates are presented in Table 4 and Table 5 respectively.

Table 4. Summary statistics of continuous covariates

	Placebo (N=710)	BMS-986165 6 mg QD (N=710)	BMS-986165 12 mg QD (N=65)	Overall (N=1485)
Age (years)				
Mean (SD)	50.6 (12.4)	50.3 (12.4)	50.9 (13.7)	50.4 (12.5)
Median [Min, Max]	51.0 (21.0, 83.0)	51.0 (21.0, 86.0)	48.0 (24.0, 76.0)	51.0 (21.0, 86.0)
Baseline body weight (kg)				
Mean (SD)	84.5 (18.9)	85.2 (19.3)	89.2 (17.5)	85.0 (19.1)
Median [Min, Max]	82.6 (43.0, 189)	83.1 (38.5, 172)	88.1 (51.0, 149)	83.0 (38.5, 189)
Baseline BMI (kg/m^2)				
Mean (SD)	30.1 (6.16)	30.1 (6.42)	30.4 (5.44)	30.1 (6.25)
Median [Min, Max]	29.3 (17.0, 63.2)	29.4 (15.2, 65.2)	29.8 (19.4, 45.1)	29.4 (15.2, 65.2)
Missing	0 (0%)	2 (0.3%)	0 (0%)	2 (0.1%)
Baseline PASI score				
Mean (SD)	5.64 (6.59)	5.55 (6.11)	6.43 (6.03)	5.63 (6.34)
Median [Min, Max]	3.40 (0, 57.7)	3.50 (0, 39.6)	5.45 (0, 31.8)	3.50 (0, 57.7)
Missing	6 (0.8%)	3 (0.4%)	1 (1.5%)	10 (0.7%)
DAS28-CRP				
Mean (SD)	4.97 (0.940)	4.88 (0.959)	5.07 (1.03)	4.93 (0.954)
Median [Min, Max]	4.89 (2.48, 8.16)	4.87 (1.91, 7.57)	5.04 (2.50, 7.48)	4.89 (1.91, 8.16)
Missing	3 (0.4%)	5 (0.7%)	0 (0%)	8 (0.5%)
Baseline BSA involvement (%)				
Mean (SD)	7.84 (11.2)	7.90 (11.1)	9.52 (11.5)	7.95 (11.2)
Median [Min, Max]	4.00 (0, 100)	4.00 (0, 78.0)	5.50 (0, 54.0)	4.00 (0, 100)
Missing	6 (0.8%)	3 (0.4%)	1 (1.5%)	10 (0.7%)
Disease duration (years)				
Mean (SD)	6.96 (7.24)	6.40 (7.57)	6.26 (6.54)	6.66 (7.37)
Median [Min, Max]	4.55 (0.222, 41.8)	3.84 (-0.0548, 60.2)	4.27 (0.572, 27.7)	4.15 (-0.0548, 60.2)
Baseline CRP (mg/L)				
Mean (SD)	13.9 (20.7)	12.5 (17.0)	15.7 (20.1)	13.3 (19.0)
Median [Min, Max]	7.35 (0.150, 252)	6.30 (0.220, 113)	8.29 (0.320, 85.2)	6.87 (0.150, 252)
Tender Joint Count				
Mean (SD)	17.7 (12.5)	17.3 (11.9)	19.5 (12.0)	17.6 (12.2)
Median [Min, Max]	14.0 (2.00, 68.0)	14.0 (1.00, 68.0)	16.0 (5.00, 58.0)	14.0 (1.00, 68.0)
Missing	1 (0.1%)	1 (0.1%)	0 (0%)	2 (0.1%)
Swollen Joint Count				
Mean (SD)	10.0 (7.53)	10.2 (6.80)	11.4 (9.08)	10.2 (7.27)
Median [Min, Max]	8.00 (0, 66.0)	8.00 (3.00, 61.0)	8.00 (3.00, 45.0)	8.00 (0, 66.0)
Missing	1 (0.1%)	1 (0.1%)	0 (0%)	2 (0.1%)

Baseline LEIren				
Mean (SD)	1.15 (1.54)	1.20 (1.59)	1.13 (1.69)	1.17 (1.57)
Median [Min, Max]	0 (0, 6.00)	1.00 (0, 6.00)	0 (0, 6.00)	0 (0, 6.00)
Missing	6 (0.8%)	2 (0.3%)	1 (1.5%)	9 (0.6%)
Baseline LDI				
Mean (SD)	59.6 (154)	57.5 (106)	42.6 (66.7)	57.6 (128)
Median [Min, Max]	23.1 (-40.2, 2074)	26.8 (-303, 907)	21.8 (-105, 262)	25.4 (-303, 2074)
Missing	485 (68.3%)	457 (64.4%)	38 (58.5%)	980 (66.0%)
Baseline Disease Activity Index for PsA				
Mean (SD)	41.6 (19.7)	41.1 (18.1)	45.2 (21.3)	41.5 (19.0)
Median [Min, Max]	37.0 (7.50, 154)	37.2 (6.48, 109)	41.6 (18.2, 112)	37.2 (6.48, 154)
Missing	3 (0.4%)	5 (0.7%)	0 (0%)	8 (0.5%)
Baseline PsA Disease Activity Score				
Mean (SD)	5.98 (0.945)	5.99 (1.02)	6.14 (0.920)	5.99 (0.982)
Median [Min, Max]	5.98 (2.95, 9.72)	5.98 (2.08, 9.41)	6.04 (4.30, 8.51)	5.98 (2.08, 9.72)
Missing	9 (1.3%)	9 (1.3%)	1 (1.5%)	19 (1.3%)

Table 5. Summary statistics of categorical covariates

	Placebo (N =710)	**DEUC 6 mg QD (N = 710)**	**DEUC 12 mg QD (N = 65)**	**Overall (N = 1485)**
Gender, n (%)				
Male	334 (47.0%)	367 (51.7%)	32 (49.2%)	733 (49.4%)
Female	376 (53.0%)	343 (48.3%)	33 (50.8%)	752 (50.6%)
Race, n (%)				
White	582 (82.0%)	547 (77.0%)	65 (100%)	1194 (80.4%)
Black Or African American	2 (0.3%)	7 (1.0%)	0 (0%)	9 (0.6%)
Asian	59 (8.3%)	77 (10.8%)	0 (0%)	136 (9.2%)
Others	67 (9.4%)	79 (11.1%)	0 (0%)	146 (9.8%)
Current Smoking Status, n (%)				
Non-Smoker	448 (63.1%)	436 (61.4%)	37 (56.9%)	921 (62.0%)
Current Smoker	130 (18.3%)	119 (16.8%)	17 (26.2%)	266 (17.9%)
Prior Smoker	129 (18.2%)	147 (20.7%)	11 (16.9%)	287 (19.3%)
Missing	3 (0.4%)	8 (1.1%)	0 (0%)	11 (0.7%)
Region, n (%)				
United States	58 (8.2%)	52 (7.3%)	11 (16.9%)	121 (8.1%)
European Union	372 (52.4%)	364 (51.3%)	38 (58.5%)	774 (52.1%)
RoW	280 (39.4%)	294 (41.4%)	16 (24.6%)	590 (39.7%)
Prior Biologic treatment use, n (%)				
No	656 (92.4%)	663 (93.4%)	56 (86.2%)	1375 (92.6%)
Yes	54 (7.6%)	47 (6.6%)	9 (13.8%)	110 (7.4%)

Prior biologic discontinuation reason				
inadequate efficacy response	32 (4.5%)	25 (3.5%)	0 (0%)	57 (3.8%)
intolerability	3 (0.4%)	4 (0.6%)	0 (0%)	7 (0.5%)
loss of access to treatment	0 (0%)	3 (0.4%)	0 (0%)	3 (0.2%)
other	7 (1.0%)	4 (0.6%)	0 (0%)	11 (0.7%)
Missing	668 (94.1%)	674 (94.9%)	65 (100%)	1407 (94.7%)
Age (years)				
< 65	608 (85.6%)	619 (87.2%)	52 (80.0%)	1279 (86.1%)
≥ 65	102 (14.4%)	91 (12.8%)	13 (20.0%)	206 (13.9%)
Baseline body weight (kg)				
< 90	454 (63.9%)	445 (62.7%)	35 (53.8%)	934 (62.9%)
≥ 90	256 (36.1%)	265 (37.3%)	30 (46.2%)	551 (37.1%)
Disease duration (years) at screening from onset of diagnostic				
< median	338 (47.6%)	372 (52.4%)	32 (49.2%)	742 (50.0%)
≥ median	372 (52.4%)	338 (47.6%)	33 (50.8%)	743 (50.0%)
Baseline PASI score, n (%)				
< median	353 (49.7%)	352 (49.6%)	25 (38.5%)	730 (49.2%)
≥ median	351 (49.4%)	355 (50.0%)	39 (60.0%)	745 (50.2%)
Missing	6 (0.8%)	3 (0.4%)	1 (1.5%)	10 (0.7%)

Baseline BSA involvement, n (%)				
< median	306 (43.1%)	323 (45.5%)	22 (33.8%)	651 (43.8%)
≥ median	398 (56.1%)	384 (54.1%)	42 (64.6%)	824 (55.5%)
Missing	6 (0.8%)	3 (0.4%)	1 (1.5%)	10 (0.7%)
Baseline CRP, n (%)				
Q1	169 (23.8%)	188 (26.5%)	15 (23.1%)	372 (25.1%)
Q2	168 (23.7%)	188 (26.5%)	15 (23.1%)	371 (25.0%)
Q3	195 (27.5%)	161 (22.7%)	15 (23.1%)	371 (25.0%)
Q4	178 (25.1%)	173 (24.4%)	20 (30.8%)	371 (25.0%)
Baseline LDI				
< median	117 (16.5%)	120 (16.9%)	15 (23.1%)	252 (17.0%)
≥ median	108 (15.2%)	133 (18.7%)	12 (18.5%)	253 (17.0%)
Missing	485 (68.3%)	457 (64.4%)	38 (58.5%)	980 (66.0%)
Baseline disease severity (DAS28-CRP)				
< 5.1	407 (57.3%)	420 (59.2%)	36 (55.4%)	863 (58.1%)
≥ 5.1	300 (42.3%)	285 (40.1%)	29 (44.6%)	614 (41.3%)
Missing	3 (0.4%)	5 (0.7%)	0 (0%)	8 (0.5%)
Methotrexate				
No Methotrexate	314 (44.2%)	309 (43.5%)	30 (46.2%)	653 (44.0%)
Methotrexate	396 (55.8%)	401 (56.5%)	35 (53.8%)	832 (56.0%)

Steroid				
No Steroid	567 (79.9%)	596 (83.9%)	57 (87.7%)	1220 (82.2%)
Steroid	143 (20.1%)	114 (16.1%)	8 (12.3%)	265 (17.8%)
Chinese				
Chinese	47 (6.6%)	62 (8.7%)	0 (0%)	109 (7.3%)
Non-Chinese Asian	12 (1.7%)	15 (2.1%)	0 (0%)	27 (1.8%)
Non-Asian	651 (91.7%)	633 (89.2%)	65 (100%)	1349 (90.8%)
Taiwanese				
Taiwanese	12 (1.7%)	16 (2.3%)	0 (0%)	28 (1.9%)
Non-Taiwanese Asian	47 (6.6%)	61 (8.6%)	0 (0%)	108 (7.3%)
Non-Asian	651 (91.7%)	633 (89.2%)	65 (100%)	1349 (90.8%)
Japanese				
Japanese	8 (1.1%)	9 (1.3%)	0 (0%)	17 (1.1%)
Non-Japanese Asian	51 (7.2%)	68 (9.6%)	0 (0%)	119 (8.0%)
Non-Asian	651 (91.7%)	633 (89.2%)	65 (100%)	1349 (90.8%)
East Asian				
East Asian	55 (7.7%)	71 (10.0%)	0 (0%)	126 (8.5%)
Non-East-Asian	4 (0.6%)	6 (0.8%)	0 (0%)	10 (0.7%)
Non-Asian	651 (91.7%)	633 (89.2%)	65 (100%)	1349 (90.8%)

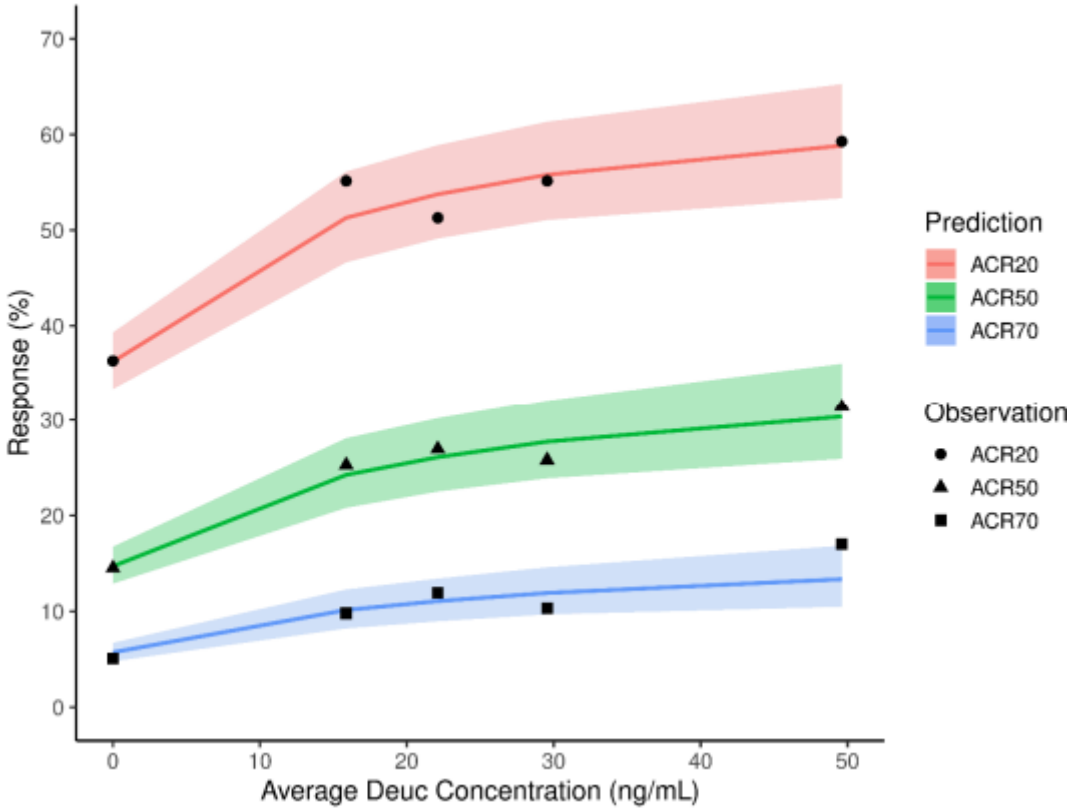
Final E-R-ACR model

C_{avgss} was pre-selected as the DEUC exposure measure for the base model. Since no covariates were retained from the full model (base model + covariates), the base model was considered as final. PD parameter estimates are presented in Table 6 and the associated VPCs in Figure 13.

Table 6. Final E-R-ACR model

Parameter	Symbol	Parameter Estimate	Standard Error	RSE (%)	Median [95% CI]
B1: logit of placebo response	θ_1	-0.56	0.08	13.60	-0.558 [-0.709, -0.414]
B2: difference in logit probability between ACR20 and ACR50	θ_2	1.20	0.06	4.75	1.2 [1.09, 1.3]
B3: difference in logit probability between ACR50 and ACR70	θ_3	1.04	0.07	7.13	1.04 [0.904, 1.21]
EMAX: maximum drug effect	θ_4	1.26	0.52	41.60	1.16 [0.698, 2.53]
Ln(EC50): concentration of drug that gives half-maximal response, ng/mL	θ_5	2.75	1.18	42.80	2.59 [0.533, 4.11]

Figure 13. Visual Predictive check (final model) Week 16 ACR20/50/70 response vs C_{avgss} DEUC

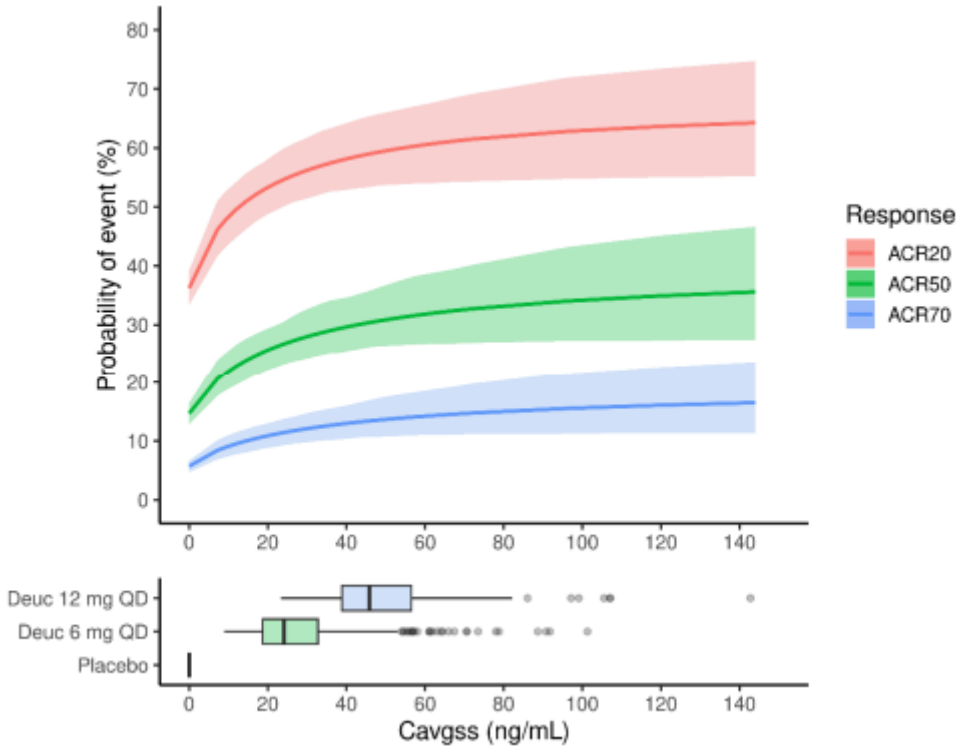


The final model at Week 16 used to predict probability of ACR20/50/70 at week 16 is presented in Table 7 and the associated plot in Figure 14. Model predictions indicate that a 50% lower DEUC exposure (C_{avgss}) leads to a slight decrease in ACR20 response relative to that achieved at the median 6 mg QD dose exposures (49.6% vs 54.6%), with response probability substantially above placebo. Increase in DEUC exposure by 100% to 200% is predicted to modestly increase ACR20 response relative to that achieved at the median 6 mg QD dose exposures, indicating that 6 mg QD dose achieves close to maximal ACR20 response. Specifically, an increase in dose from 6 mg QD to 12 mg QD was not predicted to meaningfully increase the efficacy (probability of ACR20 response at Week 16 (ACR20 of 54.6% vs. 59.3%). Similar trends are noted for predicted ACR50 and ACR70 responses.

Table 7. Model-predicted ACR20/50/70 response probabilities at Week 16 with varying DEUC C_{avgss}

Scenario	ACR20 Probability Mean [90% PI] (%)	ACR50 Probability Mean [90% PI] (%)	ACR70 Probability Mean [90% PI] (%)
Placebo	36.2 [33.5, 39.2]	14.7 [12.8, 16.5]	5.72 [4.72, 6.66]
50% lower median DEUC exposure	49.6 [44.8, 54.2]	23 [19.6, 26.6]	9.52 [7.74, 11.5]
Reference (DEUC 6 mg QD - median exposure)	54.6 [50.1, 59.9]	26.7 [23.2, 30.5]	11.4 [9.27, 13.7]
100% higher median DEUC exposure	59.3 [53.6, 65.7]	30.7 [26.4, 36.3]	13.5 [10.7, 17.3]
200% higher median DEUC exposure	61.5 [54.3, 69.1]	32.7 [26.9, 40.2]	14.7 [11.1, 19.7]

Figure 14. Predicted mean (90% PI) probability of ACR at Week 16



PD dataset

Exposure-safety analyses were conducted for Week 16 and 52, respectively with PD data from the three studies at Week 16 and only PD data from the pivotal studies for Week 52. The studied population included 1485 subjects for Week 16 and 643 for Week 52.

Table 8 presents the summary statistics of events at Week 16 and Table 9 at week 52.

Table 8. Summary statistics of safety events in the E-R safety analysis dataset (Week 16)

	Placebo (N=710)	DEUC 6 mg QD (N=710)	DEUC 12 mg QD (N=65)	Overall (N = 1485)
MACE, n (%)				
No event	709 (99.9%)	710 (100%)	65 (100%)	1484 (99.9%)
Event	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
Extended MACE, n (%)				
No event	709 (99.9%)	710 (100%)	65 (100%)	1484 (99.9%)
Event	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
Serious infection, n (%)				
No event	709 (99.9%)	702 (98.9%)	65 (100%)	1476 (99.4%)
Event	1 (0.1%)	8 (1.1%)	0 (0%)	9 (0.6%)
CK Gr3+, n (%)				
No event	705 (99.3%)	706 (99.4%)	64 (98.5%)	1475 (99.3%)
Event	5 (0.7%)	4 (0.6%)	1 (1.5%)	10 (0.7%)
Malignancies, n (%)				
No event	708 (99.7%)	710 (100%)	65 (100%)	1483 (99.9%)
Event	2 (0.3%)	0 (0%)	0 (0%)	2 (0.1%)
Infections/Infestations				
No event	555 (78.2%)	486 (68.5%)	41 (63.1%)	1082 (72.9%)
Event	155 (21.8%)	224 (31.5%)	24 (36.9%)	403 (27.1%)

Table 9. Summary statistics of safety events in the E-R safety analysis dataset (Week 52)

	DEUC 6 mg QD (N=643)
MACE, n (%)	
No event	641 (99.7%)
Event	2 (0.3%)
Extended MACE, n (%)	
No event	641 (99.7%)
Event	2 (0.3%)
Serious infection, n (%)	
No event	633 (98.4%)
Event	10 (1.6%)
CK Gr3+, n (%)	
No event	633 (98.4%)
Event	10 (1.6%)
Malignancies, n (%)	
No event	640 (99.5%)
Event	3 (0.5%)
Infections/Infestations	
No event	308 (47.9%)
Event	335 (52.1%)

Infection and infestation was the only safety endpoint with appreciable AE number of incidents (>10). Due to higher incidence of infection and infestation events at Week 16 and 52 they were

further explored using quantile analysis, which revealed that the safety events lacked correlation with exposure and was thus not considered for further model based evaluation.

2.3.5. Discussion on clinical pharmacology

In the present application, the MAH seeks approval for the use of deucravacitinib 6 mg QD in PsA subjects based on results from one Phase 2 **IM011084** and two Phase 3 studies **IM011054** and **IM011055**, in addition to a developed PPK model and E-R analyses.

The PPK analysis used PK data from the three Phase 2/ Phase 3 studies (mainly sparse PK sample) and approximately 12 Phase 1 studies performed in healthy volunteers (intensive PK sampling). Outputs of this analysis was only used to update the demographic values reported in the elderly and BW section from the Special populations section of Section 5.2 of the SmPC. Therefore, this analysis is of low impact.

The final PK model has a similar structure to that developed for the PsO indication. PK parameters (fixed effects), estimated with a good precision, are generally similar between the two PPK analysis (HV+PsO vs HV+PsA). Similarly to PsO subjects where geomean C_{avgss} was increased by 20% (19.4 vs 16.1 ng/mL) with unchanged C_{max} compared to HV, in PsA subjects C_{avgss} was increased by 39.1% (24.9 vs 17.9 ng/mL). Regarding the difference of CL/F in HV vs PsA based on PK consideration (elimination pathway), section 5.2 of the SmPC was adequately updated to reflect that deucravacitinib clearance in psoriatic arthritis subjects is moderately lower (by 29%) compared to healthy adults. This is endorsed by the CHMP.

PD biomarkers associated with PsA disease activity and joint damage were measured in Phase 2 and both pivotal Phase 3 studies. Treatment with deucravacitinib decreased levels of circulating IL-17A, IL-19 and β-defensin after 16 weeks of once daily dosing which demonstrated suppression of IL-23/IL-17 pathway. Additionally, in subjects with PsA, reduction in circulating levels of biomarkers including CRP, MMP3, MMP1, C1M, and TNF-α was also observed. This has been reflected in section 5.1 of the SmPC.

For E-R efficacy, a log-odds model for ACR20/50/70 with C_{avgss} the predicted PK metrics of interest (by the final PPK model). A suggested by the MAH, the 6 mg QD dose achieved close to maximal ACR20 response (EC50 of approximately 13.3 ng/mL, median (min-max) C_{avg} in PsA of 24.5 ng/mL (9-101 ng/mL), and any increase of the exposure by 100% (using a 12 mg QD dose) would not increase to a large extent the efficacy. Thus, based on this analysis the 6 mg QD dose is considered acceptable. This was endorsed by the CHMP.

For the E-R safety, no significant relationship was found between DEUC C_{avgss} and infections and infestations at week 16.

The DDI profile with DEUC was adequately addressed as part of the initial MAA for the psoriasis indication. As part of this extension indication, a DDI study (IM011159) with metformin was submitted. The outcomes of the study IM011159 did not evidence significant changes neither on metformin pharmacokinetics after DEUC administration nor on pharmacodynamics properties of metformin on blood glucose and insulinemia. Therefore, the proposed SmPC amendment to reflect these observations in section 4.5 was endorsed by the CHMP.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology package supports the extension of indication to PsA patients as well as the proposed dosing frequency of 6mg QD for deucravacitinib. The SmPC has been adequately updated to reflect the results of the PK/PD program in PsA patients.

2.4. Clinical efficacy

Table 10. Clinical Studies of DEUC in PsA

Study	Design/Primary Objectives	Population	Number of Treated Subjects	Regimen and Dose	Study Status
Pivotal Phase 3 Studies Supporting Efficacy and Safety					
IM011054 and **IM011055**	Phase 3, randomized, double-blind, Placebo-controlled study to evaluate the efficacy and safety of DEUC **Primary Objective:** • To compare the efficacy of DEUC to PBO in the treatment of participants with active PsA Assessed by: – Proportion of subjects meeting ACR 20 response at Week 16 **Key Secondary Efficacy Objectives at Week 16:** • To compare the efficacy of DEUC to PBO: Assessed by: – HAQ-DI – PASI 75 response – SF-36 PCS score – MDA response – Enthesitis resolution – Radiographic response (PsA-modified SvdH score) [IM011054 only] – FACIT-Fatigue score – Dactylitis resolution – DAS28-CRP Refer to Table 1.2.1.2-1 of the SCE[44] for additional secondary efficacy objectives/endpoints up to Week 16 and exploratory efficacy objectives/endpoints up to Week 52.	Adults (≥ 18 years) with a diagnosis of PsA for ≥ 3 months with a documented inadequate response, loss of response, or intolerance to standard therapies (eg, csDMARDs and/or NSAIDs) and fulfilling CASPAR at Screening, with an active plaque PsO skin lesion(s) or documented medical history of plaque PsO, active arthritis (≥ 3 swollen joints and ≥ 3 tender joints in 66/68 joint count assessments), ≥ 1 PsA related joint erosion in X-rays of hands and/or feet (IM011054 only), and hsCRP concentration ≥ 3 mg/L. In addition, subjects who failed or were intolerant to TNFi were permitted in IM011055 only.	**IM011054** Placebo-controlled Period (up to Week 16): DEUC: N = 332 PBO: N= 333 Active Treatment Period (Week 16 to Week 52): DEUC: N = 615 **IM011055** Placebo-controlled Period (up to Week 16): DEUC: N = 312 PBO: N= 311 APR[a]: N= 105 Active Treatment Period (Week 16 to Week 52): DEUC: N = 584 APR: N= 90	DEUC 6 mg QD Matched PBO DEUC 6 mg QD Matched PBO Apremilast 30 mg BID	Ongoing Ongoing

Study	Design/Primary Objectives	Population	Number of Treated Subjects	Regimen and Dose	Study Status
Supportive Study					
IM011084	Phase 2, randomized, double-blind, Placebo-controlled study to evaluate the efficacy and safety of DEUC **Primary Objective:** • Assess the dose-response relationship of DEUC (6 or 12 mg QD) at Week 16 in the treatment of subjects with active PsA **Secondary Efficacy Objectives at Week 16:** • Assess the dose-response relationship of DEUC (6 or 12 mg QD): – In daily functional activities (ie, HAQ-DI and SF-36 PCS) – In reducing PsO severity – In Patient-reported Outcomes Refer to Table 1.3.3-1 of the SCE[44] for additional secondary efficacy objectives/endpoints up to Week 16 and exploratory efficacy objectives/endpoints up to Week 52.	Adults (≥18 years) with PsA for ≥ 6 months, with at least 1 confirmed ≥ 2 cm lesion of plaque psoriasis, having active arthritis (a minimum of ≥ 3 swollen joints and ≥ 3 tender joints), and who are either biologic-naïve (approximately 70% of the study population) or who have failed or been intolerant to 1 TNFi (TNFi-experienced, approximately 30% of the study population)	Part A: Double-blind, Placebo-controlled (up to Week 16): DEUC 6 mg QD: N = 70 DEUC 12 mg QD: N = 67 PBO: N= 66 Part B: Double-blind, double-dummy (Week 16 to Week 52): Treatment group depended on Part A treatment and (in DEUC arms) achievement of MDA at Week 16. PBO-UST: N = 55 With MDA: DEUC 6 mg QD-DEUC 6 mg QD: N = 13 DEUC 12 mg QD-DEUC 12 mg QD: N = 16 Without MDA: DEUC 6 mg QD-UST: N = 47 DEUC 12 mg QD-UST: N = 42	DEUC 6 or 12 mg QD Ustekinumab SQ at Weeks 16, 20, 32, and 44 Matched PBO	Complete

[a] Safety reference arm, not included in efficacy assessments

2.4.1. Dose response study

Method

IM011084 was a two-part, randomised, double-blind, placebo-controlled, multicenter phase 2 study and was designed to evaluate the efficacy and safety of multiple doses of DEUC in subjects with

active PsA. The study was conducted in a mixed population of subjects with active PsA who were biologic-naïve (approximately 70%) or TNFi-experienced (approximately 30%).

It was divided into 4 parts: screening period (up to 4 weeks), Part A (double blind, placebo-controlled treatment for 16 weeks), Part B (optional double-bind, double-dummy controlled treatment for 36 weeks), and follow up (up to 4 weeks after either completing Part B)

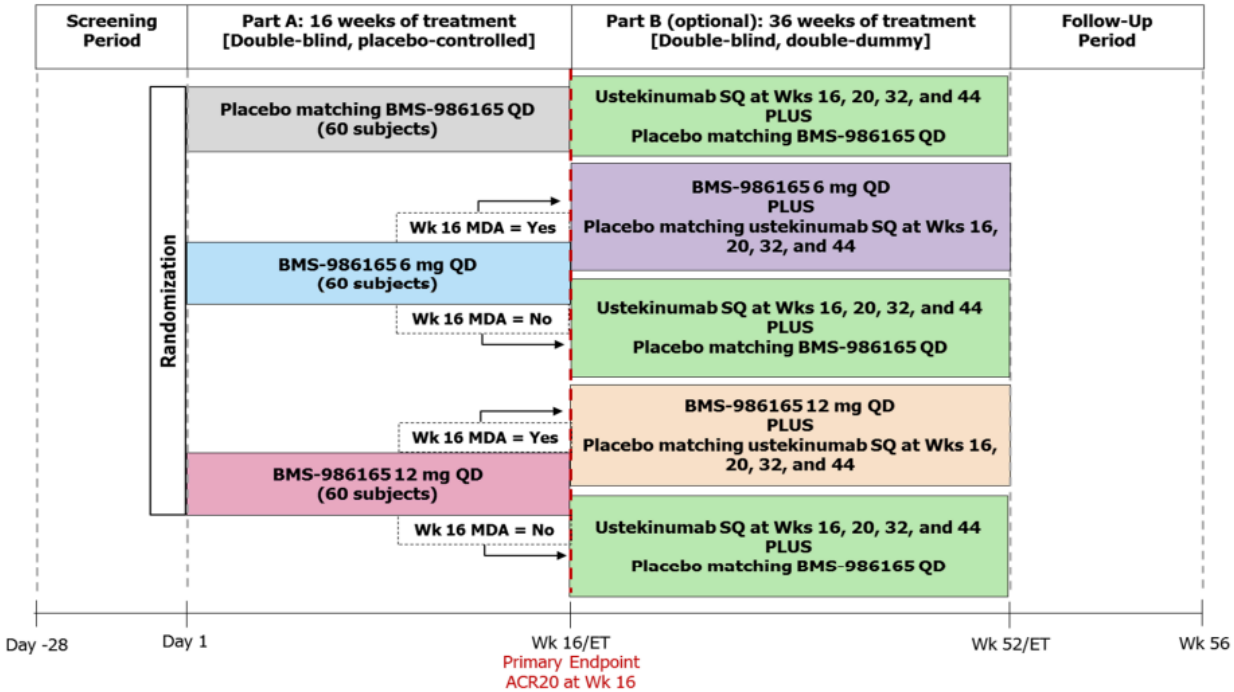
Following the screening process, eligible participants were randomised in a 1:1:1 ratio to one of the following three treatment groups through week 16: Deucravacitinib 6 mg QD, 12 mg QD, and placebo.

From Week 16 to Week 52, participants previously on placebo were switched to ustekinumab (per approved PsA labeling). Those who received DEUC and achieved MDA (minimal disease activity) continued on the same dose, while those who did not achieve MDA were switched to ustekinumab (Figure 15).

MDA response is where an MDA responder is defined as a subject fulfilling 5 of 7 of the following outcomes: tender joint count ≤ 1, swollen joint count ≤ 1, PASI ≤ 1 or body surface area (BSA) ≤ 3%, Subject Global Assessment of pain ≤ 15, Subject Global Assessment of disease activity ≤ 20, HAQ-DI ≤ 0.5, Tender entheseal points ≤ 1

The most commonly concomitant therapy used csDMARD was methotrexate: 59.1% of the placebo group, 50.0% of the DEUC 6 mg QD group, and 55.2% of the DEUC 12 mg group.

Figure 15. Study Design Schematic of study IM011084.



Notes:
1) Subjects that complete Part A (16 weeks of treatment) will be offered the opportunity to enroll in Part B (36 weeks of treatment)
2) Completion of Week 16 of Part A and the start of Part B will occur on the same day
3) Subjects that complete Part A but decline Part B will proceed into the Follow-Up Period
4) Subjects who discontinue investigational product during Part A or Part B will have an Early Termination (ET) visit followed by the Follow-Up Period
5) Treatment assignment in Part B will depend on the subject's Part A randomized treatment as well as if the subject met MDA at Week 16 (Part A)
6) At Week 48, subjects will discuss with their Investigator/treating physician plans for treatment with ustekinumab following study completion. Subjects electing to take ustekinumab following study completion will receive either an ustekinumab SQ injection or placebo matching ustekinumab SQ injection at Week 52.

Primary and secondary objectives and endpoints are presented in Table 11.

Table 11. Objectives and Endpoints of study IM011084

Objectives	Endpoints
Primary	
Efficacy	
Assess the dose-response relationship of BMS-986165 (6 or 12 mg once daily [QD]) at Week 16 in the treatment of subjects with active PsA	• ACR 20 response
Secondary	
Efficacy	
Assess the dose-response relationship of BMS-986165 (6 or 12 mg QD) at Week 16 in daily functional activities	• Change from baseline in HAQ-DI score
Assess the dose-response relationship of BMS-986165 (6 or 12 mg QD) at Week 16 in reducing psoriasis (PsO) severity	• PASI 75 response
Assess the dose-response relationship of BMS-986165 (6 or 12 mg QD) at Week 16 in Patient-reported Outcomes	• Change from baseline in the PCS score of the SF-36 Questionnaire

Results

A total of 314 subjects were screened at 67 sites in 7 countries. Of the screened subjects, 203 subjects were randomised. The FPFV date was 01-Apr-2019, the last patient randomisation date was 30-Dec-2019, and the LPLV date for Part A was 27-Apr-2020. For Part B of this study, the FPFV date was 01-Apr-2019 and the LPLV date for was 27-Jan-2021.

Study IM011084 met its primary objective of showing a statistically significant dose-response relationship of deucravacitinib (6 mg QD and 12 mg QD) in the primary endpoint ACR 20 response rate at Week 16 for the treatment of subjects with active PsA (Table 12).

Table 12. Summary of Primary, Secondary, and Additional Efficacy Endpoints at Week 16: Part A- Full Analysis Set

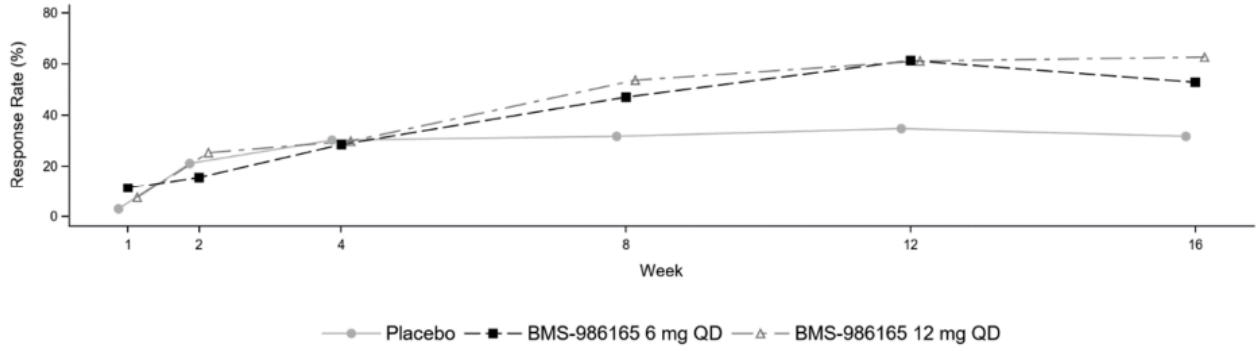
Response	Placebo N=66	BMS-985165 6 mg QD N=70	BMS-985165 12 mg QD N=67
Primary Endpoint			
ACR 20 Response			
Responders (%)	21 (31.8)	37 (52.9)	42 (62.7)
Imputed responses (%)	8 (12.1)	7 (10.0)	7 (10.4)
Response rate (95% CI)	31.8 (20.6, 43.1)	52.9 (41.2, 64.6)	62.7 (51.1, 74.3)
Adjusted odds ratio (95% CI) vs placebo	NA	2.40 (1.19, 4.84)	3.59 (1.75, 7.35)
Slope coefficient of dose (95% CI) p-value	0.11 (0.05, 0.17) <0.001		

Response	Placebo N=66	BMS-985165 6 mg QD N=70	BMS-985165 12 mg QD N=67
Secondary Endpoints			
Change from Baseline in HAQ-DI Score			
Change from baseline mean (SD)	-0.15 (0.420)	-0.38 (0.525)	-0.42 (0.567)
Adjusted change from baseline mean (SE) 95% CI for mean	-0.11 (0.066) (-0.24, 0.02)	-0.37 (0.065) (-0.50, -0.24)	-0.39 (0.067) (-0.53, -0.26)
Difference vs placebo in adjusted mean change from baseline (SE) 95% CI for difference	NA	-0.26 (0.082) (-0.42, -0.10)	-0.28 (0.083) (-0.45, -0.12)
p-value	NA	0.0020	0.0008
Slope coefficient of dose (95% CI) p-value	-0.02 (-0.04, -0.01) 0.0009		
PASI 75 (in subjects with ≥ 3% BSA involvement at baseline)			
Total number of subjects	54	59	52
Responders (%)	11 (20.4)	25 (42.4)	31 (59.6)
Imputed responses (%)	6 (11.1)	5 (8.5)	6 (11.5)
Response rate (95% CI)	20.4 (9.6, 31.1)	42.4 (29.8, 55.0)	59.6 (46.3, 73.0)
Adjusted odds ratio (95% CI) vs placebo	NA	2.89 (1.25, 6.70)	5.81 (2.44, 13.81)
Slope coefficient of dose (95% CI) p-value	0.14 (0.08, 0.22) <0.001		
Change from Baseline in SF-36 PCS			
Change from Baseline Mean (SD)	2.8 (6.41)	5.9 (7.25)	5.9 (8.31)
Adjusted change from baseline mean (SE) 95% CI for Mean	2.3 (0.97) (0.4, 4.2)	5.6 (0.94) (3.8, 7.5)	5.8 (0.97) (3.9, 7.7)
Difference vs placebo in adjusted mean change from baseline (SE) 95% CI for difference	NA	3.3 (1.19) (0.9, 5.7)	3.5 (1.21) (1.1, 5.9)
p-value	NA	0.0062	0.0042

Response	Placebo N=66	BMS-985165 6 mg QD N=70	BMS-985165 12 mg QD N=67
Change from Baseline in SF-36 PCS			
Slope coefficient of dose (95% CI) p-value	0.29 (0.09, 0.49) 0.0044		

A higher proportion of subjects in both active treatment groups achieved an ACR20 response at Week 16 compared with placebo. The time course of ACR20 responses by treatment group from Week 1 through Week 16 is presented in Figure 16.

Figure 16. ACR 20 Response by Treatment Group, Week 1 through Week 16 – Full Analysis Set



2.4.2. Main studies

Study IM011054

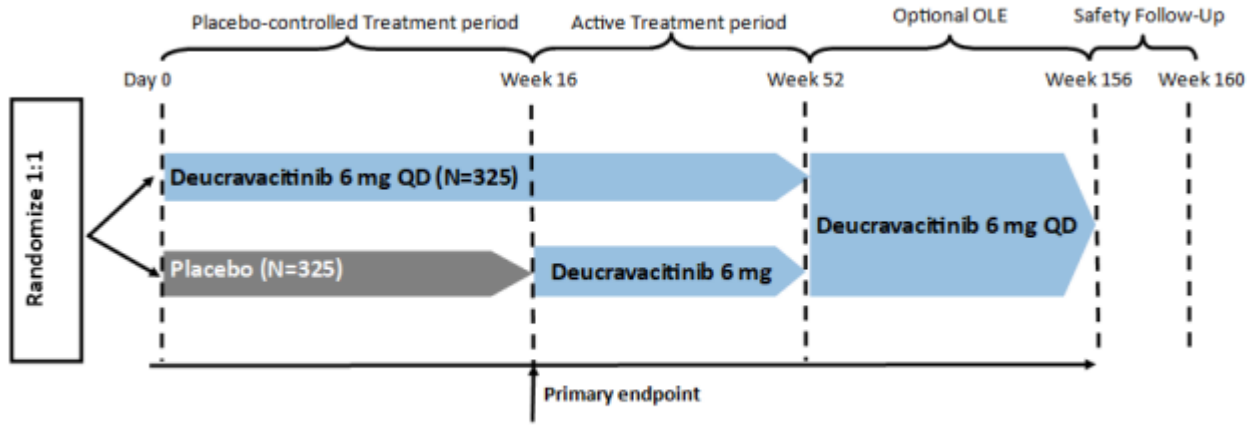
Methods

This was a 52-week, multi-center, randomised, double-blind, placebo-controlled Phase 3 comparing deucravacitinib to placebo in participants with active PsA who are naïve to biologic therapy. After completion of the 52-week visit, eligible patients could be enrolled in an optional 104-week, single-arm OLE study.

The duration of study participation was up to 164 weeks divided into the following periods (Figure 17):

- Screening Period (28 days)
- Treatment Period (52 weeks), comprised of:
    - Placebo-controlled Treatment Period (16 weeks) (Week 0 to Week 16)
    - Reallocation and continued Active Treatment Period with DEUC (36 weeks) (Week 16 to Week 52)
- Optional OLE Period (104 weeks) (Week 52 OLE to Week 156)
- Safety Follow-up Period (30 days) (following last dose of investigational product [IP] unless participant has continued in study for 30 days or more after discontinuation of IP)

Figure 17. Study Design Schematic of study IM011054



Abbreviations: N, number; OLE, Open-label Long-term Extension; QD, once daily.

Study participants

Key Inclusion Criteria:

– Participants willing to participate in the study and informed consent form signed

- active disease (see Table 13)

- adequate exposure to csDMARDs/TNFi (see Table 13)

- stable dose of concurrent csDMARDs (see Table 13)

Key Exclusion Criteria:

– Participant has nonplaque PsO (i.e., guttate, pustular, erythrodermic or drug-induced PsO) at Screening or Day 1.

– Participant has any other autoimmune condition such as systemic lupus erythematous, mixed connective tissue disease, multiple sclerosis, or vasculitis.

– Participant has prior history of or current inflammatory joint disease other than PsA (e.g., gout, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease).

– Participant has active (i.e., currently symptomatic) fibromyalgia whose symptoms or therapy will significantly impact the assessment of PsA disease manifestations and activity in the opinion of the investigator.

– Participant has received an approved or investigational biologic therapy for the treatment of PsA or PsO.

– Participant has received a JAK inhibitor for the treatment of PsA and/or PsO.

Table 13. Definitions of Active Disease, Insufficient Response/Treatment Failure, and Adequate Exposure to Prior Treatment

ACTIVE DISEASE

In both studies:

- Participant has active plaque psoriatic skin lesion(s) or documented medical history of plaque PsO at Screening.
- Participant has active arthritis as shown by ≥ 3 swollen joints and ≥ 3 tender joints (66/68 joint counts) at Screening and Day 1.

In IM011054 only:

- Participant has ≥ 1 PsA-related hand and/or foot joint erosion on X-ray during Screening Period that is confirmed by central reading. –
- Participant has hsCRP ≥ 3 mg/L at Screening

ADEQUATE EXPOSURE TO csDMARDs /TNFi

Participants were eligible for enrolment if they had received an adequate duration of prior therapy and had experienced documented inadequate response, loss of response, or intolerance to at least one of the following:

- In both studies:
  - A csDMARD (e.g., methotrexate, sulfasalazine, leflunomide, hydroxychloroquine) at maximally tolerated dose after a minimum of 12 weeks of therapy.
  - An NSAID after a minimum of 4 weeks of therapy.
- In IM011055 only:

- A TNFi (e.g., etanercept, adalimumab, golimumab, certolizumab pegol) after a minimum of 12 weeks, or infliximab after a minimum of 14 weeks (i.e., at least 4 doses). A shorter duration was acceptable if documentation of inadequate response was provided and reviewed by the Medical Monitor.

STABLE DOSE OF CONCURRENT csDMARDs

In both studies:

- Concurrent use of 1 csDMARD, and/or NSAID, and/or oral glucocorticoid is permitted but not required during the study.
  - If such treatment was administered, then participants must meet the following requirements:

    1) If on csDMARD (MTX, SSZ, LEF, hydroxychloroquine [HCQ]), the participant must have been on it for at least 12 weeks and be on a stable dose for at least 28 days prior to Day 1.

    (a) If on MTX, the route of administration and dose must be stable and the dose must be ≤ 25 mg/week.

    (b) If on SSZ, the dose must be ≤ 3 g/day.

    (c) If on HCQ, the dose must be ≤ 400 mg/day.

    (d) If on LEF, the dose must be ≤ 20 mg/day.

    Note: If currently not on MTX, SSZ, or HCQ, the participant must have not received it for at least 28 days prior to Day 1. If currently not on LEF, the participant must not have received it for at least 12 weeks prior to Day 1.

    2) If on NSAID, the participant must be on a stable dose for at least 14 days prior to Day 1.

    3) If on oral glucocorticoids, the participant must be on a stable dose of ≤ 10 mg/day prednisone equivalent for at least 28 days prior to Day 1.

    Note: If currently not on oral glucocorticoids, the participant must not have received oral glucocorticoids within 28 days prior to Day 1.

Treatments

Following the screening process, eligible participants were randomised in a 1:1 ratio to one of the following two treatment groups through week 16:

- Deucravacitinib 6 mg QD oral (selected based on observed efficacy and safety data of phase 2 study IM011084)
- Placebo QD oral

From Week 16 to Week 52, all participants received deucravacitinib 6 mg QD. Those originally randomised to placebo were reallocated, in a blinded manner with respect to their initial assignment. After Week 52, participants were offered enrolment into an optional open-label extension (OLE), during which they received deucravacitinib 6 mg QD orally up to Week 156.

Use of concomitant background medications (csDMARD and/or NSAID and/or glucocorticoid) was allowed during the study at a stable dose, when given for pre-specified periods prior to enrolment. (see Table 13).

During the optional OLE Period, topical treatments/medications, medicated shampoos, and phototherapy could be used as additional treatment for psoriasis.

From Week 16 to Week 156, all participants were eligible to receive rescue therapy. All efficacy and safety assessments had to be performed prior to starting rescue therapy. Rescue options that did not require discontinuation of IP included adjustment or initiation of NSAIDs, short oral or intra-articular glucocorticoid courses, dose increases of background glucocorticoids, dose escalation or initiation of csDMARDs (methotrexate, sulfasalazine, or leflunomide within protocol-specified limits), and short-term use of high-potency topical steroids for psoriasis symptoms.

Rescue therapies that required discontinuation of IP included initiation of a biologic DMARD (e.g., TNF, IL-17, IL-12/23, or IL-23 inhibitors), JAK inhibitors, or phosphodiesterase-4 inhibitors.

Objectives

The primary objective was to compare the efficacy of deucravacitinib to placebo in the treatment of participants with active PsA.

The secondary objectives of the study were:

- To compare the efficacy of deucravacitinib to placebo as assessed by HAQ-DI score at Week 16
- To compare the efficacy of deucravacitinib to placebo as assessed by PASI 75 response at Week 16
- To compare the efficacy of deucravacitinib to placebo as assessed by SF-36 PCS score at Week 16
- To compare the efficacy of deucravacitinib to placebo in MDA response at Week 16
- To compare the efficacy of deucravacitinib to placebo in enthesitis resolution at Week 16
- To compare the efficacy of deucravacitinib to placebo as assessed by structural damage at Week 16
- To compare the efficacy of deucravacitinib to placebo in FACIT-Fatigue score at Week 16
- To compare the efficacy of deucravacitinib to placebo in dactylitis resolution at Week 16

- To compare the efficacy of deucravacitinib to placebo at Week 16 as assessed by DAS28-CRP

Outcomes/endpoints

The primary efficacy endpoint for this study was the proportion of participants meeting ACR 20 response at Week 16. The ACR20 definition of improvement is a 20% improvement over baseline in tender (total= 68) and swollen (total= 66) joint counts and a 20% improvement in 3 of the 5 remaining core data set measures: Subject global assessment of disease activity, Subject global assessment of pain, HAQ-DI, Physician global assessment of PsA, hsCRP

The secondary efficacy endpoints for this study were amongst others:

- Change from baseline in HAQ-DI score at Week 16
- Proportion of participants meeting PASI 75 response at Week 16, in participants with at least 3% BSA involvement AND at least sPGA 2 at baseline
- Change from baseline in the SF-36 PCS score at Week 16
- Proportion of participants meeting achievement of MDA where an MDA response is achievement of 5 of 7 following outcomes at Week 16: Tender joint count ≤ 1, Swollen joint count ≤ 1, PASI ≤ 1 or BSA ≤ 3%, Patient assessment of PsA pain ≤ 15, Patient Global Assessment of PsA disease activity ≤ 20, HAQ-DI ≤ 0.5, Tender enthesial points ≤ 1

Sample size

A planned total sample size of approximately 650 subjects randomised in a 1:1 ratio in a blinded fashion (approximately 325 subjects each randomised to DEUC 6 mg QD arm and placebo arm) was determined to provide > 99% power to detect a 20% treatment difference between DEUC 6 mg QD and placebo at Week 16 for ACR 20 response assuming a response of 55% in the DEUC 6 mg QD group and of 35% in the placebo group (2-sided alpha = 0.05, chi-square test).

The planned sample size of 325 subjects treated with DEUC 6 mg QD in this study was also chosen to provide, along with subjects from other Phase 3 PsA study with DEUC (IM011055) an adequate number of subjects for the overall safety database for the PsA program.

This planned sample size was also estimated to provide enough power for all key secondary endpoints (that were tested in a testing strategy to control Type I error). The power calculations for the enthesitis resolution and dactylitis resolution were based on pooled data from the 2 phase 3 studies IM011054 and IM011055.

The targeted effect sizes used in the power calculations were based on results from the Phase 2 study IM011084 and on results of golimumab, guselkumab, secukinumab, ixekizumab, and upadacitinib (for modified total Sharp score).

Randomisation

Following the screening process, all eligible participants were centrally randomised using IRT, as per the study protocol.

Blinding (masking)

Blinding treatment assignments were managed using IRT. IP supply was controlled by IRT at each visit. All tablets were identical in appearance and were supplied in bottles, with each daily dose made up of the appropriate active or placebo tablet to provide the correct treatment. Information about treatment assignment was restricted from all subjects, site, and BMS personnel prior to Week 16 DBL (Data base Lock) as described in the approved protocol.

Statistical methods

Efficacy Analyses

All efficacy analyses were conducted on the Randomised Population unless otherwise stated. All analyses were tested using a 2-sided 0.05 level of significance, unless otherwise specified.

- Primary Endpoint
    - Main Estimand for the Primary Objective

The main estimand for the primary endpoint of this study is the difference in the proportion of subjects who achieved an ACR 20 response at Week 16 between deucravacitinib 6 mg QD and placebo in active PsA subjects who are naïve to biologic disease modifying anti-rheumatic drugs.

This estimand applies a complex estimand to the intercurrent events (ICEs) that considers both the composite variable strategy and the treatment policy strategy. Summary of the attributes of the main estimand for the primary objective:

-**Treatment:** Deucravacitinib 6 mg QD and placebo

-Population: All randomised participants with Active PsA

-Variable: ACR 20 response (yes/no) at Week 16

-**Intercurrent Events (ICEs):**

1. Treatment discontinuation (for any reason) prior to Week 16: Composite variable strategy (Early treatment discontinuation is a clinically relevant mode of treatment failure).
2. Rescue medication therapy prior to Week 16: Treatment policy strategy (Use of 1 or more rescue medications is a component of a broader treatment policy).

-**Population-level Summary**: Difference in the proportion of participants, with active PsA, who achieved an ACR 20 response at Week 16 between Deucravacitinib 6 mg QD and placebo

- Analysis Model

The primary efficacy analysis approach for the primary endpoint, ACR 20 response at Week 16 (responder/nonresponder), used a CMH test stratified by screening hsCRP concentration (< 10 mg/L versus ≥ 10 mg/L), and by csDMARD use at baseline (yes/no) to compare the response rates of DEUC 6 mg QD to placebo. The risk difference, odds ratio and the corresponding 2-sided 95% confidence interval are provided. Clopper-Pearson estimation method was used to estimate the confidence interval. The efficacy analysis model used to evaluate the supplemental estimand for the primary objective is similar to the analysis model used to evaluate the main estimand for the primary objective.

- Handling ICEs for the Main Estimand

Treatment discontinuation (for any reason) prior to Week 16: the composite outcome is set to zero=non-response (composite variable strategy; Rescue medication therapy prior to Week 16: No additional action is required in the data handling convention for that ICE.

- Handling Missing Data

Missing ACR20 composite response was treated with non-responder imputation (NRI) which assumes that the probability of responding for participants with missing data is zero.

- Sensitivity Analyses to Explore Missing Data Assumptions

A sensitivity analysis using a tipping point approach was conducted for the primary endpoint at Week 16 to examine the impact of missing data.

- Supplemental Estimand of the Primary Objective (Supportive analysis)

The supplemental estimand used similar efficacy analysis model and missing data methods as the main estimand, with the only difference being the handling of ICEs.

For the Supplemental Estimand, all ACR20 response data collected at Week 16 are used in the analysis regardless of the occurrence of an ICE:

1. Treatment discontinuation (for any reason) prior to Week 16: Treatment policy strategy.
2. Rescue medication therapy prior to Week 16: Treatment policy strategy.

- Key Secondary Efficacy Endpoints

  - Binary Key Secondary Endpoints:

Outcome measurements include PASI 75 Response at Week 16 (in subset), enthesitis resolution at Week 16 (in subset), dactylitis resolution at Week 16 (in subset), and MDA response at Week 16.

The efficacy analysis approach used to evaluate the main and supplemental estimands for each binary key secondary objective were similar to the analysis approach used to evaluate the main and supplemental estimands for the primary objective.

  - Continuous Key Secondary Endpoints:

Outcome measurements include Change from baseline in HAQ-DI score, SF-36 PCS score, PsA-modified SvdH score (structural damage), FACIT-Fatigue score, and DAS28 CRP score at Week 16.

- Main Estimand for the key secondary objectives with a continuous endpoint

Summary of the attributes of the main estimand for the key secondary objectives with a continuous endpoint:

-**Treatment:** Deucravacitinib 6 mg QD and placebo

-Population: All randomised participants with Active PsA

-Variable: As defined above.

-**Intercurrent Events (ICEs):**

A) ***All except PsA-modified SvdH score:***

1. Treatment discontinuation (for any reason) prior to Week 16: Composite variable strategy (Early treatment discontinuation is a clinically relevant mode of treatment failure. The

Week 16 value of the continuous endpoint was set to zero to imply no improvement nor worsening relative to baseline.).

2. Rescue medication therapy prior to Week 16: Treatment policy strategy (Use of 1 or more rescue medications is a component of a broader treatment policy).

B) *PsA-modified SvdH score:*

1. Treatment discontinuation (for any reason) prior to Week 16: Treatment policy strategy (Early treatment discontinuation is a component of a broader treatment policy.)
2. Rescue medication therapy prior to Week 16: Treatment policy strategy (Use of 1 or more rescue medications is a component of a broader treatment policy).

-**Population-level Summary**: Difference in mean change from baseline to Week 16 between Deucravacitinib 6 mg QD and placebo.

- Analysis Model

The efficacy analysis models for the main estimands of the continuous secondary objectives are ANCOVA models. Each model includes change from baseline of the key secondary measure as the dependent variable and treatment, randomisation stratification variables, and baseline value of the key secondary measure as independent variables. The adjusted mean change from baseline (LS Means) with SE and 95% CI per treatment group and the difference between DEUC 6 mg QD to placebo in adjusted mean change from baseline with SE and 95% CI are provided from each analysis model. P-values are based on the Wald test.

- Handling ICEs for the Main Estimand

A) *All except PsA-modified SvdH score:*

1. Treatment discontinuation (for any reason) prior to Week 16: Change from baseline value is set to zero (composite variable strategy).
2. Rescue medication therapy prior to Week 16: No additional action is required in the data handling convention for that ICE (treatment policy strategy)

B) *PsA-modified SvdH score:*

The main estimand for the analyses of PsA-modified SvdH score applied a treatment policy strategy to all ICEs.

- Handling Missing Data

Missing values were imputed with MI method assuming missing not at random (MNAR). The MNAR imputation assumes that after discontinuation of treatment, participants from the deucravacitinib 6 mg QD group (if they would have continued deucravacitinib 6 mg QD) exhibit a similar future evolution as participants from the placebo group.

- Sensitivity Analyses to Explore Missing Data Assumptions

Sensitivity analyses using Multiple Imputation with Pattern Mixture Models were conducted to examine the impact of missing data.

- Supplemental Estimand of Continuous Key Secondary Objectives (Supportive analysis) **with the exception of PsA-modified SvdH Score)**

The supplemental estimand used similar efficacy analysis model and missing data methods as the main estimand for each continuous key secondary objective, with the only difference being the handling of ICEs.

- Subgroup Analyses

Subgroup analyses of primary endpoint were performed using logistic regression models to evaluate the consistency of the treatment difference at Week 16 based on the main estimand of the primary objective, inclusive of the approaches used to handle ICEs and missing data.

The subgroups that were evaluated include: Geographic region, Country, Sex, Age group (<40 y, 40-<65 y, ≥65 y), Body weight categories (<90 kg; ≥90 kg) – from case report form, BMI categories (<25 kg/m2, 25-<30 kg/m2, 30-<35 kg/m2, >35 kg/m2), Race, Baseline non-biologic DMARD use history (yes/no), Baseline csDMARD use (yes/no), Baseline glucocorticoid use (yes/no), Baseline MTX use (yes/no), Baseline NSAID use (yes/no), Baseline disease severity (DAS28 <5.1 vs DAS28 ≥5.1), Baseline number of swollen joints (≤4 vs >4), Baseline presence of enthesitis (yes/no), Baseline presence of dactylitis (yes/no), Screening hsCRP (<10 mg/L vs <10 mg/L; as determined by IRT), Duration of disease at screening (< median y, ≥ median y).

- Adjustments for Multiplicity:

To control the overall Type I error rate at 5%, a testing strategy for the primary and key secondary endpoints was implemented. The primary endpoint, ACR 20 response at Week 16, was tested at two-sided 0.05 significance level. If the primary endpoint was significant at alpha = 0.05, then statistical analysis of the key secondary endpoints was performed in a hierarchical fashion.

The data from studies IM011054 and IM011055 were pooled for the analysis of the key secondary endpoints, enthesitis resolution and dactylitis resolution.

To preserve the overall Type I error rate, a fixed-sequence testing method was implemented for the below specified endpoints. Testing order of secondary endpoints was in the below order and could only proceed to the next secondary endpoint if the null hypothesis was rejected at two-sided alpha = 0.05 for the prior endpoint showing a significant treatment difference in that endpoint. If an endpoint failed at any step, then all subsequent p-values were considered nominal.

There was no multiplicity adjustment for testing of additional secondary endpoints analyses. Nominal p-values were to be provided as descriptive statistics only.

Changes to planned analyses

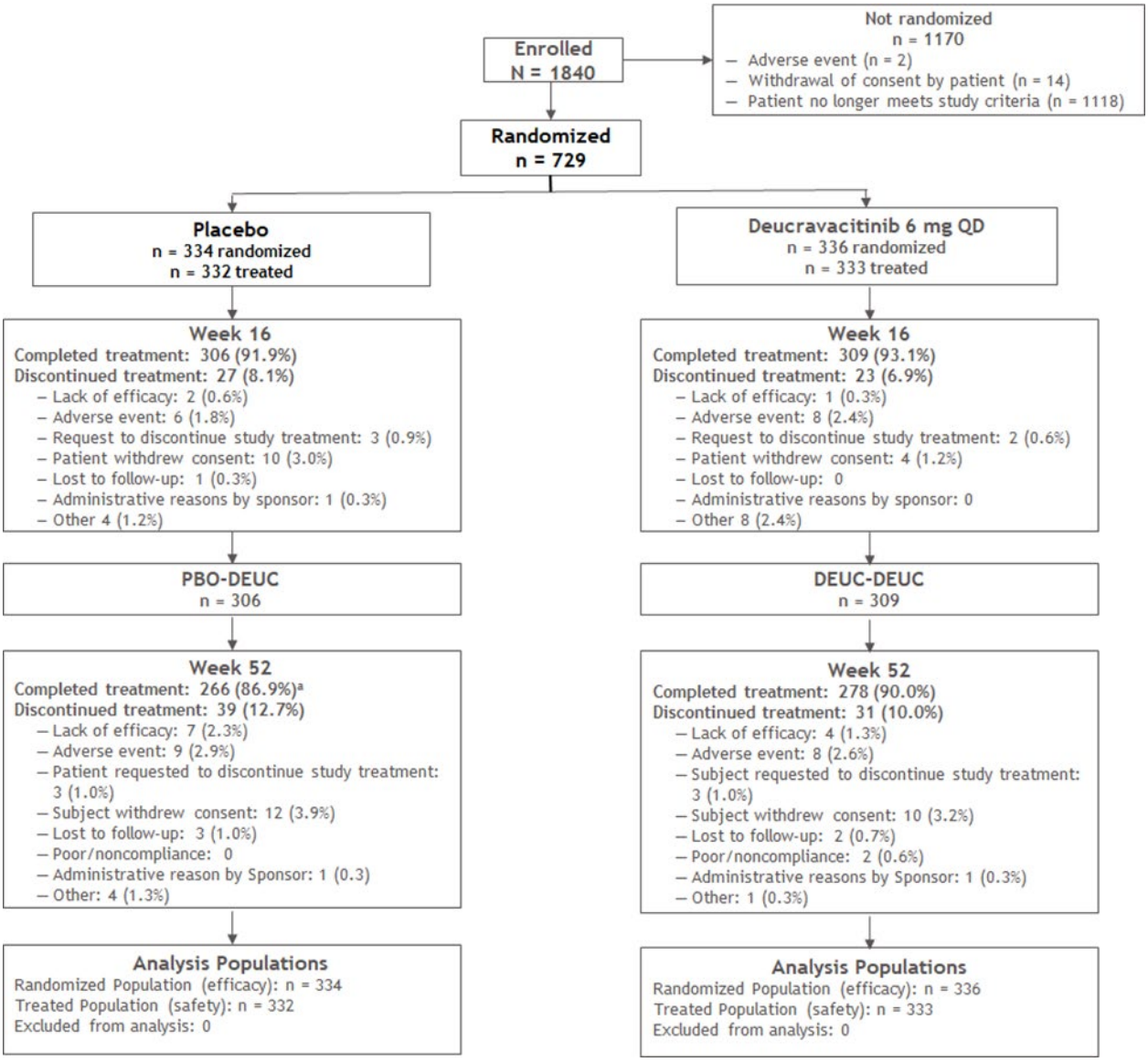
- Tipping point analysis:

In the statistical analysis plan (SAP), the purpose of the prespecified tipping point analysis of the binary endpoint was to evaluate the impact of the composite variable estimand strategy as well as the use of NRI as the missing data handling approach (i.e., subjects with an ICE are treated as nonresponders in the tipping point analysis instead of ICEs being treated as separate modes of treatment failure). Per the SAP, an exhaustive tipping point analysis was to be conducted by changing the status of nonresponders due to ICE and nonresponders due to missing data to responders. As performed in this study, the tipping point analysis was only designed to evaluate the impact of missing data handling, meaning only the status of nonresponders due to missing data was changed to responders, while nonresponders due to ICE were still considered as nonresponders.

Results

Participant flow

Figure 18: Participant flow diagram



[a] One additional subject completed the Active Treatment Period on 04-Mar-2025 but data were entered in the clinical database after the CSR addendum data cut-off date, on 09-May-2025, thus this subject is not included in the total for completed treatment.

Recruitment

Subjects were recruited across 155 sites in 21 countries (Argentina, Australia, Brazil, Bulgaria, Chile, China mainland, Colombia, Czech Republic, Finland, France, Hungary, Ireland, Italy, Mexico, Poland, Romania, Russia, Spain, Taiwan, United Kingdom, and United States).

Conduct of the study

The original protocol for this study was dated 11-Mar-2021. As of the 10-Oct-2024 data cut-off date, there were 2 global revisions (with 2 global amendments), 12 country-specific amendments,

and 9 administrative letters. During the Placebo-controlled Period, the most common category of important protocol deviations (IPD) in both arms were trial procedures and study intervention (study treatment). During the Active Treatment Period, the most common category of IPD in both arms was informed consent and/or ethics.

After unblinding, quality issues with lab samples were retrospectively identified in study IM011054 with 0.04% samples assayed outside the stability window, affecting inclusion/exclusion criteria and endpoint assessments (including the primary ACR20 response). Post-hoc exclusions and sensitivity analyses were conducted.

Baseline data

Table 14. Baseline Demographic Characteristics Summary, Randomised Population of IM011054 study

	DEUC 6 mg N = 336	PBO N = 334	Total N = 670
AGE (YEARS)			
N	336	334	670
MEAN (SD)	51.7 (12.52)	52.3 (12.32)	52.0 (12.41)
MEDIAN (MIN, MAX)	52.0 (23, 86)	52.0 (21, 83)	52.0 (21, 86)
AGE CATEGORIZATION n (%)			
<45	98 (29.2)	83 (24.9)	181 (27.0)
45 - 65	187 (55.7)	194 (58.1)	381 (56.9)
≥ 65	51 (15.2)	57 (17.1)	108 (16.1)
SEX n(%)			
MALE	172 (51.2)	164 (49.1)	336 (50.1)
FEMALE	164 (48.8)	170 (50.9)	334 (49.9)
RACE n (%)			
WHITE	263 (78.3)	279 (83.5)	542 (80.9)
BLACK OR AFRICAN AMERICAN	4 (1.2)	1 (0.3)	5 (0.7)
AMERICAN INDIAN OR ALASKA NATIVE	17 (5.1)	19 (5.7)	36 (5.4)
OTHER	27 (8.0)	21 (6.3)	48 (7.2)
ASIAN	25 (7.4)	14 (4.2)	39 (5.8)
CHINESE	24 (7.1)	14 (4.2)	38 (5.7)
ASIAN OTHER	1 (0.3)	0	1 (0.1)
ETHNICITY n(%)			
HISPANIC OR LATINO	101 (30.1)	94 (28.1)	195 (29.1)
NOT HISPANIC OR LATINO	165 (49.1)	165 (49.4)	330 (49.3)
NOT REPORTED	70 (20.8)	75 (22.5)	145 (21.6)
COUNTRY BY GEOGRAPHIC REGION n(%)			
NORTH AMERICA	51 (15.2)	50 (15.0)	101 (15.1)
MEXICO	32 (9.5)	26 (7.8)	58 (8.7)
UNITED STATES OF AMERICA	19 (5.7)	24 (7.2)	43 (6.4)

	DEUC 6 mg N = 336	PBO N = 334	Total N = 670
SOUTH/LATIN AMERICA	88 (26.2)	97 (29.0)	185 (27.6)
EUROPE	171 (50.9)	172 (51.5)	343 (51.2)
ASIA	25 (7.4)	13 (3.9)	38 (5.7)
CHINA	15 (4.5)	7 (2.1)	22 (3.3)
TAIWAN, PROVINCE OF CHINA	10 (3.0)	6 (1.8)	16 (2.4)
REST OF THE WORLD	1 (0.3)	2 (0.6)	3 (0.4)
AUSTRALIA	1 (0.3)	2 (0.6)	3 (0.4)
BASELINE WEIGHT (KG)			
N	334	334	668
MEAN (SD)	84.22 (18.571)	82.41 (17.108)	83.31 (17.864)
MEDIAN (MIN, MAX)	83.00 (38.5, 138.5)	80.40 (43.0, 133.6)	82.05 (38.5, 138.5)
WEIGHT CATEGORIZATION n (%)			
< 90 KG	220 (65.5)	227 (68.0)	447 (66.7)
≥ 90 KG	114 (33.9)	107 (32.0)	221 (33.0)
NOT REPORTED	2 (0.6)	0	2 (0.3)
BASELINE BMI (KG/M^2)			
N	332	334	666
MEAN (SD)	30.26 (6.391)	29.61 (5.617)	29.94 (6.019)
MEDIAN (MIN, MAX)	29.40 (15.6, 57.2)	29.19 (17.0, 46.2)	29.30 (15.6, 57.2)

Age presented is age at date of informed consent.

Table 15. Baseline Disease Characteristics Summary, Randomised Population

	DEUC 6 mg N = 336	PBO N = 334	Total N = 670
BASELINE CSDMARD USE FROM CRF n (%)			
YES	237 (70.5)	231 (69.2)	468 (69.9)
NO	99 (29.5)	103 (30.8)	202 (30.1)
DURATION OF DISEASE (YEARS)	N = 333	N = 334	N = 667
MEAN (SD)	7.27 (8.287)	8.03 (7.604)	7.65 (7.955)
MEDIAN (MIN, MAX)	4.59 (-0.1, 60.2)	5.42 (0.3, 41.8)	4.96 (-0.1, 60.2)[a]
PSA SUB-TYPE n (%)			
POLYARTHRITIS	262 (78.0)	261 (78.1)	523 (78.1)
OLIGOARTHRITIS	36 (10.7)	33 (9.9)	69 (10.3)
PREDOMINANT DISTAL INTERPHALANGEAL JOINT INVOLVEMENT	29 (8.6)	27 (8.1)	56 (8.4)
PREDOMINANT AXIAL INVOLVEMENT	1 (0.3)	5 (1.5)	6 (0.9)

	DEUC 6 mg N = 336	PBO N = 334	Total N = 670
ARTHRITIS MUTILANS	5 (1.5)	8 (2.4)	13 (1.9)
NOT REPORTED	3 (0.9)	0	3 (0.4)
PSA PHENOTYPE n (%)			
PERIPHERAL ARTHRITIS	278 (82.7)	285 (85.3)	563 (84.0)
PERIPHERAL PLUS PSORIATIC SPONDYLOARTHRITIS	55 (16.4)	49 (14.7)	104 (15.5)
NOT REPORTED	3 (0.9)	0	3 (0.4)
BASELINE ACR COMPONENTS:			
BASELINE TENDER (68) JOINT COUNT	N = 334	N = 333	N = 667
MEAN (SD)	19.0 (12.79)	19.0 (13.74)	19.0 (13.26)
MEDIAN (MIN, MAX)	16.0 (1, 66)	15.0 (3, 68)	15.0 (1, 68)
BASELINE SWOLLEN (66) JOINT COUNT	N = 334	N = 333	N = 667
MEAN (SD)	10.7 (6.86)	10.3 (7.47)	10.5 (7.17)
MEDIAN (MIN, MAX)	9.0 (3, 53)	8.0 (0, 66)	9.0 (0, 66)
BASELINE SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY	330	331	661
MEAN (SD)	63.6 (22.55)	63.4 (20.12)	63.5 (21.35)
MEDIAN (MIN, MAX)	66.0 (50.0, 80.0)	63.0 (51.0, 77.0)	65.0 (51.0, 78.0)
BASELINE SUBJECT GLOBAL ASSESSMENT OF PAIN	330	331	661
MEAN (SD)	64.5 (20.03)	62.6 (20.07)	63.6 (20.06)
MEDIAN (MIN, MAX)	66.0 (52.0, 79.0)	64.0 (52.0, 77.0)	65.0 (52.0, 78.0)
BASELINE HAQ-DI SCORE	N = 330	N = 331	N = 661
MEAN (SD)	1.4061 (0.62753)	1.3308 (0.61844)	1.3684 (0.62366)
MEDIAN (MIN, MAX)	1.5000 (0.000, 3.000)	1.375 (0 0.000, 3.000)	1.5000 (0.000, 3.000)
BASELINE HSCRP (MG/L)	N = 336	N = 334	N = 670
MEAN (SD)	12.909 (16.0611)	14.180 (19.3990)	13.543 (17.8015)
MEDIAN (MIN, MAX)	7.390 (0.36, 112.50)	7.825 (0.36, 181.54)	7.605 (0.36, 181.54)
BASELINE PASI SCORE IN SUBJECTS WITH AT LEAST 3% BSA AND AT LEAST SPGA 2 AT BASELINE	N = 162	N = 170	N = 332
MEAN (SD)	8.94 (6.185)	9.66 (7.761)	9.31 (7.035)
MEDIAN (MIN, MAX)	7.80 (1.2, 39.6)	7.40 (1.2, 57.7)	7.55 (1.2, 57.7)
BASELINE PASI SCORE n (%)			
≤ 1	69 (20.5)	71 (21.3)	140 (20.9)

	DEUC 6 mg N = 336	PBO N = 334	Total N = 670
> 1	262 (78.0)	261 (78.1)	523 (78.1)
NOT REPORTED	5 (1.5)	2 (0.6)	7 (1.0)
BASELINE BSA n (%)			
≤ 3%	153 (45.5)	139 (41.6)	292 (43.6)
> 3%	178 (53.0)	193 (57.8)	371 (55.4)
NOT REPORTED	5 (1.5)	2 (0.6)	7 (1.0)
BASELINE TENDER ENTHESIAL POINTS (LEI) n (%)			
< 1	154 (45.8)	165 (49.4)	319 (47.6)
≥ 1	178 (53.0)	167 (50.0)	345 (51.5)
NOT REPORTED	4 (1.2)	2 (0.6)	6 (0.9)
BASELINE LEEDS ENTHESITIS INDEX (LEI)[b]	N = 178	N = 167	N = 345
MEAN (SD)	2.6 (1.53)	2.3 (1.44)	2.4 (1.49)
MEDIAN (MIN, MAX)	2.0 (1, 6)	2.0 (1, 6)	2.0 (1, 6)
BASELINE SPARCC ENTHESITIS INDEX[c]	N = 216	N = 211	N = 427
MEAN (SD)	5.1 (3.72)	4.2 (3.41)	4.7 (3.59)
MEDIAN (MIN, MAX)	4.0 (1, 16)	3.0 (1, 16)	4.0 (1, 16)
BASELINE TENDER DACTYLITIS COUNT	N = 132	N = 108	N = 240
MEAN (SD)	3.6 (3.70)	3.0 (3.50)	3.3 (3.62)
MEDIAN (MIN, MAX)	2.0 (1, 19)	2.0 (1, 20)	2.0 (1, 20)
BASELINE TENDER DACTYLITIS COUNT n (%)	N = 336	N = 334	N = 670
< 1	199 (59.2)	224 (67.1)	423 (63.1)
≥ 1	132 (39.3)	108 (32.3)	240 (35.8)
NOT REPORTED	5 (1.5)	2 (0.6)	7 (1.0)
BASELINE DACTYLITIS INDEX (LDI)	N = 137	N = 112	N = 249
MEAN (SD)	67.328 (122.9399)	53.543 (78.2663)	61.128 (105.2491)
MEDIAN (MIN, MAX)	31.952 (-125.00, 907.16)	25.113 (0.00, 506.78	29.508 (-125.00, 907.16)
BASELINE FACIT-FATIGUE SCORE	N= 330	N= 331	N= 661
MEAN (SD)	28.9 (11.11)	29.4 (10.77)	29.2 (10.94)
MEDIAN (MIN, MAX)	29.0 (3, 51)	30.0 (5, 52)	29.0 (3, 52)
BASELINE SF-36 PCS SCORE	N= 330	N= 331	N= 661
MEAN (SD)	34.802 (7.6539)	35.175 (7.9406)	34.989(7.7951)
MEDIAN (MIN, MAX)	34.255 (16.04, 61.67)	34.390 (15.74, 56.92)	34.340 (15.74, 61.67)

[a] CRF entry for date of disease onset was incomplete for 1 subject. Imputation resulted in an apparent negative disease duration.

[b] Baseline LEI score is based on the number of subjects in the Randomized Population with enthesitis at baseline by LEI.
[c] Baseline SPARCC Enthesitis Index is based on the number of subjects in the Randomized Population with enthesitis at baseline by SPARCC.

Table 16. Medications of Interest at Day 1 Summary – Treated Population

Category	DEUC 6 mg N = 332	PBO N = 333	Total N = 665
bDMARD	0	0	0
csDMARD	235 (70.8)	230 (69.1)	465 (69.9)
NSAID	190 (57.2)	200 (60.1)	390 (58.6)
Corticosteroid	56 (16.9)	58 (17.4)	114 (17.1)
Opioid	8 (2.4)	10 (3.0)	18 (2.7)
Retinoid	0	0	0
Vitamin D Analog	4 (1.2)	7 (2.1)	11 (1.7)
Non-opioid Analgesic	17 (5.1)	19 (5.7)	36 (5.4)
JAK Inhibitor	0	0	0
Other	0	0	0

UMC WHO Drug Global Dictionary: DDEHDBSEP24.
A generic name may appear in multiple therapeutic classes to represent overall medication use.
Subjects are counted only once at the anatomic class and therapeutic class levels.
Medications at Day 1 are defined as medications used at first dose date of study medication.

Numbers analysed

The first patient was enrolled on 21 Jul 2021. As of the cut-off date 10 Oct 2024, the Placebo-controlled Period is completed (Week0-16), and a total of 615 subjects entered the Active Treatment Period (Week 16-52) which is still ongoing.

As of the clinical data cutoff (10-Oct-2024) for the IM011054 Primary CSR, 670 subjects were randomised: 336 to the DEUC 6 mg QD arm and 334 to the PBO arm. Of these, 665 subjects were treated (332 with DEUC 6 mg QD and 333 with PBO).

During the procedure updated data were submitted with a data cutoff of 09-May-2025 corresponding to the last subject's Week 52 visit in IM011054.

Outcomes and estimation

Primary endpoint

The primary efficacy endpoint of this study, the proportion of participants who achieved an ACR20 response at Week 16, was met.

Table 17. ACR 20 Response at Week 16 – Main Estimand-Randomised

	DEUC 6 mg N = 336	PBO N = 334
TOTAL NUMBER OF SUBJECTS	336	334
RESPONDERS n (%)	182 (54.2)	114 (34.1)
NONRESPONDERS n (%)	154 (45.8)	220 (65.9)
NONRESPONDERS DUE TO ICE n (%)	19 (5.7)	23 (6.9)
NONRESPONDERS DUE TO MISSING DATA n (%)	11 (3.3)	9 (2.7)
RESPONSE RATE	54.2	34.1
(95% CI)	(48.7, 59.6)	(29.1, 39.5)
DIFFERENCE VS PLACEBO	20.0	N.A.
(95% CI)	(12.7, 27.4)	N.A.
P-VALUE	< 0.0001	N.A.
ODDS RATIO VS PLACEBO	2.29	N.A.
(95% CI)	(1.67, 3.13)	N.A.

Total number of subjects is the number of subjects in the Randomized Population.
Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for use of rescue medication therapy prior to Week 16.
The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using Cochran Mantel Haenszel (CMH) test stratified by screening hsCRP concentration (< 10 mg/L, ≥ 10 mg/L) and csDMARD use at baseline (yes/no).
Missing ACR20 composite response is treated with nonresponder imputation.

Key secondary efficacy endpoints

Analysis did not demonstrate a statistically significant difference between DEUC and PBO for the 5th pre-specified secondary endpoint of enthesitis resolution per LEI (in the pooled analysis of IM011054 and IM011055). Therefore, analysis obtained for the subsequent endpoints in the hierarchy, i.e., FACIT-fatigue, dactylitis resolution (in the pooled analysis of IM011054 and IM011055), and DAS28-CRP, are considered explorative only.

- Change from baseline in HAQ-DI score at Week 16 (Table 18)

Table 18. Change from Baseline in HAQ-DI Score at Week 16- Main Estimand – Randomised Population

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
BASELINE		
N1	330	331
MEAN (SD)	1.4061 (0.62753)	1.3308 (0.61844)
MEDIAN	1.5000	1.3750
MIN, MAX	0.000, 3.000	0.000, 3.000
WEEK 16		
N1	327	327
MEAN (SD)	0.9973 (0.64800)	1.1170 (0.68841)
MEDIAN	1.0000	1.2500
MIN, MAX	0.000, 3.000	0.000, 2.875
CHANGE FROM BASELINE AT WEEK 16		
N1	326	327
MEAN (SD)	-0.4103 (0.52303)	-0.2118 (0.51583)
MEDIAN	-0.2500	-0.1250
MIN, MAX	-2.125, 1.500	-2.250, 1.250
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES(SE)	-0.3850 (0.02897)	-0.2163- (0.02888)
95% CONFIDENCE INTERVAL FOR MEAN	(-0.4418, -0.3282)	(-0.2729, -0.1597)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	-0.1688 (0.03850)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(-0.2442, -0.0933)	N.A.
P VALUE	<0.0001	N.A.

N1 represents the total number of subjects at the visit timepoint.
Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables,

- Proportion of participants meeting PASI 75 response at Week 16, in participants with at least 3% BSA involvement AND at least sPGA 2 at baseline (Table 19)

Table 19. Change from baseline in PASI 75 at Week 16- Main Estimand – Randomised Population

PASI 75 Response at Week 16- Main Estimand - Randomized Population

	DEUC 6 mg N = 336	PBO N = 334
TOTAL NUMBER OF SUBJECTS	162	170
RESPONDERS n (%)	84 (51.9)	12 (7.1)
NONRESPONDERS n (%)	78 (48.1)	158 (92.9)
NONRESPONDERS DUE TO ICE n (%)	9 (5.6)	14 (8.2)
NONRESPONDERS DUE TO MISSING DATA n (%)	7 (4.3)	2 (1.2)
RESPONSE RATE (%)	51.9	7.1
(95% CI)	(43.9, 59.8)	(3.7, 12.0)
DIFFERENCE VS PLACEBO (%)	44.1	N.A.
(95% CI)	(35.4, 52.7)	N.A.
P-VALUE	<0.0001	N.A.
ODDS RATIO VS PLACEBO	14.08	
(95% CI)	(7.19, 27.59)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with at least 3% BSA and at least sPGA 2 at baseline. Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by screening hsCRP concentration (< 10 mg/L, >= 10 mg/L) and csDMARD use at baseline (yes/no). Missing PASI 75 Response is treated with nonresponder imputation.
Source: Table 14.2.2.1.5

- Change from baseline in the SF-36 PCS score at Week 16 (Table 20)

Table 20. Change from baseline in SF-36 PCS Score at Week 16, Randomized Population

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
BASELINE		
N1	330	331
MEAN (SD)	34.802 (7.6539)	35.175 (7.9406)
MEDIAN	34.255	34.390
MIN, MAX	16.04, 61.67	15.74, 56.92
WEEK 16		
N1	327	327
MEAN (SD)	41.252 (8.3978)	39.037 (8.0811)
MEDIAN	40.610	39.440
MIN, MAX	18.77, 60.15	20.13, 59.12
CHANGE FROM BASELINE AT WEEK 16		
N1	326	327
MEAN (SD)	6.410 (8.2883)	3.847 (7.2929)
MEDIAN	5.230	2.700
MIN, MAX	-27.86, 40.57	-13.33, 39.98
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES(SE)	6.055 (0.4103)	3.711 (0.4086)
95% CONFIDENCE INTERVAL FOR MEAN	(5.250, 6.859)	(2.910, 4.512)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	2.344 (0.5445)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(1.277, 3.411)	N.A.
P VALUE	<0.0001	N.A.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables.

Composite variable strategy is used for treatment discontinuation prior to week 16 to set change from baseline to zero.

Treatment policy strategy used for use of rescue therapy prior to week 16.

Missing data are imputed by control-based pattern multiple imputation.

Observed data after adjusting for ICE are used for descriptive statistics. Imputed data after considering ICE and multiple imputation are used in ANCOVA model.

N1 represents the total number of subjects at the visit timepoint.

Source: Table 14.2.2.3.2

- Proportion of participants meeting achievement of MDA at Week 16:

Table 21. MDA Response at Week 16 - Main Estimand, Randomised Population

Table 14.2.2.1.8
MDA Response at Week 16 - Main Estimand
Randomized Population

	DEUC 6 mg N = 336	PBO N = 334
TOTAL NUMBER OF SUBJECTS	336	334
RESPONDERS n (%)	64 (19.0)	34 (10.2)
NON RESPONDERS n (%)	272 (81.0)	300 (89.8)
NON RESPONDERS DUE TO ICE n (%)	19 (5.7)	23 (6.9)
NON RESPONDERS DUE TO MISSING DATA n (%)	10 (3.0)	7 (2.1)
RESPONSE RATE (%)	19.0	10.2
(95% CI)	(15.0, 23.7)	(7.2, 13.9)
DIFFERENCE VS PLACEBO (%)	8.9	N.A.
(95% CI)	(3.6, 14.2)	N.A.
P-VALUE	0.0012	N.A.
ODDS RATIO VS PLACEBO	2.08	N.A.
(95% CI)	(1.33, 3.26)	N.A.

Total number of subjects is the number of subjects in the Randomized Population.
ICE: Intercurrent event.
Responders are subjects fulfilling 5 of 7 of the MDA outcomes.
MDA: Minimal Disease Activity.
Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method.
N.A.: Not Applicable. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by screening hsCRP concentration (< 10 mg/L, >= 10 mg/L) and csDMARD use at baseline (yes/no).
Missing MDA Response is treated with non-responder imputation.
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- Proportion of participants meeting enthesitis resolution (score of 0) among participants with enthesitis at baseline by LEI at Week 16 (Table 22)

Enthesitis resolution was evaluated in the subset of subjects with at least 1 tender entheseal point at baseline. Using LEI as the assessment tool, this accounted for nearly one half of the subject population (n = 178 [53.0%] in the DEUC group and 167 [50.0%] in the PBO group).

No statistically significant difference was observed between the groups at week 16. At this stage, the hierarchical testing procedure was discontinued; therefore, subsequent efficacy results are considered nominal and should be interpreted descriptively

Table 22. Enthesitis by LEI Resolution at Week 16- Main Estimand - Randomised Population - IM011054

	DEUC 6 mg N = 336	PBO N = 334
TOTAL NUMBER OF SUBJECTS	178	167
RESPONDERS n (%)	86 (48.3)	77 (46.1)
NONRESPONDERS n (%)	92 (51.7)	90 (53.9)
NONRESPONDERS DUE TO ICE n (%)	12 (6.7)	16 (9.6)
NONRESPONDERS DUE TO MISSING DATA n (%)	3 (1.7)	3 (1.8)
RESPONSE RATE (%)	48.3	46.1
(95% CI)	(40.8, 55.9)	(38.4, 54.0)
DIFFERENCE VS PLACEBO (%)	3.0	N.A.
(95% CI)	(-7.3, 13.4)	N.A.
P-VALUE	0.5699	N.A.
ODDS RATIO VS PLACEBO	1.13	N.A.
(95% CI)	(0.74, 1.75)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with Enthesitis at baseline by LEI.
Resolution of enthesitis is reaching a Leeds Enthesitis index score of 0 among subjects with enthesitis at baseline by LEI.
Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method.
Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by screening hsCRP concentration (< 10 mg/L, ≥ 10 mg/L) and csDMARD use at baseline (yes/no).
Missing Enthesitis Resolution is treated with nonresponder imputation.
Source: Table 14.2.2.1.6

- Change from baseline in PsA-modified SvdH score at Week 16 (Table 23), inhibition of Progression of Structural Damage by Change from Baseline to Week 16 in Total SvdH Score

Table 23. Proportion of Subjects with no Radiographic Progression at Week 16 by Categorical Change from Baseline in Total SvdH Score, Randomised Population

Categorical Changes from Baseline in Total SvdH Score	DEUC 6 mg N = 336	PBO N = 334
Total SvdH Score Change from Baseline ≤ 0, n (%)	**200 (59.5)**	**180 (53.9)**
Nonresponders (progressors), n (%)	136 (40.5)	154 (46.1)
Nonresponders due to ICE, n (%)	19 (5.7)	23 (6.9)
Nonresponders due to missing data, n (%)	73 (21.7)	63 (18.9)
Difference vs placebo (95% CI), %	5.6 (-1.8, 13.0)	
P-value	0.1384	
Odds ratio vs placebo (95% CI)	1.26 (0.93, 1.72)	

Note: Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16.
The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a CMH test stratified by screening hsCRP concentration and csDMARD use at baseline. SDC is calculated as 1.96* SD of the paired differences of change from baseline/ square root of (2*k); k is the number of reviewers and is default to 2 in this study.
Source: Table 14.2.2.7.19.

- Change from baseline in FACIT-Fatigue score at Week 16 (Table 24)

Table 24. Change from baseline in FACIT-Fatigue score at Week 16, Randomised Population

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
BASELINE		
N1	330	331
MEAN (SD)	28.9 (11.11)	29.4 (10.77)
MEDIAN	29.0	30.0
MIN, MAX	3, 51	5, 52
WEEK 16		
N1	327	326
MEAN (SD)	33.8 (10.90)	31.6 (11.26)
MEDIAN	34.0	31.0
MIN, MAX	2, 52	2, 52
CHANGE FROM BASELINE AT WEEK 16		
N1	326	326
MEAN (SD)	4.9 (8.84)	2.2 (8.81)
MEDIAN	4.0	1.0
MIN, MAX	-18, 36	-36, 31
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES (SE)	4.6 (0.48)	2.0 (0.48)
95% CONFIDENCE INTERVAL FOR MEAN	(3.7, 5.6)	(1.1, 2.9)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	2.6 (0.63)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(1.4, 3.9)	N.A.
P VALUE	<0.0001	N.A.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables.

Composite variable estimand strategy is used for treatment discontinuation prior to week 16 which sets change from baseline to zero.

Treatment policy strategy used for use of rescue therapy prior to week 16.

Missing data are imputed by control-based pattern multiple imputation.

Observed data after adjusting for ICE are used for descriptive statistics. Imputed data after considering ICE and multiple imputation are used in ANCOVA model.

N1 represents the total number of subjects at the visit timepoint.

Source: Table 14.2.2.3.3

- Proportion of participants meeting dactylitis resolution at Week 16 among the participants with dactylitis at baseline, where resolution is defined as a tender dactylitis count of 0 in participants with a tender dactylitis count ≥ 1 at baseline (Table 25)

Table 25. dactylitis resolution at Week 16, Randomised Population-IM011054

	DEUC 6 mg N = 336	PBO N = 334
TOTAL NUMBER OF SUBJECTS	132	108
RESPONDERS n (%)	78 (59.1)	47 (43.5)
NONRESPONDERS n (%)	54 (40.9)	61 (56.5)
NONRESPONDERS DUE TO ICE n (%)	9 (6.8)	9 (8.3)
NONRESPONDERS DUE TO MISSING DATA n (%)	3 (2.3)	1 (0.9)
RESPONSE RATE (%)	59.1	43.5
(95% CI)	(50.2, 67.6)	(34.0, 53.4)
DIFFERENCE VS PLACEBO (%)	14.2	N.A.
(95% CI)	(1.7, 26.7)	N.A.
P-VALUE	0.0270	N.A.
ODDS RATIO VS PLACEBO	1.80	N.A.
(95% CI)	(1.07, 3.03)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with tender dactylitis count ≥ 1 at baseline.

Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method.

Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by screening hsCRP concentration (< 10 mg/L, ≥ 10 mg/L) and csDMARD use at baseline (yes/no).

Missing Dactylitis Resolution is treated with nonresponder imputation.

Source: Table 14.2.2.1.7

- Change from baseline in DAS28-CRP score at Week 16 (Table 26)

Table 26. Change from baseline in DAS28-CRP score at Week 16-Main Estimand, Randomised Population

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
BASELINE		
N1	330	331
MEAN (SD)	4.9855 (0.93524)	5.0175 (0.94191)
MEDIAN	4.9839	4.9265
MIN, MAX	1.909, 7.183	2.475, 7.620
WEEK 16		
N1	318	317
MEAN (SD)	3.5726 (1.22232)	4.1235 (1.28542)
MEDIAN	3.5358	4.1022
MIN, MAX	1.234, 6.793	1.325, 8.216
CHANGE FROM BASELINE AT WEEK 16		
N1	317	317
MEAN (SD)	-1.4106 (1.13277)	-0.8902 (1.10750)
MEDIAN	-1.3707	-0.7561
MIN, MAX	-4.808, 1.079	-4.254, 2.360
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES (SE)	-1.3334 (0.06378)	-0.8284 (0.06362)
95% CONFIDENCE INTERVAL FOR MEAN	(-1.4584, -1.2084)	(-0.9531, -0.7037)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	-0.5051 (0.08462)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(-0.6709, -0.3392)	N.A.
P VALUE	<0.0001	N.A.

N1 represents the total number of subjects at the visit timepoint.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables.

Composite variable estimand strategy is used for treatment discontinuation prior to week 16 which sets change from baseline to zero. Treatment policy strategy used for use of rescue therapy prior to week 16.

Missing data are imputed by control-based pattern multiple imputation.

Observed data after adjusting for ICE are used for descriptive statistics. Imputed data after considering ICE and multiple imputation are used in ANCOVA model.

Source: Table 14.2.2.3.4

Ancillary analyses

Table 27. IM011054: Subgroup Analysis of the Primary and Key Secondary Endpoints by Concomitant csDMARD Use

	With a Concomitant csDMARD			Without a Concomitant csDMARD			
	Response rate (%)[b] or Adjusted mean change from BL(SE)[c]			Response rate (%)[b] or Adjusted mean change from BL (SE)[c]			
Endpoints[a]	DEUC 6 mg (N = 237)	PBO (N = 231)	Δ (95% CI)[d]	DEUC 6 mg (N =99)	PBO (N = 103)	Δ (95% CI)[d]	Interaction p-value[e]
ACR 20	55.7%	37.7%	18.0 (8.6, 26.9)	50.5%	26.2%	24.3 (9.5, 37.3)	0.3641
HAQ-DI	-0.4008 (0.03221)	-0.2529 (0.03267)	-0.1479 (-0.2378, -0.0580)	-0.3743 (0.05072)	-0.1588 (0.04877)	-0.2155 (-0.3527, -0.0772)	0.4217

Table 27. IM011054: Subgroup Analysis of the Primary and Key Secondary Endpoints by Concomitant csDMARD Use

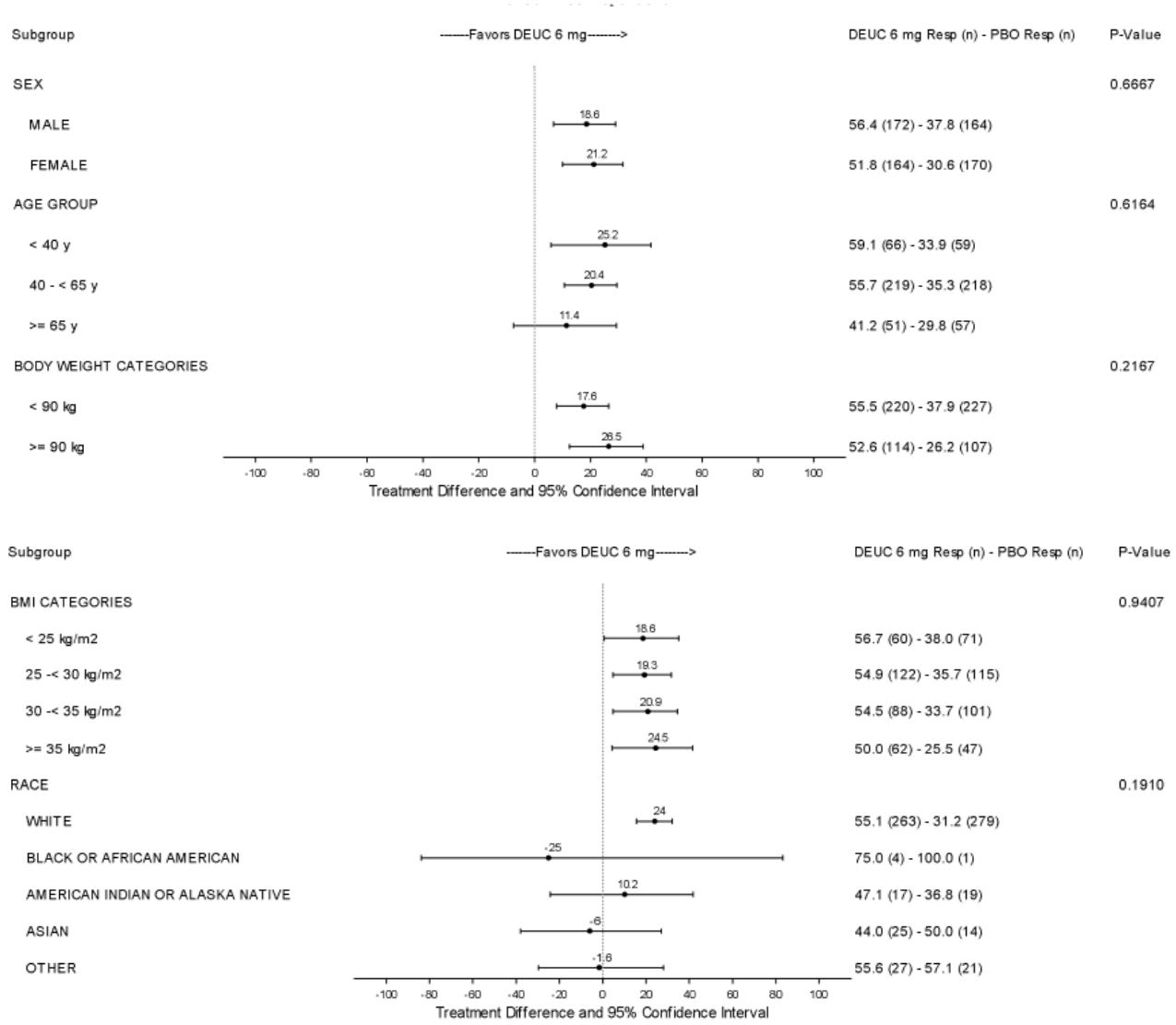
Endpoints [a]	With a Concomitant csDMARD			Without a Concomitant csDMARD			Interaction p-value[e]
	Response rate (%)[b] or Adjusted mean change from BL(SE)[c]			Response rate (%)[b] or Adjusted mean change from BL (SE)[c]			
	DEUC 6 mg (N = 237)	PBO (N = 231)	Δ (95% CI)[d]	DEUC 6 mg (N =99)	PBO (N = 103)	Δ (95% CI)[d]	
PASI 75[f]	56.5%	9.9%	46.6 (34.6, 57.4)	42.6%	2.9%	39.7 (25.7, 53.9)	0.3869
SF-36 PCS	6.531 (0.4560)	4.535 (0.4636)	1.996 (0.723, 3.270)	5.825 (0.7158)	2.723 (0.6901)	3.102 (1.151, 5.053))	0.3525
MDA	20.3%	11.7%	8.6 (1.3, 15.3)	16.2%	6.8%	9.4 (0.4, 19.0)	0.5560
Enthesitis Resolution by LEI (pooled analysis) [g]	55.5%	50.5%	5.0 (-4.6, 14.5)	40.2%	35.1%	5.1 (-7.8, 17.9)	0.9579
Enthesitis resolution by SPARCC (pooled analysis)	52.9%	37.1%	15.8 (7.4, 24.1)	35.4%	34.3%	1.1 (-10.3, 12.5)	0.0535
PsA-modified SvdH	0.56 (0.420)	0.33 (0.382)	0.23 (-0.88, 1.33)	0.91 (0.546)	0.96 (0.527)	-0.04 (-1.50, 1.42)	0.7722
- Post hoc Population 3	0.27 (0.124)	0.38 (0.128)	-0.11 (-0.46, 0.24)	0.78 (0.197)	0.96 (0.186)	-0.18 (-0.71, 0.36)	0.8437
FACIT-Fatigue	4.9 (0.53)	2.8 (0.54)	2.1 (0.6, 3.6)	4.6 (0.84)	0.8 (0.80)	3.8 (1.6, 6.1)	0.2028
Dactylitis Resolution (pooled analysis)[g]	62.8%	50.0%	12.8 (0.9, 24.8)	45.2%	34.3%	10.9 (-5.8, 27.5)	0.8777
DAS28-CRP	-1.4390 (0.07124)	-0.9550 (0.07261)	-0.4841 (-0.6832, -0.2849)	-1.2540 (0.11201)	(-0.7114 (0.10699)	-0.5426 (-0.8461, -0.2390)	0.7524

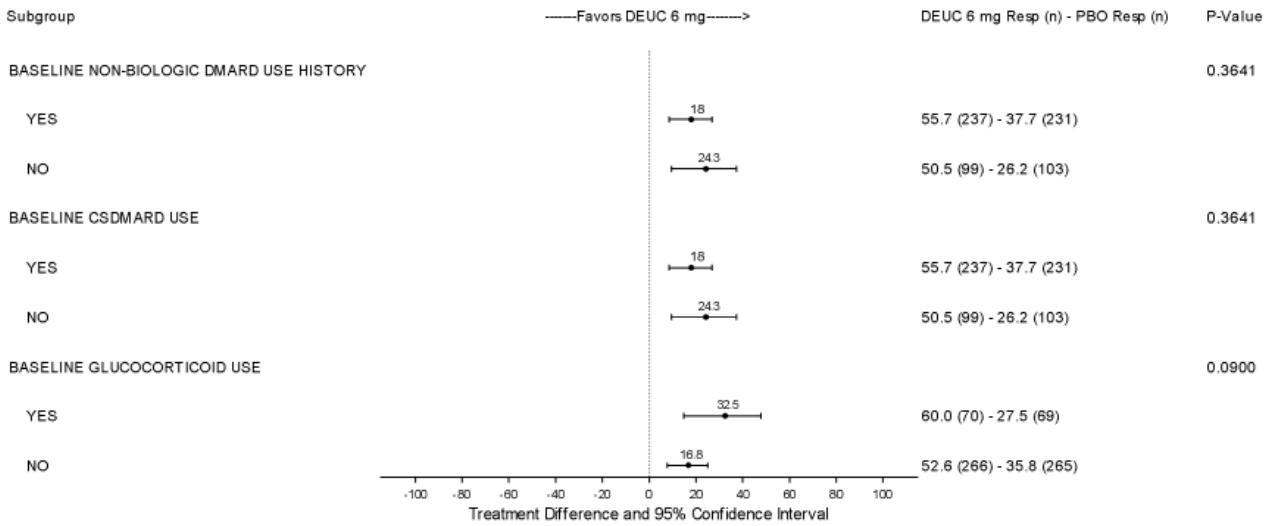
a Treatment policy strategy used for use of rescue therapy prior to Week 16. For binary endpoints, missing data are treated with non-responder imputation. For continuous endpoints, missing data are imputed by control-based pattern multiple imputation.
b Response rate is the proportion of responders to total number of subjects in the Randomized Population or within subset, as noted.
c Change from baseline analysed using ANCOVA with treatment, randomization stratification variables, and baseline value as independent variables.
d P-value is for the interaction of the treatment group with subgroup factor, based on a logistic regression model including treatment group, subgroup factor, and the interaction between treatment group and subgroup factor.
d Δ is the response rate risk difference for binary endpoint or adjusted change from baseline mean treatment difference for continuous endpoints. 95% CI for continuous endpoint is calculated using Wald method and Clopper-Pearson exact method for response rate.

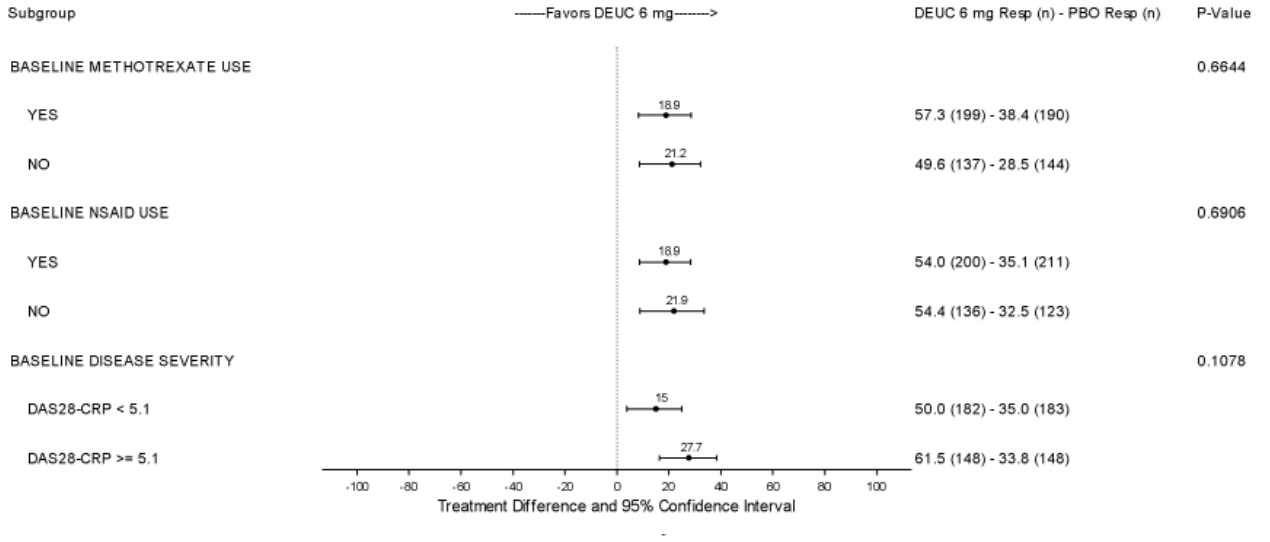
e PASI-75 is calculated among subjects with at least 3% BSA and sPGA of at least 2 at baseline.
f Enthesitis resolution and dactylitis resolution are calculated based on pooled data from Studies IM011054 and IM011055 among subjects with enthesitis or dactylitis, respectively, at baseline.

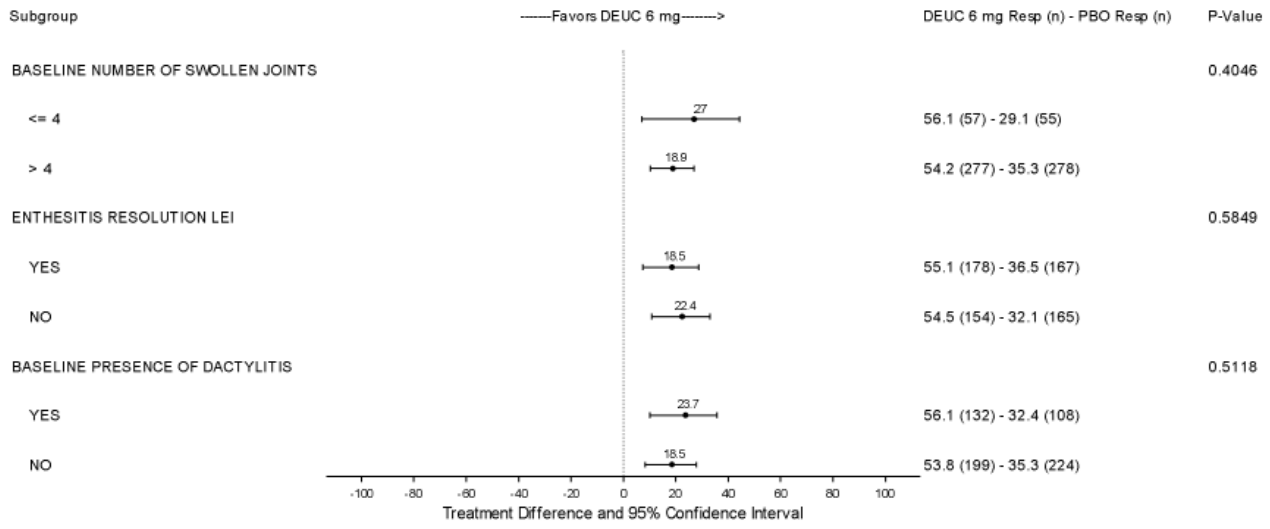
Subgroup analysis of the primary efficacy endpoint

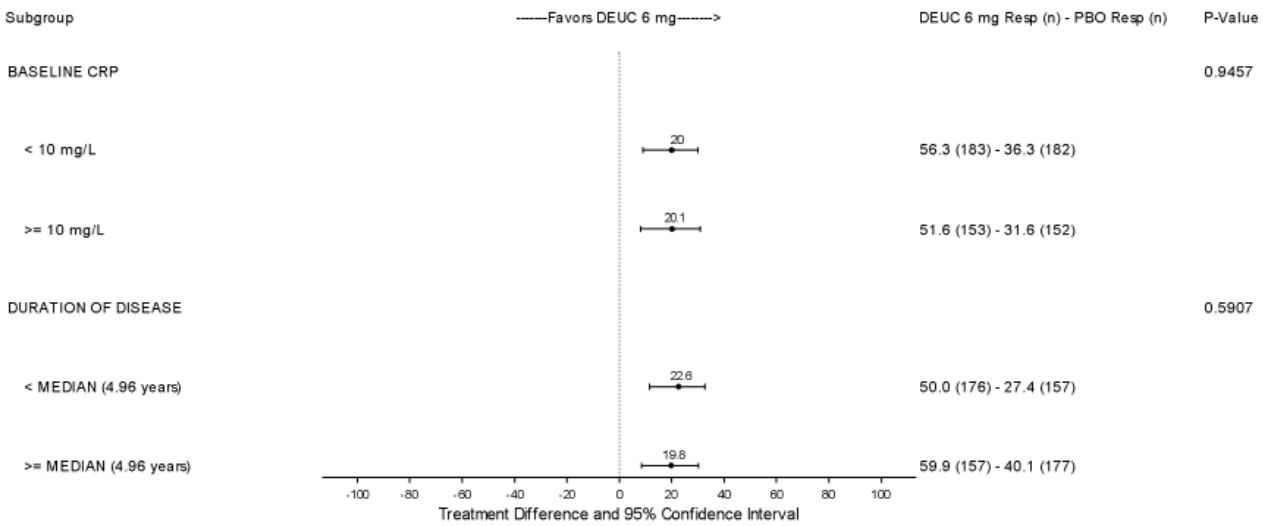
Figure 19. Forest Plot of Subgroup Analysis for ACR 20 response at Week 16 - Treatment difference for Main Estimand, Randomised Population




Subgroup
------Favors DEUC 6 mg------>
DEUC 6 mg Resp (n) - PBO Resp (n)
P-Value
BASELINE NON-BIOLOGIC DMARD USE HISTORY
0.3641
YES
18
55.7 (237) - 37.7 (231)
NO
24.3
50.5 (99) - 26.2 (103)
BASELINE CSDMARD USE
0.3641
YES
18
55.7 (237) - 37.7 (231)
NO
24.3
50.5 (99) - 26.2 (103)
BASELINE GLUCOCORTICOID USE
0.0900
YES
32.5
60.0 (70) - 27.5 (69)
NO
16.8
52.6 (266) - 35.8 (265)
-100 -80 -60 -40 -20 0 20 40 60 80 100
Treatment Difference and 95% Confidence Interval


Subgroup
------Favors DEUC 6 mg------>
DEUC 6 mg Resp (n) - PBO Resp (n)
P-Value
BASELINE METHOTREXATE USE
0.6644
YES
18.9
57.3 (199) - 38.4 (190)
NO
21.2
49.6 (137) - 28.5 (144)
BASELINE NSAID USE
0.6906
YES
18.9
54.0 (200) - 35.1 (211)
NO
21.9
54.4 (136) - 32.5 (123)
BASELINE DISEASE SEVERITY
0.1078
DAS28-CRP < 5.1
15
50.0 (182) - 35.0 (183)
DAS28-CRP >= 5.1
27.7
61.5 (148) - 33.8 (148)
-100 -80 -60 -40 -20 0 20 40 60 80 100
Treatment Difference and 95% Confidence Interval


Subgroup
------Favors DEUC 6 mg------>
DEUC 6 mg Resp (n) - PBO Resp (n)
P-Value
BASELINE NUMBER OF SWOLLEN JOINTS
0.4046
<= 4
27
56.1 (57) - 29.1 (55)
> 4
18.9
54.2 (277) - 35.3 (278)
ENTHESITIS RESOLUTION LEI
0.5849
YES
18.5
55.1 (178) - 36.5 (167)
NO
22.4
54.5 (154) - 32.1 (165)
BASELINE PRESENCE OF DACTYLITIS
0.5118
YES
23.7
56.1 (132) - 32.4 (108)
NO
18.5
53.8 (199) - 35.3 (224)
-100 -80 -60 -40 -20 0 20 40 60 80 100
Treatment Difference and 95% Confidence Interval



ACR Responses

A numerical difference was observed in proportion of subjects in the DEUC arm achieved ACR 50 and ACR70 response at Week 16 compared with the PBO arm with difference versus placebo of 11.2 [95% CI: 5.3, 17.1] and 6.2 [95% CI: 2.0, 10.4] respectively.

Table 28. ACR 50/70 Responses at Week 16 and 52, Randomised Population

	POETYK PsA-1		
	Deucravacitinib (N = 336)	**Placebo** (N = 334)	**Difference from Placebo** (95% CI)
ACR50 Response			
Week 16 (%)	24.7	13.5	11.2 (5.3, 17.1) [a]
Week 52 (%) *	48.9 (136/278)		
ACR70 Response			
Week 16 (%)	11.6	5.4	6.2 (2.0, 10.4) [b]
Week 52 (%) *	30.2 (84/278)		

Non-responder imputation (NRI) was used up to week 16. After week 16, observed data is shown with no imputation.
N is number of randomised patients.
[a] Nominal p≤0.0002
[b] Nominal p≤0.02
* Data are shown for available subjects in the format of % (n/N) observed

Change from Baseline in ACR Component Scores by Visit

At Week 16, the mean changes from baseline in all ACR components are presented below based on Tender joint count (68), Swollen joint count (66) and subject global assessment of disease activity.

Table 29. Change from Baseline in ACR 20/50/70 Components up to Week 52, Randomised population

TENDER (68) JOINT COUNT

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
WEEK 16		
N1	334	333
MEAN (SD)	9.8 (11.27)	12.6 (12.69)
MEDIAN	6.0	8.0
MIN, MAX	0, 61	0, 68
CHANGE FROM BASELINE AT WEEK 16		
N1	334	333
MEAN (SD)	-9.2 (10.97)	-6.5 (10.82)
MEDIAN	-7.0	-5.0
MIN, MAX	-60, 27	-53, 29

SWOLLEN (66) JOINT COUNT

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
WEEK 16		
N1	334	333
MEAN (SD)	4.3 (5.45)	6.4 (7.55)
MEDIAN	2.0	4.0
MIN, MAX	0, 34	0, 50
CHANGE FROM BASELINE AT WEEK 16		
N1	334	333
MEAN (SD)	-6.4 (6.69)	-3.9 (5.83)
MEDIAN	-5.0	-3.0
MIN, MAX	-47, 9	-37, 26

SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY

Timepoint Statistic	DEUC 6 mg N = 336	PBO N = 334
WEEK 16		
N1	332	332
MEAN (SD)	41.4 (24.64)	50.1 (23.91)
MEDIAN	40.0	52.0
MIN, MAX	0, 100	0, 100
CHANGE FROM BASELINE AT WEEK 16		
N1	331	331
MEAN (SD)	-22.1 (28.34)	-13.4 (26.48)
MEDIAN	-20.0	-8.0
MIN, MAX	-100, 79	-90, 72

PGA-F

The proportion of randomised subjects with PGA-F scores ≥3 at baseline who had a PGA-F 0/1 response at Week 16 are presented below.

Table 30. Proportion of subjects subset Meeting Achievement of PGA-F at Week 16, Randomised Population

Proportion of Subjects Subset Meeting Achievement of PGA-F of 0/1 up to Week 16
Randomized Population

	DEUC 6 mg N = 336	PBO N = 334
WEEK 16		
TOTAL NUMBER OF SUBJECTS	71	61
RESPONDERS n (%)	17 (23.9)	9 (14.8)
NON RESPONDERS n (%)	54 (76.1)	52 (85.2)
NON RESPONDERS DUE TO ICE n (%)	2 (2.8)	7 (11.5)
NON RESPONDERS DUE TO MISSING DATA n (%)	2 (2.8)	1 (1.6)
RESPONSE RATE (%)	23.9	14.8
(95% CI)	(14.6, 35.5)	(7.0, 26.2)
DIFFERENCE VS PLACEBO (%)	11.3	N.A.
(95% CI)	(-2.1, 24.6)	N.A.
P-VALUE	0.1147	N.A.
ODDS RATIO VS PLACEBO	2.12	N.A.
(95% CI)	(0.84, 5.39)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with a baseline PGA-F score of >= 3.
Composite variable strategy is used for treatment discontinuation prior to Week 16.
Treatment policy strategy is used for rescue medication therapy prior to Week 16.
The 95% CI is calculated using Clopper-Pearson exact method.
Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by screening hsCRP concentration and csDMARD use at baseline.
Missing PGA-F score achievement is treated with non-responder imputation. N.A. = Not Applicable.
ICE: Intercurrent event.

Study IM011055

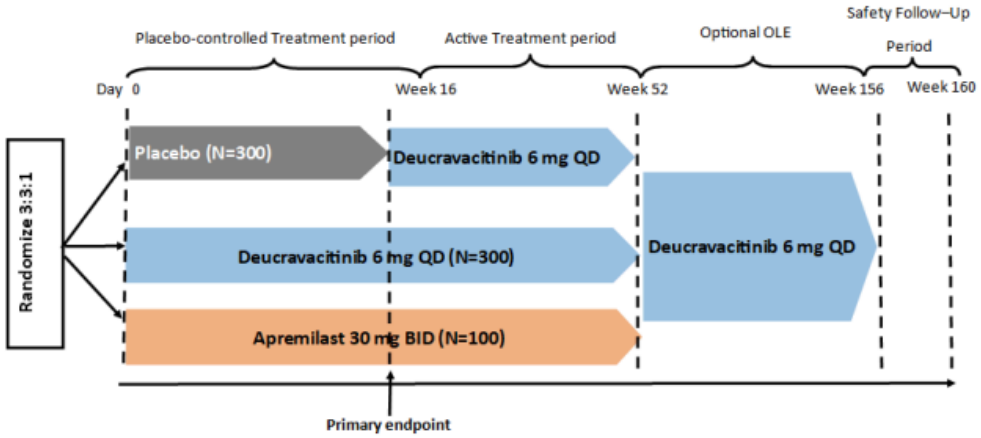
Methods

This was a Phase 3, 52-week, multi-center, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of deucravacitinib versus placebo in participants with active PsA who were naïve to bDMARDs or had previously received TNFα inhibitor treatment, with an optional 104-week single-arm OLE Period to eligible participants after completion of the 52-week Visit.

The duration of study participation was up to 164 weeks and divided into the following periods: Figure 20.

- Screening Period (28 days)
- Treatment Period (52 weeks), comprised of:
    - o Placebo-controlled Treatment Period (16 weeks) (Week 0 to Week 16)
    - o Reallocation and continued Active Treatment Period (36 weeks) (Week 16 to Week 52)
- Optional OLE Period (104 weeks) (Week 52 OLE to Week 156)
- Safety Follow-up Period (30 days) (following last dose of IP unless participant has continued in study for 30 days or more after discontinuation of IP)

Figure 20. Study Design Schematic IM011055



Note: Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
Abbreviations: BID, twice daily; N, number; OLE, Open-label Long-term Extension; QD, once daily.

Study participants

Key Inclusion Criteria:

- Participants willing to participate in the study and informed consent form signed.
- active disease (see Table 13)
- adequate exposure to csDMARDs/TNFi (see Table 13)
- stable dose of concurrent csDMARDs (see Table 13)

Key Exclusion Criteria:

- Participant has nonplaque PsO (i.e., guttate, pustular, erythrodermic or drug-induced PsO) at Screening or Day 1.
- Participant has any other autoimmune condition such as systemic lupus erythematous, mixed connective tissue disease, multiple sclerosis, or vasculitis.
- Participant has prior history of or current inflammatory joint disease other than PsA (e.g., gout, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease).
- Participant has active (i.e., currently symptomatic) fibromyalgia whose symptoms or therapy will significantly impact the assessment of PsA disease manifestations and activity in the opinion of the investigator.
- Participant has received a biologic disease-modifying anti-rheumatic drug (bDMARD) other than TNFi for the treatment of PsA and/or PsO (e.g., agents that modulate lymphocyte trafficking [e.g., natalizumab, efalizumab], agents that modulate B cells or T cells [e.g., alemtuzumab, abatacept, alefacept, or visilizumab], monoclonal antibodies against interleukin [IL]-17 [e.g., secukinumab, ixekizumab, brodalumab, bimekizumab], IL-12/IL-23p40 [e.g., ustekinumab], or IL-23 [e.g., guselkumab, risankizumab, tildrakizumab, mirikizumab]).
- Participant has received > 2 TNFis or has had documented inadequate response or loss of response to > 1 TNFi for the treatment of PsA and/or PsO.

- Participant has received a Janus kinase inhibitor (e.g., baricitinib, tofacitinib, upadacitinib) for the treatment of PsA and/or PsO.
- Participant has received a phosphodiesterase 4 inhibitor (e.g., apremilast) for the treatment of PsA and/or PsO.

Treatments

Following the 28 days screening process, eligible participants were randomised in a 3:3:1 ratio to one of the following three treatment groups through week 16 (stratified globally by TNFi exposure [Yes/No], screening hsCRP concentration [< 10 mg/L versus ≥ 10 mg/L], and by csDMARD use at baseline [Yes/No]):

- Deucravacitinib 6 mg QD orally (selected based on observed efficacy and safety data of phase 2 study IM011084)
- Placebo orally
- Apremilast 30 mg twice daily (BID) orally: This was supplied in an 18-day titration kit as follows: one 10 mg tablet in the morning on Day 1; two 10 mg tablets (one in the morning, one in the evening) on Day 2; one 10 mg tablet in the morning and one 20 mg tablet in the evening on Day 3; two 20 mg tablets (one in the morning, one in the evening) on Day 4; one 20 mg tablet in the morning and one 30 mg tablet in the evening on Day 5; one 30 mg tablet in the morning and one 30 mg tablet in the evening for each Day 6 through Day 18.

From Week 16 to Week 52, participants previously on placebo switched to DEUC while those in the DEUC arm continued with DEUC and participants on apremilast remained on apremilast until Week 52.

After Week 52, participants were offered enrolment into an optional OLE period, during which they received deucravacitinib 6 mg QD orally up to Week 152.

Use of concomitant background medications (1 csDMARD and/or 1 NSAID and/or 1 glucocorticoid) was allowed during the study at a stable dose for pre-specified periods prior to enrolment (see Table 13).

In the optional OLE period, additional psoriasis treatments such as topical therapies, medicated shampoos, and phototherapy were permitted at the investigator's discretion.

Rescue therapy could be provided prior to Week 16 only after consultation with the Medical Monitor. From Week 16 to Week 156, participants were eligible to receive rescue therapy at the discretion of the investigator. If rescue therapy was required at Week 16, all efficacy and safety assessments were performed prior to initiation. After Week 16, assessments were conducted prior to rescue therapy whenever possible until Week 52. Consultation with the Medical Monitor was also required if rescue therapy was needed > 2 times between Week 16 and Week 52 or > 2 times between Week 52 OLE and Week 156.

Rescue therapy that did not require discontinuation of IP included: initiation, switch, or dose increase of NSAIDs; a short oral course of glucocorticoids; dose increase of oral glucocorticoids up to 10 mg/day (with tapering considered at each visit); intra-articular glucocorticoids; initiation, adjustment, or addition of csDMARDs (MTX ≤25 mg/week, SSZ ≤3 g/day, LEF ≤20 mg/day; combination MTX + LEF not permitted); and high-potency topical steroids for psoriasis for up to 2 weeks. Injected joints were considered active up to Week 52.

Rescue therapy requiring discontinuation of IP included initiation of biologic DMARDs (TNFi, IL-17, IL-12/23, or IL-23 inhibitors) or JAK inhibitors (e.g., tofacitinib, upadacitinib).

Objectives

The primary objective was to compare the efficacy of deucravacitinib to placebo in the treatment of participants with active PsA.

The key secondary objectives of the study were:

- To compare the efficacy of deucravacitinib to placebo as assessed by HAQ-DI at Week 16
- To compare the efficacy of deucravacitinib to placebo as assessed by PASI 75 response at Week 16
- To compare the efficacy of deucravacitinib to placebo as assessed by SF-36 PCS score at Week 16
- To compare the efficacy of deucravacitinib to placebo in MDA response at Week 16
- To compare the efficacy of deucravacitinib to placebo in enthesitis resolution at Week 16
- To compare the efficacy of deucravacitinib to placebo in FACIT-Fatigue score at Week 16
- To compare the efficacy of deucravacitinib to placebo in dactylitis resolution at Week 16
- To compare the efficacy of deucravacitinib to placebo at Week 16 as assessed by DAS28-CRP

Outcomes/endpoints

The primary efficacy endpoint for this study was the proportion of participants meeting ACR 20 response at Week 16. The ACR definition of improvement was the same as in study IM011054.

The key secondary efficacy endpoints for this study were as follows:

- Change from baseline in HAQ-DI score at Week 16
- Proportion of participants meeting PASI 75 response at Week 16, in participants with at least 3% BSA involvement AND at least sPGA 2 at baseline
- Change from baseline in the SF-36 PCS score at Week 16
- Proportion of participants meeting achievement of MDA. The definition of an MDA response was the same as in study IM011054.
- Proportion of participants meeting enthesitis resolution (score of 0) among participants with enthesitis at baseline by LEI at Week 16
- Change from baseline in FACIT-Fatigue score at Week 16
- Proportion of participants meeting dactylitis resolution at Week 16 among the participants with dactylitis at baseline, where resolution is defined as a tender dactylitis count of 0 in participants with a tender dactylitis count ≥ 1 at baseline
- Change from baseline in DAS28-CRP score at Week 16

Sample size

A total sample size of approximately 700 subjects randomised in a 3:3:1 ratio in a blinded fashion (approximately 300 subjects each randomised to deucravacitinib 6 mg QD arm and placebo and 100 subjects randomised to 30 mg apremilast BID) would provide > 99% power to detect an 18% treatment difference, between deucravacitinib 6mg QD and placebo, at Week 16 for ACR 20 response assuming a response of 51% for 6 mg deucravacitinib QD and of 33% for placebo (2-sided alpha = 0.05, chi-square test).

The sample size of 300 subjects treated with deucravacitinib 6 mg QD in this study, along with subjects from one other Phase 3 PsA studies with deucravacitinib (IM011054), should provide an adequate number of subjects for the overall safety database for the PsA program.

In addition, this sample size would provide enough power for all key secondary endpoints (that are tested in a testing strategy to control Type I error). The power calculations for the enthesitis resolution and dactylitis resolution were based on pooled data from IM011054 and IM011055. The targeted effect sizes used in the power calculations were based on results from the deucravacitinib Phase 2 study (IM011084). Utilising an active apremilast arm of 100 participants is expected to provide context for the observed safety of deucravacitinib without formal statistical comparisons.

Randomisation

Following the screening process, all eligible participants were centrally randomised using IRT, as per the study protocol.

Blinding (masking)

Blinding treatment assignments were managed using IRT. All tablets were identical in appearance and were supplied in bottles, with each daily dose made up of the appropriate combination of active and/or placebo tablets to provide the correct treatment. Investigative site staff, Sponsor and designee personnel, and participants and their families remained blinded to treatment assignments. Access to treatment codes was restricted from all participants and site and BMS personnel prior to Week 56 database lock, with some exceptions as described in the protocol.

Statistical methods

Populations for Analyses

Similar to study IM011054.

Efficacy Analyses

All efficacy analyses were conducted on the Randomised Population unless otherwise stated. Only DEUC and placebo data were included in the statistical analysis models and no comparisons versus APR (reference safety arm) was provided. All analyses were tested using a 2-sided 0.05 level of significance, unless otherwise specified. The analytical framework for the primary and key secondary objectives considers both main and supplemental estimands.

The main estimand for the primary endpoint of this study is the difference in the proportion of subjects who achieved an ACR 20 response at Week 16 and completed 16 weeks of treatment between deucravacitinib 6 mg QD and placebo in active PsA subjects who are naïve to biologic disease modifying anti-rheumatic drugs or had previously received TNFα inhibitor treatment. This estimand applies a complex estimand to the ICEs that considers both the composite variable

strategy and the treatment policy strategy. The attributes of the main estimand for the primary objective in study IM011055 was identical to IM011054.

- Analysis Model

The primary efficacy analysis approach for the primary endpoint, ACR 20 response at Week 16 (responder/non-responder), used a Cochran Mantel Haenszel (CMH) test stratified by TNFα inhibitor (Yes/No), screening hsCRP concentration (< 10 mg/L versus ≥ 10 mg/L), and by csDMARD use at baseline (yes/no) to compare the response rates of Deucravacitinib 6 mg QD to placebo. The common risk difference (weighted by stratum size) and adjusted odds ratio and the corresponding 2-sided 95% confidence interval (CI) were provided. Clopper-Pearson estimation method was used to estimate the confidence interval.

The efficacy analysis model used to evaluate the supplemental estimand for the primary objective is similar to the analysis model used to evaluate the main estimand for the primary objective.

Handling ICEs for the Main Estimand, Handling Missing Data, Sensitivity Analyses to Explore Missing Data Assumptions, Supplemental Estimand of the Primary Objective (Supportive analysis) were similar to study IM011054.

- Key Secondary Efficacy Endpoints

  - Binary Key Secondary Endpoints:

Outcome measurements include PASI 75 Response at Week 16 (in subset), enthesitis resolution at Week 16 (in subset), dactylitis resolution at Week 16 (in subset), and MDA response at Week 16.

The efficacy analysis approach used to evaluate the main and supplemental estimands for each binary key secondary objective were similar to the analysis approach used to evaluate the main and supplemental estimands for the primary objective.

  - Continuous Key Secondary Endpoints:

Outcome measurements include Change from baseline in HAQ-DI score, SF-36 PCS score, PsA-modified, FACIT-Fatigue score, and DAS28 CRP score at Week 16.

Summary of the attributes of the main estimand for the key secondary objectives with a continuous endpoint:

-**Treatment:** Deucravacitinib 6 mg QD and placebo

-Population: All randomised participants with Active PsA

-Variable: As defined above.

-**Intercurrent Events (ICEs):**

1. Treatment discontinuation (for any reason) prior to Week 16: Composite variable strategy (Early treatment discontinuation is a clinically relevant mode of treatment failure. The Week 16 value of the continuous endpoint was set to zero to imply no improvement nor worsening relative to baseline.).
2. Rescue medication therapy prior to Week 16: Treatment policy strategy (Use of 1 or more rescue medications is a component of a broader treatment policy).

-**Population-level Summary**: Difference in mean change from baseline to Week 16 between Deucravacitinib 6 mg QD and placebo.

- Analysis Model

The efficacy analysis models for the main estimands of the continuous secondary objectives are ANCOVA models. Each model includes change from baseline of the key secondary measure as the dependent variable and treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables. The adjusted mean change from baseline (LS Means) with SE and 95% CI per treatment group and the difference between DEUC 6 mg QD to placebo in adjusted mean change from baseline with SE and 95% CI are provided from each analysis model. P-values are based on the Wald test.

- Handling ICEs for the Main Estimand

    1. Treatment discontinuation (for any reason) prior to Week 16: Change from baseline value is set to zero (composite variable strategy).

    2. Rescue medication therapy prior to Week 16: No additional action is required in the data handling convention for that ICE (treatment policy strategy)

- Handling Missing Data

Missing values were imputed with MI method assuming missing not at random (MNAR). The MNAR imputation assumes that after discontinuation of treatment, participants from the deucravacitinib 6 mg QD group (if they would have continued deucravacitinib 6 mg QD) exhibit a similar future evolution as participants from the placebo group.

- Sensitivity Analyses to Explore Missing Data Assumptions

Sensitivity analyses using Multiple Imputation with Pattern Mixture Models were conducted to examine the impact of missing data.

- Supplemental Estimand of Continuous Key Secondary Objectives (Supportive analysis).

The supplemental estimand used similar efficacy analysis model and missing data methods as the main estimand for each continuous key secondary objective, with the only difference being the handling of ICEs.

For the Supplemental Estimand, all continuous data collected for the outcome of interest at Week 16 were used in the analysis regardless of the occurrence of an ICE:

1. Treatment discontinuation (for any reason) prior to Week 16: Treatment policy strategy.

2. Rescue medication therapy prior to Week 16: Treatment policy strategy.

- Additional Secondary Endpoints

For additional secondary endpoints, the main estimand definition, analysis model, handling of ICEs, and approach to missing data are similar to those described above.

- Subgroup Analyses

Subgroup analyses of primary endpoint were performed using logistic regression models to evaluate the consistency of the treatment difference at Week 16 based on the main estimand of the primary objective, inclusive of the approaches used to handle ICEs and missing data.

The logistic regression models included the treatment group, subgroup factor, and the interaction between treatment group and subgroup factor. The difference in response rates with 95% CI, and the p-value for the interaction of treatment group and the subgroup factor were provided. Results were displayed via a forest plot. Descriptive statistics were to be provided if there are not enough subjects to estimate the statistics listed above.

The subgroups that were evaluated include: Geographic region, Country, Sex, Age group (<40 y, 40-<65 y, ≥65 y), Body weight categories (<90 kg; ≥90 kg) – from case report form, BMI categories (<25 kg/m2, 25-<30 kg/m2, 30-<35 kg/m2, >35 kg/m2), Race, Baseline TNFα inhibitor use history (experienced/naïve) – from case report form, Baseline non-biologic DMARD use history (yes/no), Baseline csDMARD use (yes/no), Baseline glucocorticoid use (yes/no), Baseline MTX use (yes/no), Baseline NSAID use (yes/no), Baseline disease severity (DAS28 <5.1 vs DAS28 ≥5.1), Baseline number of swollen joints (≤4 vs >4), Baseline presence of enthesitis (yes/no), Baseline presence of dactylitis (yes/no), Screening hsCRP (<10 mg/L vs ≥10 mg/L; as determined by IRT), Duration of disease at screening (< median y, ≥ median y).

- Adjustments for Multiplicity:

To control the overall Type I error rate at 5%, a testing strategy for the primary and key secondary endpoints was implemented. The primary endpoint, ACR 20 response at Week 16, was tested at two-sided 0.05 significance level. If the primary endpoint was significant at alpha = 0.05, then statistical analysis of the key secondary endpoints was performed in a hierarchical fashion. The data from studies IM011054 and IM011055 were pooled for the analysis of the key secondary endpoints, enthesitis resolution and dactylitis resolution.

No comparisons versus apremilast, a reference safety arm, was provided.

To preserve the overall Type I error rate, a fixed-sequence testing method was implemented for the below specified endpoints. Testing order of secondary endpoints was in the below order and could only proceed to the next secondary endpoint if the null hypothesis was rejected at two-sided alpha = 0.05 for the prior endpoint showing a significant treatment difference in that endpoint. If an endpoint failed at any step, then all subsequent p-values were considered nominal.

Changes to planned analyses

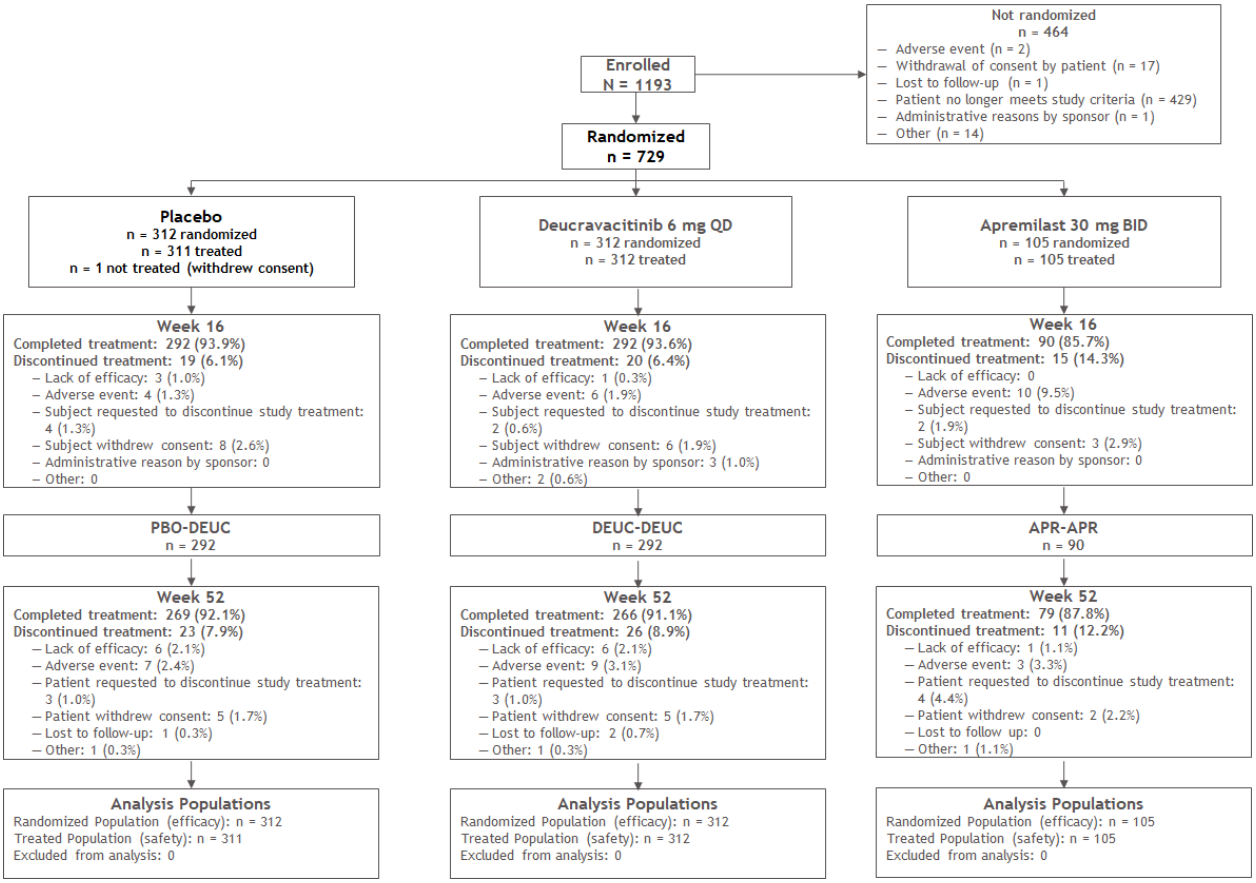
- Additional Analyses:

In addition to the planned analysis in the SAP, other post hoc analyses were performed after the primary analysis and were included in the CSR.

Results

Participant flow

Figure 21. IM011055: Participant Flow Diagram



Recruitment

Subjects were recruited across 124 sites in 18 countries (Argentina, Australia, Belgium, Canada, China, Colombia, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russia, Spain, Taiwan, United Kingdom, and United States)

Conduct of the study

The original protocol for this study was dated 12-Mar-2021. As of the 07-Nov2024 data cut-off date, there were a total of 1 global amendment, 3 country specific amendments, and 5 administrative letters (2 global and 3 countries specific)

A total of 178 and 156 deviations were reported in the placebo-controlled and active-treatment period, respectively.

After unblinding, quality issues with lab samples were retrospectively identified in study IM011055 with 0.06 % samples assayed outside the stability window and affecting inclusion/exclusion criteria and endpoint assessments (including the primary ACR20 response). Post-hoc exclusions and sensitivity analyses were conducted.

Baseline data

Baseline demographics and disease characteristics in the randomised population are presented in the below tables.

Table 31. Demographic and Baseline Characteristics Summary, Randomised Population-IM011055

	DEUC 6 mg N = 312	PBO N = 312	APR 30 mg N = 105	Total N = 729
AGE (YEARS)				
N	312	312	105	729
MEAN (SD)	48.7 (11.73)	49.3 (12.18)	49.1 (13.47)	49.0 (12.17)
MEDIAN	49.0	50.0	48.0	49.0
Q1, Q3	40.0, 57.0	40.0, 58.0	39.0, 59.0	40.0, 58.0
MIN, MAX	21, 80	22, 78	18, 83	18, 83
AGE CATEGORIZATION n(%)				
<45	112 (35.9)	117 (37.5)	42 (40.0)	271 (37.2)
45-<65	171 (54.8)	156 (50.0)	46 (43.8)	373 (51.2)
>=65	29 (9.3)	39 (12.5)	17 (16.2)	85 (11.7)
SEX n(%)				
MALE	159 (51.0)	144 (46.2)	49 (46.7)	352 (48.3)
FEMALE	153 (49.0)	168 (53.8)	56 (53.3)	377 (51.7)
RACE n(%)				
WHITE	223 (71.5)	240 (76.9)	65 (61.9)	528 (72.4)
AMERICAN INDIAN OR ALASKA NATIVE	13 (4.2)	7 (2.2)	4 (3.8)	24 (3.3)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (0.3)	0	1 (0.1)
OTHER	22 (7.1)	19 (6.1)	8 (7.6)	49 (6.7)
ASIAN	54 (17.3)	45 (14.4)	28 (26.7)	127 (17.4)
ASIAN INDIAN	3 (1.0)	2 (0.6)	0	5 (0.7)
CHINESE	38 (12.2)	33 (10.6)	19 (18.1)	90 (12.3)
JAPANESE	9 (2.9)	7 (2.2)	7 (6.7)	23 (3.2)
ASIAN OTHER	4 (1.3)	3 (1.0)	2 (1.9)	9 (1.2)
ETHNICITY n(%)				
HISPANIC OR LATINO	54 (17.3)	50 (16.0)	16 (15.2)	120 (16.5)
NOT HISPANIC OR LATINO	195 (62.5)	200 (64.1)	64 (61.0)	459 (63.0)
NOT REPORTED	63 (20.2)	62 (19.9)	25 (23.8)	150 (20.6)
COUNTRY BY GEOGRAPHIC REGION n(%)				
NORTH AMERICA	47 (15.1)	58 (18.6)	12 (11.4)	117 (16.0)
CANADA	6 (1.9)	7 (2.2)	0	13 (1.8)

	DEUC 6 mg N = 312	PBO N = 312	APR 30 mg N = 105	Total N = 729
MEXICO	21 (6.7)	31 (9.9)	7 (6.7)	59 (8.1)
UNITED STATES OF AMERICA	20 (6.4)	20 (6.4)	5 (4.8)	45 (6.2)
SOUTH/LATIN AMERICA	43 (13.8)	32 (10.3)	11 (10.5)	86 (11.8)
ARGENTINA	26 (8.3)	27 (8.7)	5 (4.8)	58 (8.0)
COLOMBIA	17 (5.4)	5 (1.6)	6 (5.7)	28 (3.8)
EUROPE	163 (52.2)	171 (54.8)	51 (48.6)	385 (52.8)
BELGIUM	0	4 (1.3)	1 (1.0)	5 (0.7)
CZECHIA	37 (11.9)	37 (11.9)	7 (6.7)	81 (11.1)
GERMANY	22 (7.1)	31 (9.9)	8 (7.6)	61 (8.4)
HUNGARY	24 (7.7)	20 (6.4)	10 (9.5)	54 (7.4)
ITALY	0	0	1 (1.0)	1 (0.1)
POLAND	51 (16.3)	53 (17.0)	13 (12.4)	117 (16.0)
RUSSIAN FEDERATION	3 (1.0)	0	0	3 (0.4)
SPAIN	25 (8.0)	23 (7.4)	8 (7.6)	56 (7.7)
UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND	1 (0.3)	3 (1.0)	3 (2.9)	7 (1.0)
ASIA	48 (15.4)	42 (13.5)	27 (25.7)	117 (16.0)
CHINA	32 (10.3)	28 (9.0)	16 (15.2)	76 (10.4)
JAPAN	9 (2.9)	8 (2.6)	7 (6.7)	24 (3.3)
TAIWAN, PROVINCE OF CHINA	7 (2.2)	6 (1.9)	4 (3.8)	17 (2.3)
REST OF THE WORLD	11 (3.5)	9 (2.9)	4 (3.8)	24 (3.3)
AUSTRALIA	11 (3.5)	9 (2.9)	4 (3.8)	24 (3.3)
BASELINE WEIGHT (KG)				
N	312	312	105	729
MEAN (SD)	85.58 (20.754)	85.39 (19.485)	85.04 (21.398)	85.42 (20.289)
MEDIAN	82.10	83.00	81.30	82.70
Q1, Q3	71.05, 99.15	71.00, 96.00	70.20, 95.00	71.00, 97.00
MIN, MAX	44.5, 172.4	47.0, 171.0	45.1, 151.6	44.5, 172.4
WEIGHT CATEGORIZATION n(%)				
< 90 KG	192 (61.5)	197 (63.1)	66 (62.9)	455 (62.4)
>= 90 KG	120 (38.5)	115 (36.9)	39 (37.1)	274 (37.6)
BASELINE BMI (KG/M^2)				
N	312	312	105	729
MEAN (SD)	30.02 (6.693)	30.34 (6.429)	30.51 (7.547)	30.22 (6.705)
MEDIAN	29.05	29.18	29.23	29.13
Q1, Q3	25.77, 33.26	25.63, 33.44	24.95, 34.87	25.58, 33.46
MIN, MAX	15.2, 65.2	17.7, 51.6	18.7, 59.6	15.2, 65.2

Age presented is age at date of informed consent.
Source: Table 14.1.3.1

Table 32. Key Baseline Disease Characteristics Summary, Randomised Population- IM011055

	DEUC 6 mg N = 312	PBO N = 312	APR 30 mg N = 105	Total N = 729
TNFI USE FROM CRF n(%)				
YES	39 (12.5)	45 (14.4)	14 (13.3)	98 (13.4)
NO	273 (87.5)	267 (85.6)	91 (86.7)	631 (86.6)
BASELINE CSDMARD USE FROM CRF n(%)				
YES	194 (62.2)	196 (62.8)	68 (64.8)	458 (62.8)
NO	118 (37.8)	116 (37.2)	37 (35.2)	271 (37.2)
DURATION OF DISEASE (YEARS)				
MEAN (SD)	5.03 (5.987)	5.90 (6.938)	4.70 (6.448)	5.35 (6.485)
MEDIAN	2.88	3.25	2.42	3.01
MIN, MAX	0.2, 32.1	0.2, 39.8	0.3, 39.0	0.2, 39.8
PSA SUB-TYPE n(%)				
POLYARTHRITIS	222 (71.2)	234 (75.0)	72 (68.6)	528 (72.4)

	DEUC 6 mg N = 312	PBO N = 312	APR 30 mg N = 105	Total N = 729
OLIGOARTHRITIS	55 (17.6)	51 (16.3)	17 (16.2)	123 (16.9)
PREDOMINANT DISTAL INTERPHALANGEAL JOINT INVOLVEMENT	29 (9.3)	24 (7.7)	12 (11.4)	65 (8.9)
PREDOMINANT AXIAL INVOLVEMENT	5 (1.6)	3 (1.0)	4 (3.8)	12 (1.6)
ARTHRITIS MUTILANS	1 (0.3)	0	0	1 (0.1)
PSA PHENOTYPE n(%)				
PERIPHERAL ARTHRITIS	264 (84.6)	264 (84.6)	84 (80.0)	612 (84.0)
PERIPHERAL PLUS PSORIATIC SPONDYLOARTHRITIS	48 (15.4)	48 (15.4)	21 (20.0)	117 (16.0)
BASELINE ACR COMPONENTS:				
BASELINE TENDER (68) JOINT COUNT MEAN (SD)	15.2 (10.91)	16.6 (11.53)	16.8 (11.92)	16.0 (11.33)
BASELINE SWOLLEN (66) JOINT COUNT MEAN (SD)	9.2 (6.53)	9.6 (7.53)	10.6 (7.10)	9.6 (7.06)
BASELINE SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY MEAN (SD)	58.7 (22.03)	61.2 (21.92)	61.0 (22.07)	60.1 (21.99)
BASELINE SUBJECT GLOBAL ASSESSMENT OF PAIN (SD)	58.9 (20.52)	60.2 (21.26)	59.3 (20.48)	59.5 (20.82)
BASELINE HAQ-DI SCORE, N	311	312	104	727
MEAN (SD)	1.1013 (0.63029)	1.1783 (0.64163)	1.1755 (0.59287)	1.1449 (0.63031)
BASELINE HSCRP (MG/L)				
MEAN (SD)	11.714 (17.8781)	12.200 (15.5280)	10.333 (13.9282)	11.723 (16.3597)
PASI Score with at least 3% BSA and at least sPGA 2 at baseline				
N	154	149	43	346
Mean (SD)	9.13 (7.137)	8.48 (6.852)	8.82 (7.779)	8.81 (7.085)

	DEUC 6 mg N = 312	PBO N = 312	APR 30 mg N = 105	Total N = 729
BASELINE MDA COMPONENTS:				
BASELINE PASI SCORE, n(%)				
<= 1	52 (16.7)	67 (21.5)	28 (26.7)	147 (20.2)
> 1	260 (83.3)	244 (78.2)	75 (71.4)	579 (79.4)
NOT REPORTED	0	1 (0.3)	2 (1.9)	3 (0.4)
BASELINE BSA, n(%)				
<= 3%	148 (47.4)	154 (49.4)	57 (54.3)	359 (49.2)
> 3%	164 (52.6)	157 (50.3)	46 (43.8)	367 (50.3)
NOT REPORTED	0	1 (0.3)	2 (1.9)	3 (0.4)
BASELINE TENDER ENTHESEAL POINTS (LEI), n(%)				
<= 1	226 (72.4)	210 (67.3)	71 (67.6)	507 (69.5)
> 1	86 (27.6)	101 (32.4)	33 (31.4)	220 (30.2)
NOT REPORTED	0	1 (0.3)	1 (1.0)	2 (0.3)
BASELINE TENDER ENTHESEAL POINTS (LEI), n(%)				
< 1	172 (55.1)	161 (51.6)	55 (52.4)	388 (53.2)
>= 1	140 (44.9)	150 (48.1)	49 (46.7)	339 (46.5)
NOT REPORTED	0 (0.0)	1 (0.3)	1 (1.0)	2 (0.3)
BASELINE LEEDS ENTHESITIS INDEX (LEI), N[a]	140	150	49	339
Mean (SD)	2.1 (1.34)	2.3 (1.35)	2.4 (1.43)	2.2 (1.36)
BASELINE SPARCC ENTHESITIS INDEX, N[b]	177	196	62	435
Mean (SD)	3.7 (3.00)	4.0 (3.00)	4.1 (3.52)	3.9 (3.08)

	DEUC 6 mg N = 312	PBO N = 312	APR 30 mg N = 105	Total N = 729
BASELINE TENDER DACTYLITIS COUNT n(%)				
< 1	234 (75.0)	231 (74.0)	70 (66.7)	535 (73.4)
>= 1	78 (25.0)	80 (25.6)	33 (31.4)	191 (26.2)
NOT REPORTED	0	1 (0.3)	2 (1.9)	3 (0.4)
BASELINE DACTYLITIS INDEX (LDI, N	81	84	33	198
MEAN (SD)	45.062 (83.4363)	76.357 (233.6459)	82.550 (125.3361)	64.586 (169.2592)
BASELINE TENDER DACTYLITIS COUNT, N[c]	78	80	33	191
Mean (SD)	3.3 (3.42)	3.5 (3.52)	3.8 (3.88)	3.5 (3.53)
BASELINE FACIT-FATIGUE SCORE, N	311	311	103	725
MEAN (SD)	33.6 (10.70)	33.0 (11.88)	32.9 (11.13)	33.2 (11.27)
BASELINE SF-36 PCS SCORE, N	311	311	103	725
MEAN (SD)	36.335 (8.4202)	35.860 (9.2393)	35.888 (8.1985)	36.068 (8.7426)

[a]Baseline LEI score is based on the number of subjects in the Randomized Population with enthesitis at baseline by LEI.
[b]Baseline SPARCC Enthesitis Index is based on the number of subjects in the Randomized Population with enthesitis at baseline by SPARCC.
[c]Baseline Tender Dactylitis Count is based on the number of subjects in the Randomized Population with tender dactylitis count >=1 at baseline.
Source: Table 14.1.4.1, Table 14.1.4.11 (baseline PASI score), and Table 14.1.4.12 (baseline tender enthesitis), Table 14.1.4.6 (enthesitis) and Table 14.1.4.9 (dactylitis).

Numbers analysed

The first patient was enrolled 15 Jul 2021. As of the cut-off date 07 Nov 2024, the Placebo-controlled Period was completed (Week 0-16) and the Active Treatment Period (Week 16-52) were completed. The optional open label period is ongoing.

As of the clinical cut-off (07-Nov-2024) for the IM011055 Primary CSR, 729 subjects were randomised: 312 to the DEUC 6 mg QD arm, 312 to the PBO arm, and 105 to the APR safety reference arm. Of these, 728 subjects were treated (312 with DEUC 6 mg QD, 311 with PBO, and 105 with APR). Efficacy was analysed in the 624 subjects randomised to DEUC or PBO.

Outcomes and estimation

Primary endpoint

The primary efficacy endpoint of this study, the proportion of participants who achieved an ACR20 response at Week 16, was met.

Table 33. ACR 20 Response at Week 16 – Main Estimand-Randomised

	DEUC 6 mg N = 312	PBO N = 312
TOTAL NUMBER OF SUBJECTS	312	312
RESPONDERS n (%)	169 (54.2)	123 (39.4)
NON-RESPONDERS n (%)	143 (45.8)	189 (60.6)
NON-RESPONDERS DUE TO ICE n (%)	19 (6.1)	19 (6.1)
NON-RESPONDERS DUE TO MISSING DATA n (%)	6 (1.9)	3 (1.0)
RESPONSE RATE	54.2	39.4
(95% CI)	(48.5, 59.8)	(34.0, 45.1)
DIFFERENCE VS PLACEBO	14.8	N.A.
(95% CI)	(7.0, 22.5)	N.A.
P-VALUE	0.0002	N.A.
ODDS RATIO VS PLACEBO	1.82	N.A.
(95% CI)	(1.32, 2.50)	N.A.

Total number of subjects is the number of subjects in the Randomized Population.
Responders are subjects with ≥ 20% improvement from baseline, with respect to main estimand strategy. Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for use of rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using Cochran Mantel Haenszel (CMH) test stratified by TNFa inhibitor (yes/no), screening hsCRP concentration (< 10 mg/L, ≥ 10 mg/L), and csDMARD use at baseline (yes/no). Missing ACR20 composite response is treated with non-responder imputation.
ICE: Intercurrent event; N.A.: Not Applicable.
Source: Table 14.2.1.1.2

Key secondary efficacy endpoints

Analysis did not demonstrate a statistically significant difference between DEUC and PBO for the 5th pre-specified secondary endpoint of enthesitis resolution per LEI (in the pooled analysis of IM011054 and IM011055). Therefore, analysis obtained for the subsequent endpoints in the hierarchy, i.e., FACIT-fatigue, dactylitis resolution (in the pooled analysis of IM011054 and IM011055), and DAS28-CRP, are considered exploratory only.

- Change from baseline in HAQ-DI score at Week 16

Table 34. Change from Baseline in HAQ-DI Score at Week 16- Main Estimand – Randomised Population

Timepoint Statistic	DEUC 6 mg N = 312	PBO N = 312
BASELINE		
N1	311	312
MEAN (SD)	1.1013 (0.63029)	1.1783 (0.64163)
MEDIAN	1.1250	1.2500
MIN, MAX	0.000, 3.000	0.000, 2.875
WEEK 16		
N1	308	311
MEAN (SD)	0.7873 (0.64146)	0.9546 (0.64812)
MEDIAN	0.7500	1.0000
MIN, MAX	0.000, 3.000	0.000, 2.375
CHANGE FROM BASELINE AT WEEK 16		
N1	307	311
MEAN (SD)	-0.3103 (0.46159)	-0.2219 (0.46858)
MEDIAN	-0.2500	-0.1250
MIN, MAX	-1.875, 1.125	-2.000, 1.000
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES (SE)	-0.3246 (0.03196)	-0.2120 (0.03216)
95% CONFIDENCE INTERVAL FOR MEAN	(-0.3873, -0.2620)	(-0.2751, -0.1490)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	-0.1126 (0.03511)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(-0.1814, -0.0438)	N.A.
P VALUE	0.0013	N.A.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables. Composite variable estimand strategy is used for treatment discontinuation prior to Week 16 which sets change from baseline value to zero. Treatment policy strategy used for use of rescue therapy prior to Week 16. Missing data are imputed by control-based pattern multiple imputation. Observed data after adjusting for ICE are used for descriptive statistics. Imputed data after considering ICE and multiple imputation are used in ANCOVA model. N1 represents the total number of subjects at the visit time point.
ICE: Intercurrent event; N.A. = Not Applicable.
Source: Table 14.2.2.3.1

- Proportion of participants meeting PASI 75 response at Week 16, in participants with at least 3% BSA involvement AND at least sPGA 2 at baseline

Table 35. PASI 75 Response at Week 16 - Main Estimand, Randomised Population

	DEUC 6 mg N = 312	PBO N = 312
TOTAL NUMBER OF SUBJECTS	154	149
RESPONDERS n (%)	63 (40.9)	23 (15.4)
NON-RESPONDERS n (%)	91 (59.1)	126 (84.6)
NON-RESPONDERS DUE TO ICE n (%)	7 (4.5)	8 (5.4)
NON-RESPONDERS DUE TO MISSING DATA n (%)	1 (0.6)	4 (2.7)
RESPONSE RATE	40.9	15.4
(95% CI)	(33.1, 49.1)	(10.0, 22.3)
DIFFERENCE VS PLACEBO	25.6	N.A.
(95% CI)	(15.7, 35.5)	N.A.
P-VALUE	<0.0001	N.A.
ODDS RATIO VS PLACEBO	3.67	N.A.
(95% CI)	(2.13, 6.33)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with at least 3% BSA and at least sPGA 2 at baseline. ICE: Intercurrent event. Responders are subjects with ≥ 75% PASI improvement from baseline. Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by TNFa inhibitor (yes/no), screening hsCRP concentration (< 10 mg/L, ≥ 10 mg/L), and csDMARD use at baseline (yes/no). Missing PASI 75 response is treated with non-responder imputation.
N.A.: Not Applicable.
Source: Table 14.2.2.1.1

- Change from baseline in the SF-36 PCS score at Week 16

Table 36. Change from baseline in SF-36 PCS Score at Week 16, - Main Estimand, Randomised Population

Time Point Statistic	DEUC 6 mg N = 312	PBO N = 312
BASELINE		
N1	311	311
MEAN (SD)	36.335 (8.4202)	35.860 (9.2393)
MEDIAN	35.910	35.710
MIN, MAX	16.54, 57.21	14.38, 63.00
WEEK 16		
N1	308	311
MEAN (SD)	42.532 (9.0059)	40.166 (9.4130)
MEDIAN	41.965	41.110
MIN, MAX	18.20, 63.49	15.96, 60.88
CHANGE FROM BASELINE AT WEEK 16		
N1	307	310
MEAN (SD)	6.194 (7.4640)	4.262 (7.0328)
MEDIAN	5.100	3.125
MIN, MAX	-11.46, 29.03	-13.65, 30.73
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES (SE)	5.838 (0.4931)	3.796 (0.4962)
95% CONFIDENCE INTERVAL FOR MEAN	(4.871, 6.804)	(2.823, 4.768)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	2.042 (0.5421)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(0.980, 3.105)	N.A.
P Value	0.0002	N.A.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables. Composite variable estimand strategy is used for treatment discontinuation prior to Week 16 which sets change from baseline value to zero. Treatment policy strategy used for use of rescue therapy prior to Week 16. Missing data are imputed by control-based pattern multiple imputation. Observed data after adjusting for ICE are used for descriptive statistics. Imputed data after considering ICE and multiple imputation are used in ANCOVA model. N1 represents the total number of subjects at the visit time point.
ICE: Intercurrent event; N.A.: Not Applicable.
Source: Table 14.2.2.3.2

- Proportion of participants meeting achievement of MDA where an MDA response is achievement at Week 16:

Table 37. MDA Response at Week 16 - Main Estimand, Randomised Population

	DEUC 6 mg N = 312	PBO N = 312
TOTAL NUMBER OF SUBJECTS	312	312
RESPONDERS n (%)	80 (25.6)	46 (14.7)
NON-RESPONDERS n (%)	232 (74.4)	266 (85.3)
NON-RESPONDERS DUE TO ICE n (%)	19 (6.1)	19 (6.1)
NON-RESPONDERS DUE TO MISSING DATA n (%)	8 (2.6)	6 (1.9)
RESPONSE RATE	25.6	14.7
(95% CI)	(20.9, 30.9)	(11.0, 19.2)
DIFFERENCE VS PLACEBO	10.9	N.A.
(95% CI)	(4.6, 17.1)	N.A.
P-VALUE	0.0007	N.A.
ODDS RATIO VS PLACEBO	1.99	N.A.
(95% CI)	(1.33, 2.98)	N.A.

Total number of subjects is the number of subjects in the Randomized Population. Responders are subjects fulfilling 5 of 7 of the MDA outcomes. Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by TNFa inhibitor (yes/no), screening hsCRP concentration (< 10 mg/L, ≥ 10 mg/L), and csDMARD use at baseline (yes/no). Missing MDA Response is treated with non-responder imputation.
Source: Table 14.2.2.1.4

MDA responders continued to increase from Week 16 to Week 40 in DEUC-DEUC arm and to Week 48 in PBO-DEUC arm and up to Week 52.

- Proportion of participants meeting enthesitis resolution (score of 0) among participants with enthesitis at baseline by LEI at Week 16

Enthesitis resolution was assessed in the subset of subjects with at least 1 tender entheseal point at baseline. Using LEI as the assessment tool, represented nearly half of the study population (n = 140 [44.9%] DEUC arm and n=150 [48.1%] PBO arm).

No statistically significant difference was observed between the groups at week 16. At this stage, the hierarchical testing procedure was discontinued; therefore, subsequent efficacy results are considered nominal and should be interpreted descriptively

Table 38. Enthesitis by LEI Resolution at Week 16- Main Estimand - Randomised Population

	DEUC 6 mg N = 312	PBO N = 312
TOTAL NUMBER OF SUBJECTS	140	150
RESPONDERS n (%)	74 (52.9)	66 (44.0)
NON-RESPONDERS n (%)	66 (47.1)	84 (56.0)
NON-RESPONDERS DUE TO ICE n (%)	7 (5.0)	10 (6.7)
NON-RESPONDERS DUE TO MISSING DATA n (%)	4 (2.9)	4 (2.7)
RESPONSE RATE	52.9	44.0
(95% CI)	(44.2, 61.3)	(35.9, 52.3)
DIFFERENCE VS PLACEBO	8.9	N.A.
(95% CI)	(-2.5, 20.3)	N.A.
P-VALUE	0.1302	N.A.
ODDS RATIO VS PLACEBO	1.44	N.A.
(95% CI)	(0.90, 2.31)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with enthesitis at baseline by LEI. Resolution of enthesitis is considered reaching a Leeds Enthesitis index score of 0 among subjects with enthesitis at baseline by LEI. Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by TNFa inhibitor (yes/no), screening hsCRP

The proportion of subjects with a baseline LEI score ≥1 who achieved enthesitis resolution (i.e., score of 0) at Week 16 and up to Week 52 increased modestly from Week 16 through Week 52 in both DEUC- DEUC and PBO- DEUC groups.

- Change from baseline in FACIT-Fatigue score at Week 16

Table 39. Change from baseline in FACIT-Fatigue score at Week 16 – Main Estimand, Randomised Population

Time Point Statistic	DEUC 6 mg N = 312	PBO N = 312
BASELINE		
N1	311	311
MEAN (SD)	33.6 (10.70)	33.0 (11.88)
MEDIAN	34.0	35.0
MIN, MAX	4, 52	4, 52
WEEK 16		
N1	308	311
MEAN (SD)	36.1 (10.82)	35.0 (11.07)
MEDIAN	38.0	37.0
MIN, MAX	0, 52	4, 52
CHANGE FROM BASELINE AT WEEK 16		
N1	307	310
MEAN (SD)	2.6 (8.17)	1.9 (8.54)
MEDIAN	2.0	1.0
MIN, MAX	-21, 31	-34, 34
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES (SE)	2.5 (0.56)	1.8 (0.56)
95% CONFIDENCE INTERVAL FOR MEAN	(1.4, 3.6)	(0.7, 2.8)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	0.8 (0.61)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(-0.4, 2.0)	N.A.
P VALUE	0.2017	N.A.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables. Composite variable estimand strategy is used for treatment discontinuation prior to week 16 which sets change from baseline value to zero. Treatment policy strategy used for use of rescue therapy prior to Week 16. Missing data are imputed by control-based pattern multiple imputation. Observed data after adjusting for ICE are used for descriptive statistics. Imputed data after considering ICE and multiple imputation are used in ANCOVA model. N1 represents the total number of subjects at the visit time point.
Source: Table 14.2.2.3.3

- Proportion of participants meeting dactylitis resolution at Week 16 among the participants with dactylitis at baseline, where resolution is defined as a tender dactylitis count of 0 in participants with a tender dactylitis count ≥ 1 at baseline

Table 40. Dactylitis resolution at Week 16, Randomised Population- IM011055

	DEUC 6 mg N = 312	PBO N = 312
TOTAL NUMBER OF SUBJECTS	78	80
RESPONDERS n (%)	43 (55.1)	36 (45.0)
NON RESPONDERS n (%)	35 (44.9)	44 (55.0)
NON RESPONDERS DUE TO ICE n (%)	5 (6.4)	5 (6.3)
NON RESPONDERS DUE TO MISSING DATA n (%)	1 (1.3)	1 (1.3)
RESPONSE RATE	55.1	45.0
(95% CI)	(43.4, 66.4)	(33.8, 56.5)
DIFFERENCE VS PLACEBO	9.3	N.A.
(95% CI)	(-6.1, 24.8)	N.A.
P-VALUE	0.2373	N.A.
ODDS RATIO VS PLACEBO	1.48	N.A.
(95% CI)	(0.77, 2.83)	N.A.

Total number of subjects is the number of subjects in the Randomized Population with tender dactylitis count >=1 at baseline.
ICE: Intercurrent event.
Resolution of Dactylitis is considered reaching a tender dactylitis count of 0 among subjects with tender dactylitis count >=1 at baseline.
Composite variable strategy is used for treatment discontinuation prior to Week 16. Treatment policy strategy is used for rescue medication therapy prior to Week 16. The 95% CI is calculated using Clopper-Pearson exact method.
N.A.: Not Applicable. Risk difference and odds ratio are obtained from stratified contingency tables. P-value is obtained using a Cochran Mantel Haenszel (CMH) test stratified by TNFa inhibitor (yes/no), screening hsCRP concentration (< 10 mg/L, >= 10 mg/L), and csDMARD use at baseline (yes/no).
Missing dactylitis resolution is treated with non-responder imputation.
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From Week 16 through Week 52, the proportion of subjects achieving dactylitis resolution (i.e., score of 0) increased in both DEUC- DEUC and PBO- DEUC groups.

- Change from baseline in DAS28-CRP score at Week 16

Table 41. Change from baseline in DAS28-CRP score at Week 16-Main Estimand, Randomised Population- IM011055

Timepoint Statistic	DEUC 6 mg N = 312	PBO N = 312
BASELINE		
N1	311	312
MEAN (SD)	4.7091 (0.95752)	4.9030 (0.91131)
MEDIAN	4.6537	4.8708
MIN, MAX	2.092, 7.571	2.834, 7.095
WEEK 16		
N1	301	299
MEAN (SD)	3.3687 (1.18670)	3.9847 (1.22577)
MEDIAN	3.3058	3.9777
MIN, MAX	1.013, 6.626	1.155, 7.158
CHANGE FROM BASELINE AT WEEK 16		
N1	300	299
MEAN (SD)	-1.3133 (1.17420)	-0.9095 (1.10470)
MEDIAN	-1.2820	-0.7785
MIN, MAX	-5.046, 2.239	-4.472, 1.605
DIFFERENCE AT WEEK 16		
ADJUSTED MEAN CHANGES (SE)	-1.2781 (0.07914)	-0.8038 (0.08085)
95% CONFIDENCE INTERVAL FOR MEAN	(-1.4332, -1.1230)	(-0.9623, -0.6454)
VS PLACEBO		
ADJUSTED MEAN DIFFERENCE (SE)	-0.4743 (0.08735)	N.A.
95% CONFIDENCE INTERVAL FOR DIFFERENCE	(-0.6455, -0.3031)	N.A.
P VALUE	<0.0001	N.A.

Analysis of Covariance presents change from baseline as the dependent variable with treatment, randomization stratification variables, and baseline value of the key secondary measure as independent variables. Composite variable estimand strategy is used for treatment discontinuation

Ancillary analyses

Subgroup Analysis of the Primary and Key Secondary Endpoints by Concomitant csDMARD Use

Table 42. IM011055: Subgroup Analysis of the Primary and Key Secondary Endpoints by Concomitant csDMARD Use

	With a Concomitant csDMARD			Without a Concomitant csDMARD			
	Response rate (%)[b] or Adjusted mean change from BL (SE)[c]			Response rate (%)[b] or Adjusted mean change from BL (SE)[c]			
Endpoints[a]	DEUC 6 mg (N = 194)	PBO (N = 196)	Δ (95% CI)[d]	DEUC 6 mg (N = 118)	PBO (N = 116)	Δ (95% CI)[d]	Interaction p-value[e]
ACR 20	52.6%	42.9%	9.7 (-0.4, 19.6)	56.8%	33.6%	23.2 (10.0, 35.5)	0.0969
HAQ-DI	-0.3025 (0.03142)	-0.2105 (0.03140)	-0.0920 (-0.1791, -0.0049)	-0.3611 (0.04068)	-0.2152 (0.04061)	-0.1459 (-0.2585, -0.0334)	0.4574
PASI 75[f]	39.6%	19.5%	20.0 (4.7, 32.9)	43.1%	9.7%	33.4 (16.7, 48.5)	0.1139
SF-36 PCS	5.946 (0.4874)	4.127 (0.4852)	1.819 (0.427, 3.167)	6.715 (0.6297)	4.325 (0.6312)	2.390 (0.644, 4.137)	0.6117
MDA	22.7%	14.3%	8.4 (0.4, 16.2)	30.5%	15.5%	15.0 (3.3, 25.7)	0.4666
Enthesitis Resolution by LEI (pooled analysis) g	55.5%	50.5%	5.0 (-4.6, 14.5)	40.2%	35.1%	5.1 (-7.8, 17.9)	0.9579
Enthesitis resolution by SPARCC (pooled analysis)	52.9%	37.1%	15.8 (7.4, 24.1)	35.4%	34.3%	1.1 (-10.3, 12.5)	0.0535
FACIT-Fatigue	2.5 (0.55)	2.2 (0.55)	0.4 (-1.1, 1.9)	2.8 (0.71)	1.3 (0.71)	1.4 (-0.5, 3.4)	0.4105
Dactylitis Resolution (pooled analysis)[g]	62.8%	50.0%	12.8 (0.9, 24.8)	45.2%	34.3%	10.9 (-5.8, 27.5)	0.8777
DAS28-CRP	-1.3118 (0.07756)	-0.9722 (0.07819)	-0.3395 (-0.5558, -0.1232)	-1.4461 (0.10018)	-0.7537 (0.10001)	-0.6924 (-0.9697, -0.4151)	0.0489

[a] Treatment policy strategy used for use of rescue therapy prior to Week 16. For binary endpoints, missing data are treated with non-responder imputation. For continuous endpoints, missing data are imputed by control-based pattern multiple imputation.

[b] Response rate is the proportion of responders to total number of subjects in the Randomized Population or within subset, as noted.

[c] Change from baseline analysed using ANCOVA with treatment, randomization stratification variables, and baseline value as independent variables.

[d] Δ is the response rate risk difference for binary endpoint or adjusted change from baseline mean treatment difference for continuous endpoints. 95% CI for continuous endpoint is calculated using Wald method and Clopper-Pearson exact method for response rate.

e P-value is for the interaction of the treatment group with subgroup factor, based on a logistic regression model including treatment group, subgroup factor, and the interaction between treatment group and subgroup factor.

f PASI-75 is calculated among subjects with at least 3% BSA and sPGA of at least 2 at baseline.

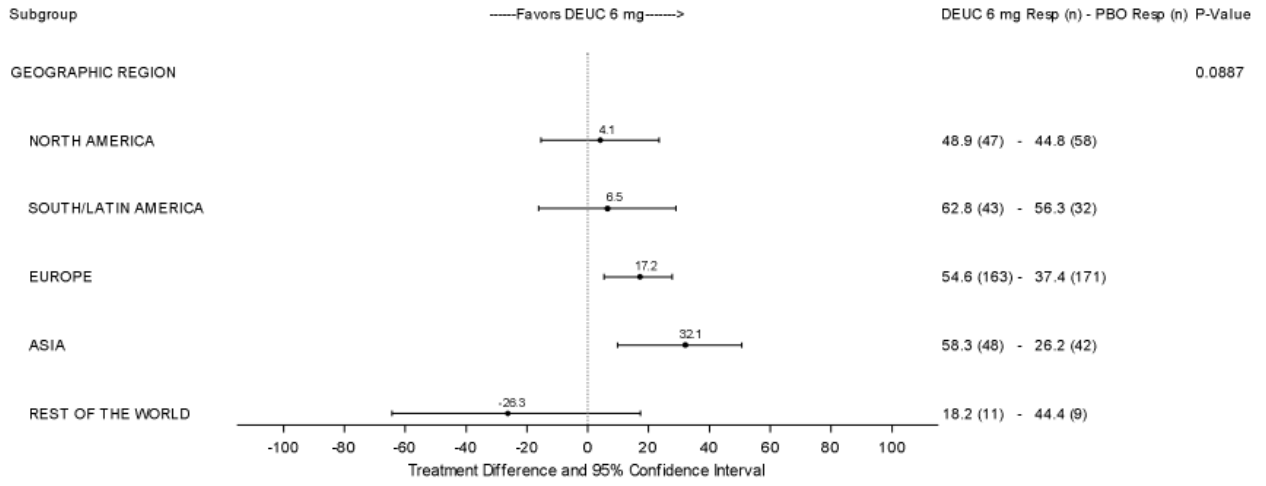
[g] Enthesitis resolution and dactylitis resolution are calculated based on pooled data from Studies IM011054 and IM011055 among subjects with enthesitis or dactylitis, respectively, at baseline.

Subgroup analysis of the primary efficacy endpoint

Subgroup Analyses Pre-specified subgroup analyses of ACR 20 response at Week 16 were performed, and the treatment effect of DEUC versus PBO observed across subgroups was generally consistent with the overall treatment effect except for:

- Body weight (≥ 90 kg) and BMI category (≥ 35)
- Countries by geographic region, Australia (ROW only includes Australia), GBR, and US.

Figure 22. Forest Plot of Subgroup Analysis for ACR 20 response at Week 16 - Treatment difference for Main Estimand, Randomised Population



Resp = Response Rate; n = number of subjects in the treatment group in the subgroup.
P-value is for the interaction of the treatment group for each subgroup, based on a logistic regression model including treatment group, subgroup factor, and the interaction between treatment group and subgroup factor.
N.A.: Not Applicable; N.E.: Not Estimable.
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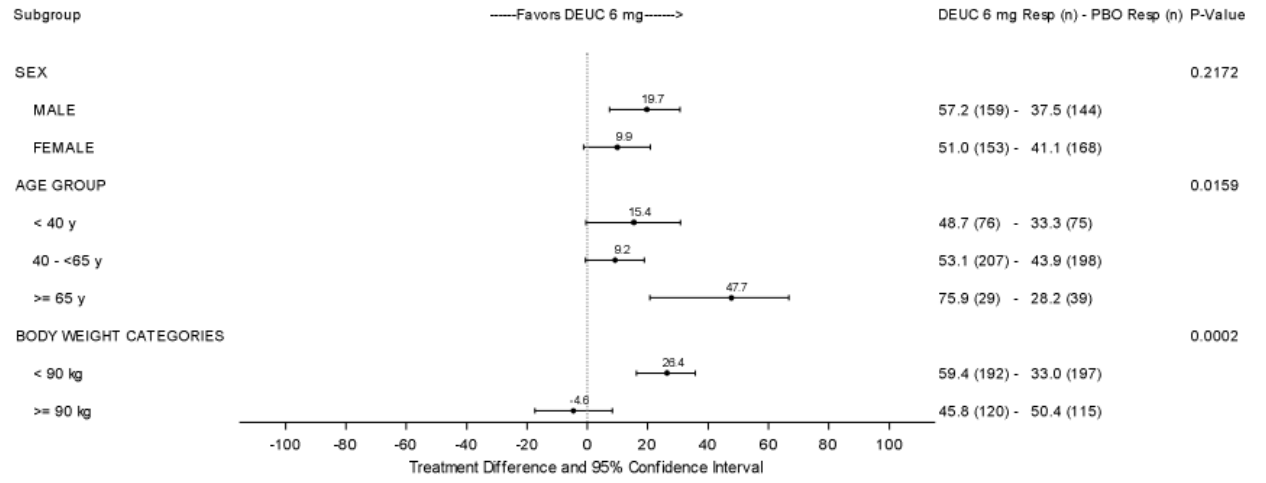

Resp = Response Rate; n = number of subjects in the treatment group in the subgroup.
P-value is for the interaction of the treatment group for each subgroup, based on a logistic regression model including treatment group, subgroup factor, and the interaction between treatment group and subgroup factor.
N.A.: Not Applicable; N.E.: Not Estimable.
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Program Name: rg-ef-acr20subgrp.sas
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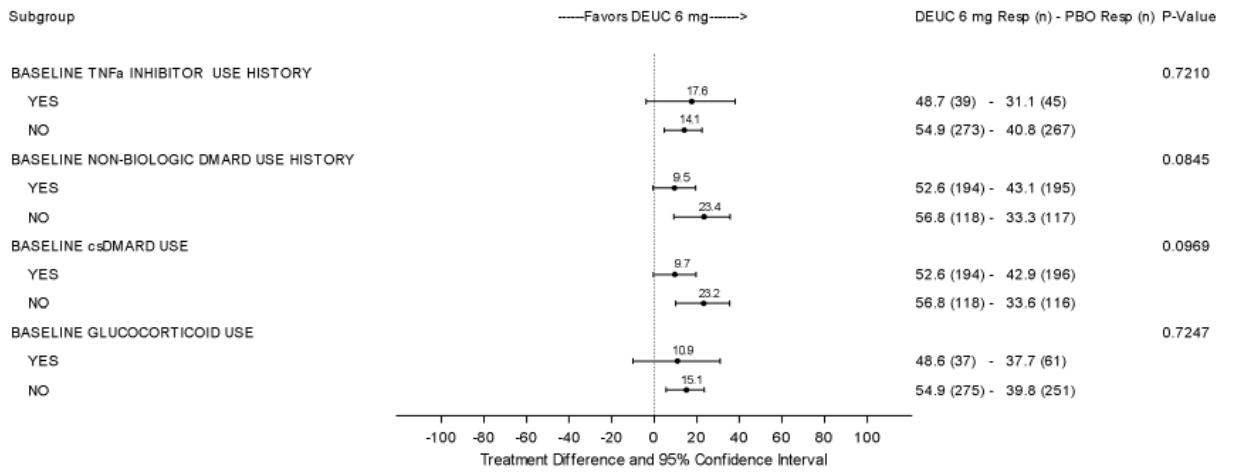
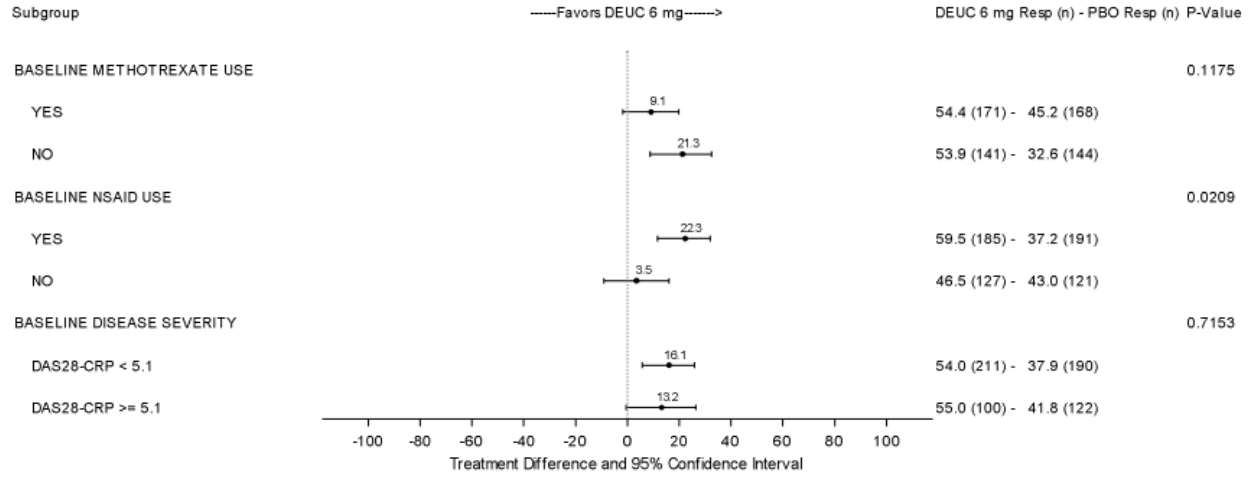


Resp = Response Rate; n = number of subjects in the treatment group in the subgroup.
P-value is for the interaction of the treatment group for each subgroup, based on a logistic regression model including treatment group, subgroup factor, and the interaction between treatment group and subgroup factor.
N.A.: Not Applicable; N.E.: Not Estimable.
Program Path: BMS_GBS\IM011\HAB31377\Biostatistics\Production\Figures\CSR
Program Name: rg-ef-acr20subgrp.sas 23DEC2024:02:48:43



Resp = Response Rate; n = number of subjects in the treatment group in the subgroup.
P-value is for the interaction of the treatment group for each subgroup, based on a logistic regression model including treatment group, subgroup factor, and the interaction between treatment group and subgroup factor.
N.A.: Not Applicable; N.E.: Not Estimable.
Program Path: BMS_GBS\IM011\HAB31377\Biostatistics\Production\Figures\CSR
Program Name: rg-ef-acr20subgrp.sas 23DEC2024:02:48:43

ACR Responses

Results in ACR 20/50/70 Components at Week16 are presented below.

Table 43. Change from Baseline in ACR 20/50/70 Components at Week16, Randomised Population

Tender Joint Count

Timepoint Statistic	DEUC 6 mg N = 312	PBO N = 312
WEEK 12		
N1	312	312
MEAN (SD)	8.3 (8.69)	11.2 (11.30)
MEDIAN	6.0	8.0
MIN, MAX	0, 55	0, 65
CHANGE FROM BASELINE AT WEEK 12		
N1	312	312
MEAN (SD)	-7.0 (8.88)	-5.4 (9.30)
MEDIAN	-6.0	-4.0
MIN, MAX	-55, 27	-54, 28
WEEK 16		
N1	312	312
MEAN (SD)	7.1 (8.22)	10.8 (11.25)
MEDIAN	4.0	7.0
MIN, MAX	0, 50	0, 67
CHANGE FROM BASELINE AT WEEK 16		
N1	312	312
MEAN (SD)	-8.1 (9.12)	-5.8 (10.60)
MEDIAN	-6.0	-4.0
MIN, MAX	-63, 18	-55, 37

Composite variable strategy is used for treatment discontinuation prior to week 16 to set change from baseline to zero.
Treatment policy strategy used for use of rescue therapy prior to week 16.
Observed data after adjusting for intercurrent events (ICEs) occurring up to week 16 are used for descriptive statistics.

Swollen Joint Count

Timepoint Statistic	DEUC 6 mg N = 312	PBO N = 312
WEEK 12		
N1	312	312
MEAN (SD)	4.1 (6.40)	5.8 (7.48)
MEDIAN	2.0	4.0
MIN, MAX	0, 57	0, 51
CHANGE FROM BASELINE AT WEEK 12		
N1	312	312
MEAN (SD)	-5.1 (6.73)	-3.8 (6.08)
MEDIAN	-4.0	-3.0
MIN, MAX	-34, 37	-37, 22
WEEK 16		
N1	312	312
MEAN (SD)	3.9 (6.54)	5.6 (8.19)
MEDIAN	2.0	4.0
MIN, MAX	0, 52	0, 56
CHANGE FROM BASELINE AT WEEK 16		
N1	312	312
MEAN (SD)	-5.3 (7.22)	-4.0 (7.07)
MEDIAN	-5.0	-3.5
MIN, MAX	-55, 40	-38, 31

Composite variable strategy is used for treatment discontinuation prior to week 16 to set change from baseline to zero.
Treatment policy strategy used for use of rescue therapy prior to week 16.
Observed data after adjusting for intercurrent events (ICEs) occurring up to week 16 are used for descriptive statistics.

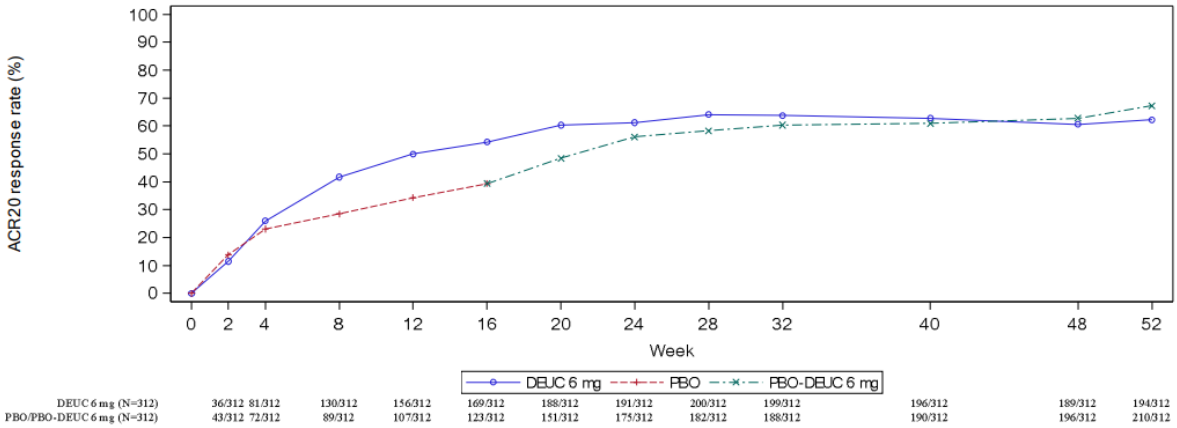
Subject Global Assessment of Disease Activity

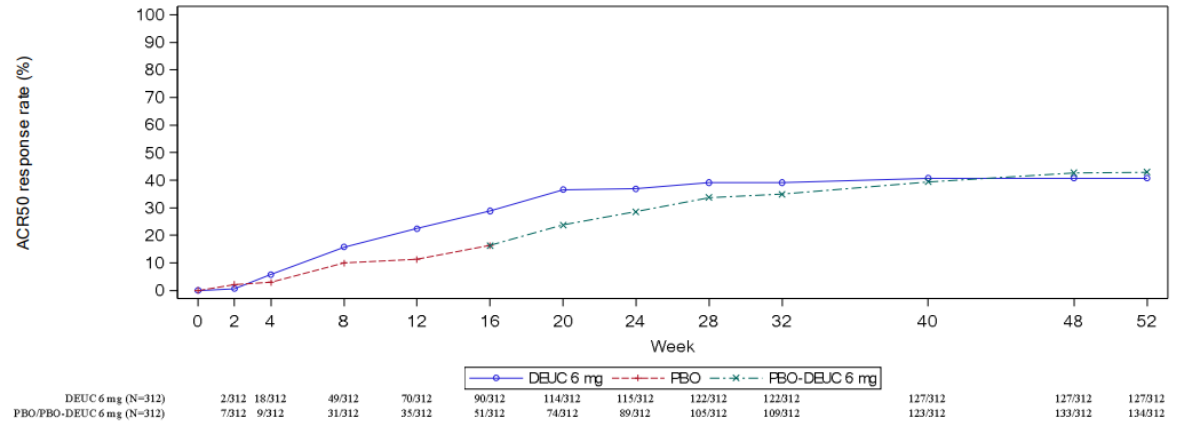
Timepoint Statistic	DEUC 6 mg N = 312	PBO N = 312
WEEK 12		
N1	312	312
MEAN (SD)	41.3 (24.76)	48.6 (23.71)
MEDIAN	41.0	50.0
MIN, MAX	0, 100	0, 100
CHANGE FROM BASELINE AT WEEK 12		
N1	311	312
MEAN (SD)	-17.5 (28.10)	-12.6 (25.09)
MEDIAN	-16.0	-9.0
MIN, MAX	-98, 78	-94, 74
WEEK 16		
N1	312	312
MEAN (SD)	38.8 (24.95)	47.7 (25.58)
MEDIAN	38.5	49.0
MIN, MAX	0, 100	0, 100
CHANGE FROM BASELINE AT WEEK 16		
N1	311	312
MEAN (SD)	-20.0 (27.70)	-13.5 (26.31)
MEDIAN	-18.0	-10.0
MIN, MAX	-98, 59	-94, 85

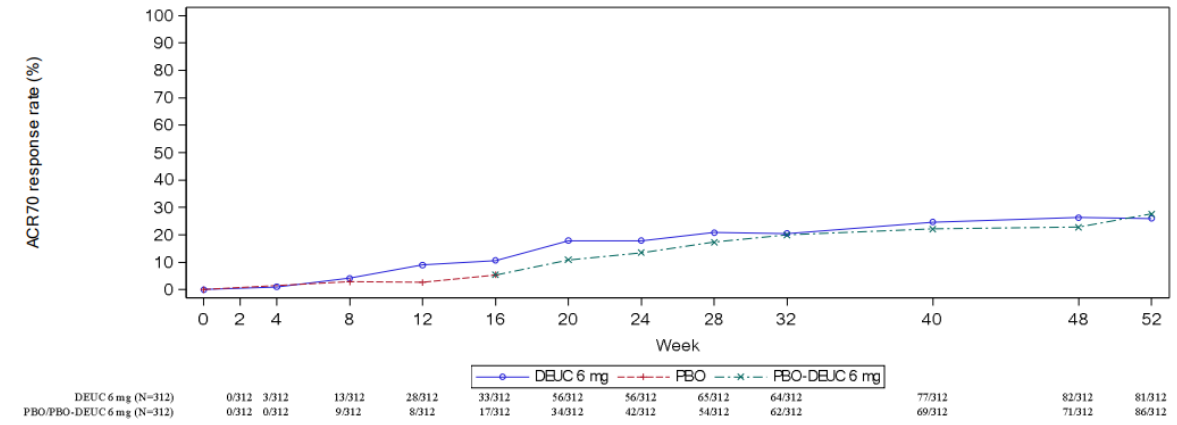
Composite variable strategy is used for treatment discontinuation prior to week 16 to set change from baseline to zero.
Treatment policy strategy used for use of rescue therapy prior to week 16.
Observed data after adjusting for intercurrent events (ICEs) occurring up to week 16 are used for descriptive statistics.

ACR 20 responses with DEUC compared with PBO were through 52 weeks presented below.

Figure 23. ACR 20/50/70 Responses by Treatment Arm Up to Week 52, Randomised Population







Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44. Summary of Efficacy for trial IM011054

Title: Efficacy and Safety of Deucravacitinib Compared with Placebo in Subjects with Active Psoriatic Arthritis (PsA) who are Naïve to Biologic Disease-modifying Anti-rheumatic Drugs			
Study identifier	IM011054		
Design	Phase 3, Randomised, Double-blind, Placebo-controlled		
	Duration of Double-Blind Period: Duration of active period: Duration of Open-label Long-term Extension: Duration of Safety Follow-up (SFU) Period		16 weeks 36 weeks 104 weeks-Optional 4 weeks following last dose of study treatment
Hypothesis	Superiority of DEUC vs Placebo		
Treatments groups	Double-Blind Treatment Period (Weeks 0-16)		6 mg deucravacitinib QD -- Placebo QD 16 weeks
	Duration of active period:		6 mg deucravacitinib QD 36 weeks
	Duration of Open-label Long-term Extension:		6 mg deucravacitinib QD 104 weeks-Optional
Endpoints and definitions	Primary endpoint	ACR20	Proportion of participants meeting ACR 20 response at Week 16
	Key Secondary	DAS28-CRP	Change from baseline in DAS28-CRP score at Week 16
	Key Secondary	HAQ-DI	Change from baseline in HAQ-DI score at Week 16
	Key Secondary	PASI 75 response	Proportion of participants meeting PASI 75 response at Week 16, in participants with at least 3% BSA involvement AND at least sPGA 2 at baseline
	Key Secondary	SF-36 PCS score	Change from baseline in the SF-36 PCS score at Week 16
	Key Secondary	enthesitis resolution	Proportion of participants meeting enthesitis resolution (score of 0) among participants with enthesitis at baseline by LEI at Week 16

	Key Secondary	achievement of MDA	Proportion of participants meeting achievement of MDA where an MDA response is achievement of 5 of 7 following outcomes at Week 16: a) Tender joint count ≤ 1 b) Swollen joint count ≤ 1 c) PASI ≤ 1 or BSA ≤ 3% d) Patient assessment of PsA pain ≤ 15 e) Patient Global Assessment of PsA disease activity ≤ 20 f) HAQ-DI ≤ 0.5 g) Tender enthesial points ≤ 1
	Key Secondary	FACIT-Fatigue score	Change from baseline in FACIT-Fatigue score at Week 16
	Key Secondary	dactylitis resolution	Proportion of participants meeting dactylitis resolution at Week 16 among the participants with dactylitis at baseline, where resolution is defined as a tender dactylitis count of 0 in participants with a tender dactylitis count ≥ 1 at baseline
	Key Secondary	PsA-modified SvdH score	Change from baseline in PsA-modified SvdH score at Week 16
Database lock	20/11/2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis was performed on the Intent-to-Treat (ITT) population, including all randomised patients, at Week 16 after randomisation.		
Descriptive statistics and estimate variability	Treatment group	DEUC 6 mg	Placebo
	Number of subject	336	334
	ACR 20 Response Rate (%)	54.2	34.1
Effect estimate per comparison	ACR 20 Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		Cochran Mantel Haenszel (CMH) test	Δ=20.0
		95% CI	[12.7 ; 27.4]
		P-value	<0.0001
Notes	Statistical significance was achieved for the primary endpoint of ACR 20 at Week 16.		
Analysis description	**Key secondary endpoints**		

Analysis population and time point description	The analysis of key secondary endpoints was performed on the ITT population, including all randomised patients, at Week 16 after randomisation.		
Descriptive statistics and estimate variability	Treatment group	DEUC 6 mg	Placebo
	Number of subject	336	334
	HAQ-DI Change From Baseline (SE)	-0.3850 (0.02897)	-0.2163 (0.02888)
	PASI 75 Response Rate (%)	(N=162 subset) 51.9	(N= 170 subset) 7.1
	SF-36 PCS Change From Baseline (SE)	6.055 (0.4103)	3.711 (0.4086)
	MDA Response Rate (%)	19.0	10.2
	Enthesitis Resolution by LEI Response Rate (%)	(N=178) 48.3	(N=167) 46.1
	PsA-modified SvdH Change From Baseline (SE)	0.78 (0.348)	0.64 (0.320)
	FACIT-Fatigue Change From Baseline (SE)	4.6 (0.48)	2.0 (0.48)
	Dactylitis Resolution Response Rate (%)	(N=132) 59.1	(N=108) 43.5
	DAS28-CRP Change From Baseline (SE)	-1.3334 (0.06378)	-0.8284 (0.06362)
Effect estimate per comparison	HAQ-DI Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= -0.1688
		95% CI	[0.2442; 0.0933]
		P-value	<0.0001
	PASI 75 Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ= 44.1
		95% CI	[35.4; 52.7]

		P-value	<0.0001
	SF-36 PCS Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= 2.344
		95% CI	[1.277; 3.411]
		P-value	<0.0001
	MDA Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ= 8.9
		95% CI	[3.6; 14.2]
		P-value	0.0012
	Enthesitis Resolution (by LEI)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ=3.0
		95% CI	[-7.32; 13.4]
		P-value	0.5699
	PsA-modified SvdH Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= 0.14
		95% CI	[-0.76 ; 1.03]
		P-value	0.7597
	FACIT-Fatigue Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= 2.6
		95% CI	[1.4; 3.9]
		P-value	<0.0001
	Dactylitis Resolution Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ= 14.2
		95% CI	[1.7; 26.7]
		P-value	0.027
	DAS28-CRP Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= -0.5051
		95% CI	[-0.6709; -0.3392]
		P-value	<0.0001

Notes	Statistical significance was achieved in the hierarchical order for HAQ-DI, PASI 75, SF-36 PCS, and MDA at week 16. No statistically significant difference was observed for enthesitis resolution per LEI (in the pooled analysis of IM011054 and IM011055). Statistical significance obtained for FACIT-fatigue, dactylitis resolution (in the pooled analysis of IM011054 and IM011055) and DAS28-CRP was considered nominal.

Table 45. Summary of Efficacy for trial 011055

Title: Efficacy and Safety of Deucravacitinib Compared with Placebo in Participants with Active Psoriatic Arthritis (PsA) who are Naïve to Biologic Disease Modifying Anti-rheumatic Drugs or had Previously Received TNFα Inhibitor Treatment			
Study identifier	IM011055		
Design	Phase 3, Randomised, Double-blind, Placebo-controlled		
	Duration of Double-Blind Period:		16 weeks
	Duration of active period: Duration of Open-label Long-term Extension:		36 weeks 104 weeks- Optional
	Duration of Safety Follow-up (SFU) Period		4 weeks following last dose of study treatment
Hypothesis	Superiority of DEUC vs Placebo		
Treatments groups	Double-Blind Treatment Period (Weeks 0-16)		6 mg deucravacitinib QD Placebo QD 30 mg apremilast BID 16 weeks
	Duration of active period:		6 mg deucravacitinib QD 30 mg tablet apremilast in the morning and the evening 36 weeks
Endpoints and definitions	Primary endpoint	ACR20	Proportion of participants meeting ACR 20 response at Week 16
	Key Secondary	DAS28-CRP	Change from baseline in DAS28-CRP score at Week 16
	Key Secondary	HAQ-DI	Change from baseline in HAQ-DI score at Week 16
	Key Secondary	PASI 75 response	Proportion of participants meeting PASI 75 response at Week 16, in participants with at least 3% BSA involvement AND at least sPGA 2 at baseline
	Key Secondary	SF-36 PCS score	Change from baseline in the SF-36 PCS score at Week 16
	Key Secondary	enthesitis resolution	Proportion of participants meeting enthesitis resolution (score of 0) among participants with enthesitis at baseline by LEI at Week 16
	Key Secondary	achievement of MDA	Proportion of participants meeting achievement of MDA where an MDA response is achievement of 5 of 7 following outcomes at Week 16: a) Tender joint count ≤ 1 b) Swollen joint count ≤ 1 c) PASI ≤ 1 or BSA ≤ 3% d) Patient assessment of PsA pain ≤ 15 e) Patient Global Assessment of PsA disease activity ≤ 20 f) HAQ-DI ≤ 0.5 g) Tender enthesial points ≤ 1
	Key Secondary	FACIT-Fatigue score	Change from baseline in FACIT-Fatigue score at Week 16
	Key Secondary	dactylitis resolution	Proportion of participants meeting dactylitis resolution at Week 16 among the participants with dactylitis at baseline,

			where resolution is defined as a tender dactylitis count of 0 in participants with a tender dactylitis count ≥ 1 at baseline
	Key Secondary	PsA-modified SvdH score	Change from baseline in PsA-modified SvdH score at Week 16
Database lock	04/12/2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis was performed on the ITT population, including all randomised patients, at Week 16 after randomisation.		
Descriptive statistics and estimate variability	Treatment group	DEUC 6 mg	Placebo
	Number of subject	312	312
	ACR 20 Response Rate (%)	54.2	39.4
Effect estimate per comparison	ACR 20 Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		Cochran Mantel Haenszel (CMH) test	Δ=14.8
		95% CI	[7.0; 22.5]
		P-value	0.0002
Notes	Statistical significance was achieved for the primary endpoint of ACR 20 at Week 16.		

Analysis description	**Key secondary endpoints**		
Analysis population and time point description	The analysis of key secondary endpoints was performed on the ITT population, including all randomised patients, at Week 16 after randomisation.		
Descriptive statistics and estimate variability	Treatment group	DEUC 6 mg	Placebo
	Number of subject	312	312
	HAQ-DI Change From Baseline (SE)	-0.3246 (0.03196)	-0.2120 (0.03216)
	PASI 75 Response Rate (%)	(N=154 subset) 40.9	(N=149 subset) 15.4
	SF-36 PCS Change From Baseline (SE)	5.838 (0.4931)	3.796 (0.4962)
	MDA Response Rate (%)	25.6	14.7
	Enthesitis Resolution by LEI Response Rate (%)	(N=140) 52.9	(N=150) 44.0
	FACIT-Fatigue Change From Baseline (SE)	2.5 (0.56)	1.8 (0.56)
	Dactylitis Resolution Response Rate (%)	(N=78) 55.1	(N=80) 45.0
	DAS28-CRP Change From Baseline (SE)	-1.2781 (0.07914)	-0.8038 (0.08085)

Effect estimate per comparison	HAQ-DI Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= -0.1126
		95% CI	[-0.1814;-0.0438]
		P-value	0.0013
	PASI 75 Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ= 25.6
		95% CI	[15.7; 35.5]
		P-value	<0.0001
	SF-36 PCS Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= 2.042
		95% CI	[0.980; 3.105]
		P-value	0.0002
	MDA Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ= 10.9
		95% CI	[4.6; 17.1]
		P-value	0.0007
	Enthesitis Resolution (by LEI)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ= 8.9
		95% CI	[-2.5;20.3]
		P-value	0.1302
	FACIT-Fatigue Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= 0.8
		95% CI	[-0.4;2.0]
		P-value	0.2017
	Dactylitis Resolution Response Rate (%)	Comparison groups	DEUC 6 mg VS placebo
		CMH test	Δ=9.3
		95% CI	[-6.1; 24.8]
		P-value	0.2373
	DAS28-CRP Change From Baseline	Comparison groups	DEUC 6 mg VS placebo
		ANCOVA	Δ= -0.4743
		95% CI	[-0.6455; -0.3031]
		P-value	<0.0001
Notes	Statistical significance was achieved in the hierarchical order for HAQ-DI, PASI 75, SF-36 PCS, and MDA at week 16. No statistically significant difference was observed for enthesitis resolution per LEI (in the pooled analysis of IM011054 and IM011055). Statistical significance obtained for dactylitis resolution (in the pooled analysis of IM011054 and IM011055) and DAS28-CRP was considered nominal.		

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis for efficacy was performed including data up to Week 52 from both Phase 3 studies, IM011054 and IM011055, based on an efficacy cut-off date determined prior to the DBL. The integrated database for the efficacy analysis was created using the Analysis Data Model (ADaM) datasets from the IM011054 and IM011055 studies.

The objectives were: to evaluate the primary and key secondary endpoints at Week 16 in PsA population, to evaluate the primary endpoint at Week 16 by subgroups in PsA population and to evaluate a subset of exploratory endpoints up to Week 52 in PsA population. The primary analysis of the hierarchised key secondary endpoints enthesitis and dactylitis was based on the pooled analysis of studies IM011054 and IM011055.

Statistical Analyses: Efficacy

Key efficacy results including primary endpoint and hierarchical testing of secondary endpoints for Studies IM011054 and IM011055 at Week 16 were as follows:

Table 46. Comparison of the Primary and Key Secondary Endpoint Hierarchy at Week 16 Across the Controlled Phase 3 Studies

	IM011054			IM011055			Pooled		
	Response rate (%)[a] or change from BL (SE)[b]			Response rate (%)[a] or change from BL (SE)[b]			Response rate (%)[a] or change from BL (SE)[b]		
Endpoints	DEUC 6 mg (N = 336)	PBO (N = 334)	Δ (95% CI)[c] P-value[d]	DEUC 6 mg (N =312)	PBO (N = 312)	Δ (95% CI)[c] P-value[d]	DEUC 6 mg (N = 648)	PBO (N = 646)	Δ (95% CI)[c] P-value[d]
Primary Endpoint									
ACR 20	54.2%	34.1%	20.0 (12.7, 27.4) **p < 0.0001***	54.2%	39.4%	14.8 (7.0, 22.5) **p = 0.0002***	54.2%	36.7%	17.5 (12.1, 22.8) *p = < 0.0001*
Secondary Endpoints									
HAQ-DI	-0.3850 (0.02897)	-0.2163 (0.02888)	-0.1688 (-0.2442, -0.0933) **p < 0.0001***	-0.3246 (0.03196)	-0.2120 (0.03216)	-0.1126 (-0.1814, -0.0438) **p = 0.0013***	-0.3642 (0.01940)	-0.2219 (0.01932)	-0.1424 (-0.1936, -0.0912) *p < 0.0001*
PASI 75 (in subset)[e]	N = 162 51.9%	N = 170 7.1%	44.1 (35.4, 52.7) **p < 0.0001***	N = 154 40.9%	N = 149 15.4%	25.6 (15.7, 35.5) **p < 0.0001***	N = 316 46.5%	N = 319 11.0%	35.2 (28.7, 41.8) *p < 0.0001*
SF-36 PCS	6.055 (0.4103)	3.711 (0.4086)	2.344 (1.277, 3.411) **p < 0.0001***	5.838 (0.4931)	3.796 (0.4962)	2.042 (0.980, 3.105) **p = 0.0002***	6.282 (0.2872)	4.063 (0.2865)	2.219 (1.462, 2.977) *p < 0.0001*
MDA	19.0%	10.2%	8.9 (3.6, 14.2) **p = 0.0012***	25.6%	14.7%	10.9 (4.6, 17.1) **p = 0.0007***	22.2%	12.4%	9.8 (5.8, 13.9) *p < 0.0001*
Enthesitis Resolution by LEI (pooled analysis) [in subset][f]	N = 318 50.3%	N = 317 45.1%	5.3 (-2.4, 12.9) p = 0.1781	N = 318 50.3%	N = 317 45.1%	5.3 (-2.4, 12.9) p = 0.1781	N = 318 50.3%	N = 317 45.1%	5.6 (-2.0, 13.3) p = 0.1515[g]
PsA-modified SVDH	0.78 (0.348)	0.64 (0.320)	0.14 (-0.76, 1.03) p = 0.7597	*Structural progression not assessed in IM011055*			N.A.		
Post hoc (rank ANCOVA)[h]	*0.4061 (SD = 1.86297)*	*0.5020 (SD = 1.61214)*	*N.A. p = 0.0187*[h]						
FACIT-Fatigue	4.6 (0.48)	2.0 (0.48)	2.6 (1.4, 3.9) *p < 0.0001*	2.5 (0.56)	1.8 (0.56)	0.8 (-0.4, 2.0) p = 0.2017	3.7 (0.33)	2.0 (0.33)	1.7 (0.9, 2.6) *p < 0.0001*
Dactylitis Resolution (pooled analysis) [in subset][f]	N = 210 57.6%	N = 188 44.1%	12.8 (3.2, 22.4) *p = 0.0100*	N = 210 57.6%	N = 188 44.1%	12.8 (3.2, 22.4) *p = 0.0100*	N = 210 57.6%	N = 188 44.1%	12.7 (3.0, 22.4) *p = 0.0107*[g]
DAS28-CRP	-1.3334 (0.06378)	-0.8284 (0.06362)	-0.5051 (-0.6709, -0.3392) *p < 0.0001*	-1.2781 (0.07914)	-0.8038 (0.08085)	-0.4743 (-0.6455, -0.3031) *p < 0.0001*	-1.3454 (0.04502)	-0.8573 (0.04502)	-0.4881 (-0.6072, -0.3690) *p < 0.0001*

Note: Statistically significant p-values are denoted using **boldface type** and an asterisk (*), and nominally significant p-values are denoted using *italicized type*

[a] Response rate is the proportion of responders to total number of subjects in the Randomized Population or within subset, as noted.

[b] Change from baseline analyzed using ANCOVA with treatment, randomization stratification variables, and baseline value as independent variables.

[c] Δ is the response rate risk difference for binary endpoint or adjusted change from baseline mean treatment difference for continuous endpoints. 95% CI for continuous endpoint is calculated using Wald method and Clopper-Pearson exact method for response rate.

[d] P-value is based on the Wald test for continuous endpoint and the CMH test for binary endpoints.

[e] PASI-75 is calculated among subjects with at least 3% BSA and sPGA of at least 2 at baseline.

[f] Enthesitis resolution and dactylitis resolution are calculated based on pooled data from Studies IM011054 and IM011055 among subjects with enthesitis or dactylitis, respectively, at baseline.

[g] The CMH test from the pooled analysis included 1 additional stratification factor, study, compared with the CMH test used in the study level hierarchy.

[h] Post hoc SvDH results are based on analysis population 1 and Rank ANCOVA model specified in Section 3.1.7.2 of the SCE without imputation. Rank ANCOVA presents rank of change from baseline as the dependent variable, with treatment, randomization stratification variables and baseline value of the SvdH total score as independent variables. ANCOVA and Rank ANVOCA are based on purely observed data. Smaller rank indicates smaller change from baseline at Week 16.

Source: Table 3.1.4.1-1 in the SCE[44]

Subgroup analyses of the Primary Endpoint (ACR 20 Response) in the Phase 3 Efficacy Pool (Studies IM011054 and IM011055) demonstrated that, overall, treatment effect favoured DEUC over PBO at Week 16.

2.4.3. Discussion on clinical efficacy

The MAH applied for the following indication: *Sotyktu, alone or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to a prior DMARD therapy.*

The proposed dose is 6 mg orally once daily for adults. The dose and regimen are similar to the ones in the already authorised indication in psoriasis. The clinical development of deucravacitinib in the above-mentioned indication is supported by two pivotal multicenter, randomised, double-blind, placebo-controlled Phase 3 studies (IM011054 (POETYK PsA-1) and IM011055 (POETYK PsA-2)) and one dose-finding phase 2 randomised, placebo-controlled, double-blind, multicentre study (IM011084).

The dose-response of deucravacitinib was assessed in the phase 2 study IM011084, which evaluated the efficacy and safety of DEUC 6 mg QD and 12 mg QD in subjects with active PsA. Eligible subjects had PsA for ≥ 6 months, met the Classification Criteria for Psoriatic Arthritis (CASPAR), and showed ≥ 2 cm plaque psoriasis, ≥ 3 swollen and ≥ 3 tender joints (66/68 count) at screening and Day 1, with hsCRP ≥ 3 mg/L at screening. The study consisted of two periods: Part A: a 16-week randomised, placebo-controlled, double-blind period followed by Part B: an optional 36-week double-bind, double-dummy controlled period.

The primary endpoint was the proportion of patients achieving an ACR20 at Week 16. Key secondary endpoints included the changes from baseline in HAQ-DI, PASI 75 and SF-36 PCS. Out of 314 subjects screened, 203 were randomised in 1:1:1 ratio in the three treatment groups. Baseline demographics were generally balanced across the groups. At baseline, 65.0% of subjects were using csDMARDs including 54.7% MTX; this is overall well balanced across the groups. In addition, 61.6% of subjects were on NSAIDs, and 12.3% of subjects were taking oral steroids.

A statistically significant dose-response relationship of deucravacitinib (6 mg QD and 12 mg QD) was obtained for the primary endpoint (slope coefficient of dose = 0.11 [95% CI: 0.05, 0.17], p-value < 0.001). The ARC20 response rate was 52.9% (95% CI: 41.2, 64.6) in the DEUC 6 mg QD group and 62.7% [95% CI: 51.1, 74.3] in the DEUC 12 mg compared with placebo (31.8% [95% CI: 20.6, 43.1]. And at Week 16, the absolute difference between the two doses appeared numerically limited.

Therefore, the dose for the pivotal studies was selected based on results from this Phase 2 dose-ranging study, and further E-R modelling of these results. The rationale for selecting the 6 mg QD dose is based on similar efficacy and somewhat better safety profile compared to 12 mg dose for the overall population in study IM011084. This was endorsed by the CHMP: at a similar efficacy, it is reasonable to favour the lowest dose for which a better safety profile is expected. The selection of a 6 mg dose for progression to Phase 3 studies is considered justified.

Design and conduct of clinical studies

Pivotal Phase 3 study IM011054 (POETYK PsA-1)

This was a 52-week, multi-center, randomised, double-blind, placebo-controlled Phase 3 study evaluating deucravacitinib in participants with active PsA who were naïve to biologic therapy and have failed or been intolerant to standard therapies (csDMARD and/or NSAID).

The design is in line with the Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis (CHMP/EWP/438/04). There was a 16-week randomised, placebo-

controlled, double-blind period, followed by an active treatment period up to Week 52, during which all participants received deucravacitinib 6 mg once daily remaining blinded of the initial assignation (deucravacitinib or placebo), and subsequently by an optional single-arm OLE study until Week 156. as per the above guideline, placebo control is acceptable for short-term (12-24 weeks). The enrolment criteria were also in accordance with the EMA PsA guideline requirements. Use of biologic DMARDs, immunosuppressive agents, and JAK inhibitors was prohibited during the study. The participants with nonplaque PsO were excluded and those with other autoimmune condition were not eligible.

Overall, demographic characteristics were well balanced across the two treatment arms. In this Phase 3 study, the majority of participants were Caucasian (approximately 81%), with a mean age of 52 years. About 16% of participants were aged ≥65 years. The proportions of female and male participants were generally similar, although sex distribution varied slightly between treatment groups. At baseline, 65.5% of participants in the deucravacitinib arm and 68.0% in the placebo arm weighed <90 kg, while 33.9% in the deucravacitinib arm and 32% in the placebo arm weighed ≥90 kg. The mean disease duration at baseline was 7.65 years in both arms.

Most subjects (84.0%) presented with peripheral arthritis (82.7% in the DEUC arm and 85.3% in the PBO). The predominant forms of PsA were polyarthritis (78.1%) followed by oligoarthritis (10.3%) and predominant DIP joint involvement (8.4%) while 15.5% of the population presented with both psoriatic spondylarthritis and peripheral arthritis. Median for TJC at baseline was 16 in the DEUC arm vs 15 in the PBO arm. Median for SJC was 9 in the DEUC arm vs 8 in the PBO arm.

All subjects (100.0% in each arm) used concomitant medications during Placebo-controlled period. The most commonly used concomitant medications of interest in all treatment arms were csDMARDs (70.8% in the DEUC arm and 69.7% in the PBO arm) and NSAIDs (59.3% in the DEUC arm and 63.4% in the PBO arm). The most commonly used csDMARD was MTX; there was slightly more patients under MTX in the DEUC group (53.0% in the DEUC arm and 50.2% in the PBO arm), but the difference remained limited.

Overall, the statistical methods, randomisation, stratification, and blinding as discussed in the above sections were considered appropriate. The two ICEs: treatment discontinuation for any reason and rescue medication therapy, have been found acceptable.

The primary endpoint was the proportion of patients achieving an ACR20 at Week 16, defined as a 20% improvement over baseline in tender (68) and swollen (66) joint counts, a 20% improvement in 3 of the 5 remaining core data set measures: Subject global assessment of disease activity, Subject global assessment of pain, HAQ-DI, Physician global assessment of PsA, hsCRP. Key secondary endpoints included the changes from baseline in HAQ-DI, PASI 75, SF-36 PCS, and MDA, enthesitis resolution, FACIT-Fatigue, dactylitis resolution and DAS-28-CRP at Week 16. These secondary endpoints covered multiple clinically relevant aspects of the PsA.

The design, conduct, and selected endpoints of this pivotal Phase 3 study are generally acceptable and aligned with EMA guidance. The study population was appropriate and representative of the target treatment population.

Pivotal Phase 3 study IM011055 (POETYK PsA-2)

The study design for study IM011055 was identical to study IM011054 except that participants who had failed or were intolerant to TNFα inhibitor treatment were allowed to be included.

The study was structured into three periods. The primary efficacy evaluation occurred during the 16-week randomised, placebo-controlled, double-blind phase, in which participants received either deucravacitinib 6 mg once daily (QD), placebo, or apremilast 30 mg twice daily (BID). It was

followed by an active treatment period through Week 52, during which all participants continued in a blinded manner on either deucravacitinib 6 mg QD or apremilast 30 mg BID. Thereafter, an optional open-label extension continued through Week 156.

Most subjects (84.0%) had peripheral arthritis while 16.0% had peripheral plus psoriatic spondylarthritis. The majority of subjects had the predominant subtype of polyarthritis (72.4%) and oligoarthritis (16.9%). 8.9% of subjects had predominant distal interphalangeal joint involvement and swollen joints and 1.6% of subjects had predominant axial involvement. The baseline tender (68) joint count mean was 15.2 in the DEUC arm vs 16.6 in the PBO arm. The baseline swollen (66) joint count mean was 9.2 in the DEUC arm vs 9.6 in the PBO arm.

Overall, demographic characteristics were well balanced across the two treatment arms. In this Phase 3 study, the majority of participants were Caucasian (approximately 72%), with a mean age of 49 years. About 12% of participants were aged ≥65 years. The proportions of female and male participants were generally similar.

At baseline, 61.5% of participants in the deucravacitinib arm and 63.1% in the placebo arm weighed <90 kg, while 38.5% in the deucravacitinib arm and 36.9% in the placebo arm weighed ≥90 kg. The mean disease duration at baseline was approximately 5 years in both arms.

All subjects (100.0% in all arms) used concomitant medications during placebo-controlled and active treatment period. The most commonly used concomitant medications of interest in all treatment arms were csDMARDs (62.5%, 63.3%, and 64.8% in the DEUC, PBO and APR arms, respectively) and NSAIDs (58.7%, 62.4%, and 68.6% in the DEUC, PBO and APR arms, respectively.

Overall, the statistical methods, randomisation, stratification, and blinding were considered appropriate.

The design, conduct, statistical evaluation and selected endpoints of this pivotal Phase 3 study are generally acceptable and aligned with EMA guidance. The study population was appropriate and representative of the target treatment population, as concluded by the CHMP.

Efficacy data and additional analyses

Pivotal Phase 3 study IM011054 (POETYK PsA-1)

Among 1840 subjects enrolled, 670 subjects were randomised. The most common reason for not randomising was that subject no longer meet study criteria. 665 subjects were treated: 332 (98.8%) subjects in the DEUC arm, 333 (99.7%) in the PBO. The higher screening failure rate was mainly driven by the additional inclusion criterion for at least 1 PsA-related hand and/or foot joint erosion on x-ray confirmed by central reading.

The proportion of subjects during Placebo-Controlled Period who discontinued study treatment was comparable between the DEUC and PBO arms; the most common reasons being AEs and subject withdrawal of consent. A total of 45 subjects discontinued study (below 7% in either arm). A total of 615 subjects entered the active treatment Period. However, as of the last subject's Week 52 visit, a total of 544 subjects completed the Active Treatment Period, 496 subjects met the eligibility criteria and entered the OLE study.

The primary endpoint, ACR20 response at Week 16, was met, demonstrating statistical significance versus placebo. A total of 182 patients (54.2%) in the deucravacitinib (DEUC) arm achieved an ACR20 response compared with 114 patients (34.1%) in the placebo (PBO) arm. Estimated

difference is 20.0% (p <0.0001, [95% CI: 12.7, 27.4]). This result is supportive of deucravacitinib's efficacy in the claimed indication.

The key secondary endpoints (HAQ-DI, PASI75, SF-36 PCS, and MDA at Week 16), demonstrated statistical significance. Supplemental estimand and sensitivity analyses for missing data were consistent with the primary analysis.

At Week 16, analyses in the DEUC arm (-0.3850) demonstrated a significantly higher improvement in HAQ-DI scores compared with placebo (-0.2163) with an adjusted mean difference –0.1688 [95% CI: –0.4418, –0.3282] (p-value<0.0001).

At Week 16, the proportion of subjects achieving PASI 75 was significantly higher in the DEUC arm compared with placebo (51.9% vs. 7.1%), corresponding to an estimated difference of 44.1% [95% CI: –35.4, 52.7] (p-value<0.0001).

At Week 16, the mean change from baseline in the SF-36 Physical Component Score (PCS) was significantly greater in the DEUC arm compared with the placebo arm (adjusted mean difference: 2.344 [95% CI: 1.277, 3.411]; nominal p < 0.0001).

At Week 16, a significantly greater proportion of subjects in the DEUC arm achieved MDA response compared to subjects in the PBO arm (19.0% vs 10.2%, difference vs PBO = 8.9 [95% CI: 3.6, 14.2], p-value = 0.0012).

The 5th pre-specified secondary endpoint of enthesitis resolution per LEI did not demonstrate a statistically significant difference between DEUC and PBO. Consequently, subsequent endpoints in the hierarchical testing sequence, FACIT-fatigue, dactylitis resolution, and DAS28-CRP, are considered as exploratory only, and should be interpreted with caution.

In terms of skin outcomes, patients in the DEUC arm achieved significantly higher improvement in psoriasis, as demonstrated by PASI 75 (ranked key secondary endpoint). A trend in favor of benefit was also observed for PASI 90 and PASI 100 at Week 16 (exploratory endpoint).

In general, the secondary endpoint results are considered supportive of the primary outcome.

*Subgroup analyse*s in ACR 20 responses at Week 16 were overall consistent for gender and body weight ≥ 90 kg and BMI category ≥ 35 kg/m2 and in the subgroups determined by prior exposure to MTX, and by steroids/NSAIDs use. Subgroup analysis by concomitant treatment status (having received MTX, NSAID and/or Corticosteroids, or having received any of these 3 treatments) during the double-blind period has been provided. No significant treatment-by-subgroup interaction was observed, suggesting that the treatment effect of DEUC is not meaningfully influenced by concomitant csDMARD use.

Pivotal Phase 3 study IM011055 (POETYK PsA-2)

Among 1193 subjects enrolled, 729 subjects were randomised. The most common reason for not randomising was that subject no longer meet study criteria. 728 subjects were treated: 292 (93.6%) subjects in the DEUC arm, 292 (93.9%) in the PBO and 90 (85.7%) in the APR arm. The higher screening failure rate was mainly driven by the additional inclusion criterion for at least 1 PsA-related hand and/or foot joint erosion on x-ray confirmed by central reading.

The proportion of subjects during Placebo-Controlled Period who discontinued study treatment was comparable between the DEUC and PBO arms; the most common reasons being AEs and subject withdrawal of consent. A total of 40 subjects discontinued study (14 subjects on DEUC arm 4.5%, 17 on Placebo arm 5.5%, 9 subjects on APR arm 8.6%) from the placebo-controlled period.

Apremilast was selected as an active comparator for safety assessment in the deucravacitinib study; no efficacy comparisons with apremilast were initially conducted. At the CHMP request, efficacy comparisons with apremilast was provided, in order to attempt to contextualise the efficacy profile. In this post-hoc analysis, the results appear to be slightly in favour of DEUC, but given the exploratory nature of the analysis, these are only considered as indicative.

The primary endpoint, ACR20 response at Week 16, was met, demonstrating statistical significance versus placebo. A total of 169 patients (54.2%) in the deucravacitinib (DEUC) arm achieved an ACR20 response compared with 123 patients (39.4%) in the placebo (PBO) arm (p = 0.0002) difference vs placebo = 14.8 [95% CI: 7.0, 22.5], which demonstrates clinical efficacy of DEUC.

The key secondary endpoints (HAQ-DI, PASI75, SF-36 PCS, and MDA at Week 16) demonstrated statistical significance versus placebo. Supplemental estimand and sensitivity analyses for missing data were consistent with the primary analysis.

At Week 16, the mean reduction in HAQ-DI score from baseline was significantly greater in the DEUC arm compared with placebo, demonstrating a statistically significant improvement (difference vs. placebo = −0.1126 [95% CI: −0.1814, −0.0438]; p = 0.0013).

A significant higher proportion of subjects in the DEUC arm achieved PASI 75 at Week 16 compared with subjects in the PBO arm (40.9% vs 15.4%; difference vs PBO = 25.6 [95% CI: 15.7, 35.5], p-value ≤ 0.0001).

At Week 16, the mean change from baseline in the SF-36 PCS was significantly higher in the DEUC arm compared with placebo (adjusted mean difference: 2.042 [95% CI: 0.980, 3.105]; nominal p < 0.0002).

The proportion of subjects in the DEUC arm achieved MDA response at Week 16 was significantly greater compared with subjects in the PBO arm. (25.6% vs 14.7%; difference vs placebo = 10.9 [95% CI: 4.6, 17.1], p-value = 0.0007)

The 5th pre-specified secondary endpoint of enthesitis resolution per LEI did not demonstrate a statistically significant difference between DEUC and PBO. Consequently, subsequent endpoints in the hierarchical testing sequence, FACIT-fatigue, dactylitis resolution, and DAS28-CRP are considered as exploratory only, and should be interpreted with caution.

A trend in favour of benefit was also observed for PASI 90 and PASI 100 at Week 16 (exploratory endpoints).

In general, the secondary endpoint results are considered supportive of the primary outcome; however, the suboptimal selection of key secondary endpoints led to a missed opportunity to gain more robust support for efficacy and deeper insight into treatment effects.

Subgroup analysis

A variability in the responses within the body weight was observed with a slight negative trend in ACR20 response at Week 16 in subject with a weight equal or superior to 90kg. This finding was not seen in study IM011054 and further analysis was hence performed to investigate the potential impact of baseline body weight on ACR response. According to the results obtained, the observed variability is explained by study-specific factors, particularly the elevated placebo response in heavier subjects in the IM011055 study. This was already seen in the initial MAA for PsA, patients with a higher body weight are expected to have a lower geometric mean steady-state deucravacitinib exposure as reflected in section 5.2 of the SmPC, nevertheless, no significant effect is expected. This was endorsed by the CHMP.

Pooled data

Primary endpoint

The primary endpoint of ACR 20 at Week 16 was also met in the pooled analysis, showing that treatment with DEUC resulted in statistically significant 17% higher response rates compared to placebo (54% vs 37%). Subjects receiving DEUC were approximately twice as likely to reach ACR 20 response compared with those in the PBO arm (OR vs PBO ranging from 1.82 to 2.33). The results of all supportive analyses of the primary efficacy variable confirmed the primary efficacy results. Improvements from baseline were shown also in all individual ACR components with DEUC at week 16. Separation in favour of the DEUC arm vs the PBO arm was observed from Week 8.

Secondary endpoints

Enthesitis and dactylitis resolution was assessed only on pooled population. Hierarchical testing of secondary endpoints was halted after enthesitis resolution endpoint did not reach statistical significance. As a result, the remaining key secondary endpoints – FACIT-Fatigue, dactylitis resolution and DAS28-CRP - were not formally adjusted for multiplicity, and the results should therefore be interpreted with caution and regarded as nominal. In both studies, a higher proportion of subjects in the DEUC arms than in the PBO arms achieved LDA and remission by week 16 according to DAS28-CRP (LDA: 15% and 18% vs 8% and 14%; remission: 22% and 27% vs 14% and 14%). Subjects receiving DEUC had mean times to LDA of 99- and 92-days and to remission of 105- and 100-days in studies IM011054 and IM011055, respectively. On the KM plots, separation of the curves was seen after approximately 30 days in Study IM011054 and approximately 60 days in Study IM011055, a difference that may be related to the higher placebo response rate observed in Study IM011055.

Deucravacitinib achieved nominal statistical significance across several composite efficacy endpoints (DAPSA, DAPSA LDA, PASDAS, PsARC) and also yielded higher response rates in stricter measures of skin (PASI 75/90) improvement. None of those results was controlled for multiplicity, therefore should be interpreted with caution.

In general, the secondary endpoint results are considered supportive of the primary outcome; however, the suboptimal selection of key secondary endpoints led to a missed opportunity to gain more robust support for efficacy and deeper insight into treatment effects.

Axial disease: Only about 15% of patients had concomitant axial involvement at baseline, which is lower than reported in the literature (reported ranges vary between 25% to 50% or even 70%, depending on the definitions and diagnostic criteria used). About 35.4% of patients with axial disease in IM011055 study achieved nominally significant ≥50% improvement from baseline in BASDAI at Week 16, compared to 8.3% of participants receiving PBO. In study IM011054 there was no significant difference between treatment arms. Therefore, a statement in section 5.1. of the SmPC was included to inform prescribers that the number of PsA patients with axial involvement/predominant spondylitis was too small to allow meaningful assessment.

Efficacy over Time

In Study IM011054, the improvements in therapeutic response across joint and skin endpoints were maintained up to week 52 in more than 80% of week 16 responders. Somewhat lower maintenance rates were observed for stricter measures of improvement, with about 71-74% of subjects maintaining their ACR70 and PASI90 response up to week 52. The MDA response was maintained by 89.1% subjects, reflecting sustained overall improvement. In study IM011055, maintenance rates were somewhat lower with about 81-85% of subjects maintaining their initial

week 16 ACR20 and MDA response, respectively. Maintenance rates for other endpoints were between 66% for PASI90 and 77% for ACR50. These results have been adequately reflected in section 5.1 of the SmPC.

Overall, the majority of week 16 responders maintained their response at Week 52, demonstrating the durability of response achieved with DEUC treatment. The efficacy seems to reach a maximum effect around Week 20 and Week 24, followed then by a plateau. Following the updated efficacy analyses, the pattern is consistent with the response kinetics previously observed in the psoriasis clinical programme and maximal or near-maximal responses were generally observed around Week 24. Therefore, the statement already included in section 4.2 of the SmPC to consider discontinuation if no evidence of therapeutic effect is shown after 24 weeks, is also applicable for PsA patients.

Justification of the indication

Subgroup analyses stratified by concomitant csDMARD use at baseline show no significant treatment-by-subgroup interaction for all primary and key secondary endpoints at Week 16. The findings were reproductible across studies and endpoints. Overall, these subgroup data demonstrate the efficacy of DEUC whenever it is used as monotherapy or in combination with csDMARDs more specifically with MTX. The substantially smaller sample size in the non-MTX csDMARD subgroup limits the robustness and interpretability of the efficacy estimates in this population and precludes definitive conclusions regarding comparative efficacy between treatment regimens. Therefore, there was not enough evidence to support the proposed broad indication including the combination of DEUC with all csDMARDs. At the CHMP request, the MAH restricted the indication to use deucravacitinib alone or in combination with MTX.

Finally, the proposed indication mentioned that the treatment is indicated in patients with inadequate or failed response to prior DMARDS, thus regardless of the type of DMARDs (csDMARDs, bDMARDs, or tsDMARDs). Although the available evidence in TNFi-experienced PsA patients is limited, the randomisation was stratified on prior biologic DMARD use and the treatment effect was demonstrated in the overall study population after adjustment for this prespecified stratification factor. No evidence was identified to suggest a differential treatment effect across the categories of this factor. The results are therefore considered applicable to all categories of prior DMARD use.

Post hoc analysis related to quality issues

After unblinding, quality issues with lab samples were identified in studies IM011054 (0,04 % samples) and IM011055 (0,06 % samples), affecting inclusion/exclusion criteria and endpoint assessments (including the primary ACR20 response). Post-hoc exclusions and sensitivity analyses were conducted, confirming minimal impact on analysis populations and statistical results, given the objective nature of lab assessments and the limited number of samples affected by the issues.

2.4.4. Conclusions on the clinical efficacy

The demonstration of the efficacy of deucravacitinib 6mg is supported by two Phase 3 studies with similar design, conducted in patients with active PsA. Both trials met the primary endpoint versus placebo, based on a ACR20 responder analysis at Week 16, showing a clinical improvement in disease activity composite measures.

Furthermore, the secondary analyses were supportive of the primary demonstration of the efficacy, PRO showed a benefit in function, disability, and quality of life.

Most of the patients used concomitant csDMARDs; predominantly MTX. Therefore, the CHMP considered that the observed clinical efficacy data do not support the use of deucravacitinib in the originally claimed, but only in the following, restricted indication:

Sotyktu, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic (DMARD) therapy (see section 5.1).

The SmPC has been adequately updated with the relevant clinical information from the conducted development programme of deucravacitinib's use in PsA.

2.5. Clinical safety

Introduction

The appraisal of DEUC safety profile in PsA patients is based on safety outcomes from the two phase 3 studies, IM011054 and IM011055, and the part A of the phase 2 study IM011084 (for methodology and design, see section 2.4), due to their similar design. All safety analyses were based on the treated population, consisting of all randomised patients who received at least 1 dose of IP in randomised phase (Placebo-Controlled Period), or all patients who received at least 1 dose of IP in non-randomised phase (i.e., Active Treatment or OLE Period). Unless otherwise specified, patients were grouped "as treated" according to the treatment they received, independent of randomisation assignment. Hence, 3 periods were also defined: Placebo-Controlled Period, 52-Week Period and Cumulative DEUC period beyond 52 weeks.

Table 47. Safety Analysis Periods, Data Pools, and Relevant Windows of Time

Analysis Period	Data Pool	Studies in Data Pool[a]	Relevant Time Window
Placebo-controlled Period	All PsA Safety Pool	IM011054, IM011055, IM011084 Part A	Week 0 - 16
52-Week Period	Phase 3 Safety Pool	IM011054, IM011055	Week 0 - 52
Cumulative DEUC Period	Phase 3 Safety Pool	IM011054, IM011055	Week 0 through the safety data cut-off date. Any available safety data up to Week 160 is included.

[a] IM011054 data cutoff: 10-Oct-2024; IM011055 data cutoff: 07-Nov-2024; IM011084 Part A data cutoff: 02-Jul-2020

Source: Table 1.1.2-1 and Table 1.1.3.2-1 of the SCS.[48]

Patient exposure

▪ *All PsA safety Pool – placebo- controlled period (week 0-16)*

The placebo-controlled period included 1 529 treated patients: 714 DEUC, 710 placebo, and 105 APR, which most of the patients completed (93.0% DEUC, 92.4% placebo, and 85.7% APR). The most common reasons for study discontinuation before week 16 were: AEs (2.4% DEUC, 1.5% placebo, and 9.5% AP), consent withdrawal (1.7% DEUC, 3.2% placebo, and 2.9% APR).

The mean duration of exposure was consistent across treatment groups with a median duration of exposure of 112 days. All patients except 1 in the placebo group received at least 1 dose of study treatment (DEUC/Placebo/APR); nearly 90% of them in the DEUC and placebo groups and 79.0% in the APR group were exposed to treatment for at least 16 weeks (Table 48).

Table 48. Duration of Exposure by Treatment: Placebo-Controlled Period (Week 0-16) (All PsA Safety Pool - Treated Population)

Statistic	DEUC 6 mg N = 714	PBO N = 710	APR 30 mg N = 105
AT LEAST ONE DOSE (%)	714 (100.0)	709 (99.9)	105 (100.0)
AT LEAST 16 WEEKS OF TOTAL EXPOSURE (%)	645 (90.3)	638 (89.9)	83 (79.0)
EXPOSURE IN WEEKS (%)			
>= 1	713 (99.9)	707 (99.6)	104 (99.0)
>= 2	710 (99.4)	706 (99.4)	103 (98.1)
>= 3	705 (98.7)	703 (99.0)	102 (97.1)
>= 4	703 (98.5)	700 (98.6)	99 (94.3)
>= 5	696 (97.5)	692 (97.5)	98 (93.3)
>= 6	691 (96.8)	689 (97.0)	97 (92.4)
>= 7	688 (96.4)	688 (96.9)	96 (91.4)
>= 8	685 (95.9)	686 (96.6)	94 (89.5)
>= 9	682 (95.5)	676 (95.2)	93 (88.6)
>= 10	678 (95.0)	672 (94.6)	92 (87.6)
>= 11	676 (94.7)	670 (94.4)	91 (86.7)
>= 12	675 (94.5)	666 (93.8)	91 (86.7)
>= 13	670 (93.8)	664 (93.5)	91 (86.7)
>= 14	667 (93.4)	661 (93.1)	89 (84.8)
>= 15	664 (93.0)	657 (92.5)	88 (83.8)
>= 16	645 (90.3)	638 (89.9)	83 (79.0)
DURATION OF EXPOSURE (DAYS)			
N	714	710	105
MEAN (SD)	108.2 (18.23)	108.0 (18.14)	101.2 (28.01)
MEDIAN	112.0	112.0	112.0
MIN, MAX	1, 131	1, 161	3, 122
TOTAL EXPOSURE IN PATIENT YEARS	211.5	209.9	29.1

Exposure is summarized according to treatments groups assigned on Day 1 and includes all exposure up to Week 16.
The duration (in days) within each study period is defined as:
Last dose date within each period - First dose date within each period + 1.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Frequency of exposure in weeks is a cumulative frequency.
Includes data from IM011054, IM011055 and IM011084 Part A.
Source: Table 14.1.5.1

▪ *Phase 3 safety pool - 52-week period (week 0-52)*

A total of 1,347 patients were included: 644 in the DEUC-DEUC group, 598 in the PBO-DEUC group, and 105 in the APR-APR group. At the cut-off date, 69.9% of patients had completed the 52-Week Period (67.4% DEUC-DEUC, 71.7% PBO-DEUC, and 75.2% APR-APR), and nearly 20% of DEUC-treated patients were still receiving treatment. The most common reason for study discontinuation before Week 52 was an AE (4.3% DEUC-DEUC, 2.5% PBO-DEUC, and 12.4% APR-APR). The mean duration of exposure was consistent in the DEUC-DEUC and APR-APR groups (311.5 and 298.5 days, respectively) with a median duration of exposure of 364 days. In the PBO-DEUC group, the median duration of exposure was 252 days. The proportion of patients who received DEUC for at least 52 weeks was comparable with the proportion that received APR (64.0% [DEUC-DEUC] and 69.5% [APR-APR], respectively).

▪ *Cumulative DEUC period – phase 3 safety pool*

Table 49 below presents the cumulative duration to DEUC exposure from the phase 3 safety pool:

Table 49. Duration of Exposure by Treatment: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool – Treated Population)

Statistic	DEUC 6 mg (N=1312)
AT LEAST 16 WEEKS OF CONTINUOUS EXPOSURE (%)	1087 (82.9)
AT LEAST 26 WEEKS OF CONTINUOUS EXPOSURE (%)	885 (67.5)
AT LEAST 52 WEEKS OF CONTINUOUS EXPOSURE (%)	444 (33.8)
AT LEAST ONE DOSE (%)	1312 (100.0)
AT LEAST 16 WEEKS OF TOTAL EXPOSURE (%)	1197 (91.2)
AT LEAST 26 WEEKS OF TOTAL EXPOSURE (%)	1082 (82.5)
AT LEAST 52 WEEKS OF TOTAL EXPOSURE (%)	757 (57.7)
AT LEAST 78 WEEKS OF TOTAL EXPOSURE (%)	387 (29.5)
AT LEAST 104 WEEKS OF TOTAL EXPOSURE (%)	195 (14.9)
EXPOSURE IN WEEKS (%)	
>=1	1307 (99.6)
>=2	1301 (99.2)
>=4	1294 (98.6)
>=8	1260 (96.0)
>=12	1237 (94.3)
>=16	1197 (91.2)
>=20	1157 (88.2)
>=24	1135 (86.5)
>=28	1074 (81.9)
>=32	1038 (79.1)
>=36	980 (74.7)
>=40	913 (69.6)
>=48	798 (60.8)
>=52	757 (57.7)
>=56	635 (48.4)
>=60	592 (45.1)
>=64	558 (42.5)
>=68	499 (38.0)
>=72	439 (33.5)
>=76	426 (32.5)
>=80	370 (28.2)
>=84	321 (24.5)
>=88	312 (23.8)
>=92	277 (21.1)
>=96	244 (18.6)
>=100	231 (17.6)
>=104	195 (14.9)
>=108	173 (13.2)
>=112	167 (12.7)
>=116	133 (10.1)
>=120	107 (8.2)
>=124	99 (7.5)
>=128	70 (5.3)
>=132	47 (3.6)
>=136	43 (3.3)
>=140	31 (2.4)
>=144	8 (0.6)
>=148	8 (0.6)
>=152	4 (0.3)
>=156	0
DURATION OF EXPOSURE (DAYS)	
N	1312
MEAN (SD)	425.2 (249.66)
MEDIAN	372.0
MIN, MAX	1, 1075
TOTAL EXPOSURE IN PATIENT YEARS	1527.2

Exposure is summarized according to the number of subjects exposed to DEUC 6 mg only.
The duration (in days) within each study period is defined as:
Last dose date within each period - First dose date within each period + 1.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Frequency of exposure in weeks is a cumulative frequency.
Continuous exposure is based on longest exposure of DEUC 6 mg.
Includes subjects who were assigned to DEUC 6 mg from IM011054 and IM011055 (Safety Cutoff Date = 10-10-2024, 07-11-2024).
Source: Table 14.1.5.3

Adverse events

Treatment emergent adverse events (TEAEs)

▪ *All PsA Safety Pool-placebo-controlled period (week 0-16)*

The overall incidence of AEs with DEUC was higher than in the placebo group (EAIR= 362.7/100 P-Y, 61.9% [DEUC] vs EAIR= 253/100 P-Y, 50.4% [placebo]. The incidence of SAEs was comparable in the DEUC and placebo groups, EAIR= 5.7 and 5.8 /100 P-Y, respectively. The incidence of AEs leading to treatment discontinuations was higher in the DEUC group than in the placebo group: EAIR= 8.5/100 P-Y 2.5% [DEUC] vs EAIR= 5.2/100 P-Y.5% [placebo].

▪ *Phase 3 safety pool-52-week period (week 0-52)*

The EAIR of AEs was 234.0/100 P-Y in the DEUC-DEUC and 201.1/100 P-Y PBO-DEUC groups and 366.8/100 P-Y in the APR-APR group. The EAIR of AEs in the DEUC-DEUC group (234.0/100 P-Y) was lower compared with the Placebo-Controlled Period (362.7/100 P-Y [DEUC]).

The EAIR of SAEs was comparable in the DEUC-DEUC and PBO-DEUC groups and lower than the APR-APR group (6.7/100 P-Y, 8.0/100-P-Y, and 12.2/100 P-Y, respectively). The EAIR of SAEs in the DEUC-DEUC group (6.7/100 P-Y) was comparable with the Placebo-Controlled Period (5.7/100 P-Y [DEUC]).

The EAIR of AEs leading to treatment discontinuation was comparable in the DEUC-DEUC (5.3/100 P-Y) and PBO-DEUC (4.5/100 P-Y) groups and lower than the APR-APR group (15.2/100 P-Y). The EAIR of AEs leading to discontinuation in the DEUC-DEUC group (5.3/100 P-Y) was lower than in the Placebo-Controlled Period (8.5/100 P-Y [DEUC]).

▪ *Cumulative DEUC period – phase 3 safety pool*

The Table 50 presents TEAEs from the cumulative DEUC period Phase 3 safety pool:

Table 50. Overall Safety Summary- Exposure Adjusted Incidence Rate: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool - Treated Population)

	DEUC 6 mg N = 1312			
Adverse Event Category	n (%)	m	P-Y	IR/ 100 P-Y
DEATHS	1 (0.1)	1	1527.2	0.1
SAEs	103 (7.9)	124	1464.9	7.0
TREATMENT RELATED SAEs	16 (1.2)	16	1521.5	1.1
AEs	1005 (76.6)	4151	532.3	188.8
TREATMENT RELATED AEs	407 (31.0)	1030	1128.9	36.1
AEs LEADING TO DC	62 (4.7)	66	1523.7	4.1

AEs are treatment emergent AEs with an onset date on or after the first dose date of study treatment up to 30 days after the last dose date of treatment in the study.
Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055. (Safety Cutoff Date = 10-10-2024, 07-11-2024).
Source: Table 14.3.1.3

Common adverse events

▪ *All PsA safety Pool - placebo-controlled period*

The Table 51 presents common treatment emergent adverse events during the All PsA Safety pool placebo-controlled period:

Table 51. AEs Summary Reported in > 1% of Patients by SOC and PT terms: Placebo-Controlled Period (Week 0-16) (All PsA Safety Pool - Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	442 (61.9) 996	121.8	362.7	358 (50.4) 769	141.5	253.0	77 (73.3) 210	15.1	510.1
Infections and infestations	224 (31.4) 312	170.4	131.5	155 (21.8) 195	184.3	84.1	34 (32.4) 43	24.2	140.6
Upper respiratory tract infection	40 (5.6) 47	204.4	19.6	23 (3.2) 25	206.0	11.2	4 (3.8) 5	28.7	13.9
COVID-19	31 (4.3) 31	206.5	15.0	24 (3.4) 25	205.8	11.7	7 (6.7) 7	27.6	25.4
Nasopharyngitis	31 (4.3) 33	205.1	15.1	38 (5.4) 39	204.1	18.6	4 (3.8) 4	28.3	14.1
Pharyngitis	16 (2.2) 17	208.8	7.7	4 (0.6) 4	209.2	1.9	1 (1.0) 1	28.9	3.5
Urinary tract infection	11 (1.5) 12	210.2	5.2	11 (1.5) 12	207.3	5.3	2 (1.9) 2	29.0	6.9
Bronchitis	9 (1.3) 9	210.5	4.3	5 (0.7) 6	209.0	2.4	3 (2.9) 3	28.5	10.5
Oral herpes	9 (1.3) 9	209.5	4.3	3 (0.4) 3	209.4	1.4	2 (1.9) 2	29.0	6.9
Respiratory tract infection	9 (1.3) 10	209.9	4.3	4 (0.6) 4	209.2	1.9	0	29.1	0
Tonsillitis	9 (1.3) 10	209.6	4.3	2 (0.3) 2	209.8	1.0	0	29.1	0
Gastroenteritis	8 (1.1) 8	210.3	3.8	8 (1.1) 8	208.4	3.8	2 (1.9) 2	29.0	6.9
Otitis externa	0	211.5	0	0	209.9	0	2 (1.9) 2	28.8	6.9
Gastrointestinal disorders	108 (15.1) 158	190.5	56.7	68 (9.6) 105	198.6	34.2	30 (28.6) 49	23.7	126.5
Diarrhoea	22 (3.1) 22	206.9	10.6	17 (2.4) 17	207.6	8.2	11 (10.5) 13	26.8	41.0
Nausea	14 (2.0) 14	208.8	6.7	9 (1.3) 10	208.1	4.3	7 (6.7) 9	28.0	25.0
Aphthous ulcer	11 (1.5) 19	209.1	5.3	0	209.9	0	0	29.1	0
Abdominal pain upper	7 (1.0) 7	210.3	3.3	9 (1.3) 9	208.4	4.3	1 (1.0) 1	28.8	3.5
Dyspepsia	6 (0.8) 6	210.4	2.9	3 (0.4) 3	209.6	1.4	3 (2.9) 3	28.6	10.5
Vomiting	6 (0.8) 7	210.7	2.8	9 (1.3) 10	208.7	4.3	5 (4.8) 5	28.7	17.4
Gastrooesophageal reflux disease	4 (0.6) 4	210.6	1.9	0	209.9	0	2 (1.9) 2	28.9	6.9
Chronic gastritis	1 (0.1) 1	211.4	0.5	1 (0.1) 4	209.7	0.5	2 (1.9) 2	28.8	6.9
Abdominal discomfort	0	211.5	0	2 (0.3) 2	209.8	1.0	2 (1.9) 2	28.8	6.9
Skin and subcutaneous tissue disorders	89 (12.5) 107	193.1	46.1	44 (6.2) 59	202.3	21.7	6 (5.7) 7	28.2	21.2
Rash	22 (3.1) 22	206.6	10.7	4 (0.6) 5	209.0	1.9	1 (1.0) 1	29.0	3.4
Acne	15 (2.1) 15	208.1	7.2	0	209.9	0	1 (1.0) 1	28.9	3.5
Dermatitis acneiform	8 (1.1) 9	209.5	3.8	2 (0.3) 2	209.8	1.0	0	29.1	0
Psoriasis	4 (0.6) 4	210.7	1.9	10 (1.4) 11	208.7	4.8	2 (1.9) 3	29.0	6.9
Musculoskeletal and connective tissue disorders	48 (6.7) 56	204.7	23.5	53 (7.5) 72	202.0	26.2	11 (10.5) 15	27.5	40.0
Psoriatic arthropathy	8 (1.1) 8	210.9	3.8	17 (2.4) 18	207.8	8.2	2 (1.9) 2	28.9	6.9
Arthralgia	7 (1.0) 7	210.5	3.3	10 (1.4) 11	208.4	4.8	2 (1.9) 2	29.0	6.9
Muscle spasms	1 (0.1) 1	211.5	0.5	6 (0.8) 7	208.9	2.9	2 (1.9) 2	28.6	7.0
Nervous system disorders	44 (6.2) 50	202.9	21.7	38 (5.4) 48	202.9	18.7	16 (15.2) 20	26.6	60.1
Headache	24 (3.4) 25	206.5	11.6	21 (3.0) 24	206.3	10.2	8 (7.6) 9	27.5	29.1

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
Dizziness	9 (1.3) 10	210.3	4.3	7 (1.0) 7	208.6	3.4	4 (3.8) 5	28.7	13.9
Somnolence	1 (0.1) 1	211.3	0.5	0	209.9	0	2 (1.9) 2	28.9	6.9
Migraine	0	211.5	0	1 (0.1) 3	209.6	0.5	3 (2.9) 3	28.8	10.4
Investigations	38 (5.3) 54	204.6	18.6	31 (4.4) 36	204.5	15.2	8 (7.6) 11	27.7	28.9
Alanine aminotransferase increased	6 (0.8) 10	210.3	2.9	8 (1.1) 8	208.2	3.8	1 (1.0) 1	29.0	3.4
Metabolism and nutrition disorders	37 (5.2) 46	204.4	18.1	35 (4.9) 42	202.7	17.3	11 (10.5) 13	27.9	39.5
Hyperuricaemia	9 (1.3) 9	209.9	4.3	8 (1.1) 11	208.0	3.8	3 (2.9) 4	28.6	10.5
Hypertriglyceridaemia	8 (1.1) 8	210.2	3.8	2 (0.3) 2	209.3	1.0	3 (2.9) 3	28.8	10.4
General disorders and administration site conditions	34 (4.8) 36	205.6	16.5	23 (3.2) 28	205.3	11.2	3 (2.9) 5	28.6	10.5
Fatigue	9 (1.3) 10	209.5	4.3	11 (1.5) 14	207.6	5.3	2 (1.9) 2	28.6	7.0
Pyrexia	9 (1.3) 9	210.3	4.3	1 (0.1) 1	209.7	0.5	1 (1.0) 1	28.8	3.5
Vascular disorders	29 (4.1) 30	206.4	14.1	25 (3.5) 28	205.7	12.2	11 (10.5) 11	27.3	40.3
Hypertension	21 (2.9) 21	207.7	10.1	18 (2.5) 18	206.8	8.7	7 (6.7) 7	27.6	25.3
Blood and lymphatic system disorders	23 (3.2) 27	207.6	11.1	14 (2.0) 17	207.2	6.8	4 (3.8) 4	28.5	14.0
Anaemia	10 (1.4) 10	209.7	4.8	5 (0.7) 5	209.1	2.4	2 (1.9) 2	28.9	6.9
Psychiatric disorders	15 (2.1) 17	208.8	7.2	12 (1.7) 14	208.3	5.8	5 (4.8) 6	28.5	17.6
Insomnia	5 (0.7) 5	210.4	2.4	4 (0.6) 5	209.1	1.9	2 (1.9) 2	28.7	7.0
Renal and urinary disorders	11 (1.5) 12	210.4	5.2	6 (0.8) 7	209.4	2.9	6 (5.7) 10	28.7	20.9
Ureterolithiasis	0	211.5	0	0	209.9	0	2 (1.9) 4	28.8	6.9
Cardiac disorders	7 (1.0) 7	210.5	3.3	6 (0.8) 10	208.9	2.9	3 (2.9) 4	28.9	10.4
Palpitations	3 (0.4) 3	211.1	1.4	1 (0.1) 1	209.7	0.5	3 (2.9) 4	28.9	10.4

Includes events with a start date between first dose and the Week 16 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054, IM011055 and IM011084 Part A.
Source: Table 14.3.1.1.1.1

- *Phase 3 safety pool-52-week period*

The Table 52 presents common treatment emergent adverse events in the phase 3 safety pool:

Table 52. AEs Reported in ≥ 2% of Patients by SOC and PT terms: 52-Week Period (Week 0-52) (Phase 3 Safety Pool - Treated Population)

Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/100 P-Y
TOTAL SUBJECTS WITH AN EVENT	507 (78.7) 1823	216.7	234.0	384 (64.2) 1073	190.9	201.1	92 (87.6) 384	25.1	366.8
Infections and infestations	335 (52.0) 651	351.9	95.2	246 (41.1) 412	257.0	95.7	54 (51.4) 94	52.7	102.5
Upper respiratory tract infection	78 (12.1) 109	505.8	15.4	53 (8.9) 67	338.7	15.6	11 (10.5) 13	81.0	13.6
COVID-19	64 (9.9) 66	515.0	12.4	37 (6.2) 38	344.9	10.7	13 (12.4) 15	77.0	16.9
Nasopharyngitis	63 (9.8) 88	516.9	12.2	58 (9.7) 64	335.4	17.3	8 (7.6) 8	80.6	9.9
Urinary tract infection	28 (4.3) 31	535.5	5.2	12 (2.0) 14	351.8	3.4	7 (6.7) 8	83.2	8.4
Pharyngitis	27 (4.2) 30	533.8	5.1	13 (2.2) 16	352.9	3.7	1 (1.0) 1	85.0	1.2
Tonsillitis	20 (3.1) 24	537.3	3.7	8 (1.3) 9	354.8	2.3	0	85.8	0
Gastroenteritis	19 (3.0) 21	538.5	3.5	9 (1.5) 12	356.1	2.5	2 (1.9) 2	85.0	2.4
Bronchitis	17 (2.6) 19	541.9	3.1	14 (2.3) 17	354.6	3.9	4 (3.8) 4	83.4	4.8
Sinusitis	15 (2.3) 18	541.7	2.8	11 (1.8) 11	355.3	3.1	3 (2.9) 5	84.4	3.6
Influenza	14 (2.2) 14	540.6	2.6	10 (1.7) 10	354.4	2.8	3 (2.9) 3	84.6	3.5
Oral herpes	14 (2.2) 16	542.0	2.6	4 (0.7) 6	357.5	1.1	2 (1.9) 2	84.3	2.4
Respiratory tract infection	13 (2.0) 17	542.1	2.4	8 (1.3) 12	354.1	2.3	0	85.8	0
Pulpitis dental	6 (0.9) 7	546.5	1.1	1 (0.2) 1	358.2	0.3	3 (2.9) 4	83.8	3.6
Vascular disorders	53 (8.2) 57	520.8	10.2	29 (4.8) 33	347.1	8.4	11 (10.5) 11	78.1	14.1
Hypertension	38 (5.9) 41	528.2	7.2	20 (3.3) 24	350.7	5.7	7 (6.7) 7	79.8	8.8
Gastrointestinal disorders	148 (23.0) 252	456.4	32.4	64 (10.7) 96	331.1	19.3	40 (38.1) 75	63.9	62.6
Diarrhoea	36 (5.6) 36	529.4	6.8	12 (2.0) 12	353.5	3.4	20 (19.0) 25	75.4	26.5
Mouth ulceration	24 (3.7) 34	530.2	4.5	15 (2.5) 23	350.9	4.3	0	85.8	0
Nausea	20 (3.1) 21	538.2	3.7	9 (1.5) 10	353.2	2.5	9 (8.6) 12	81.5	11.0
Dyspepsia	6 (0.9) 6	545.3	1.1	0	358.3	0	4 (3.8) 4	83.9	4.8
Gastrooesophageal reflux disease	6 (0.9) 7	545.4	1.1	0	358.3	0	3 (2.9) 3	84.1	3.6
Vomiting	6 (0.9) 7	545.3	1.1	6 (1.0) 6	355.7	1.7	5 (4.8) 6	82.6	6.0
Abdominal discomfort	1 (0.2) 1	548.8	0.2	4 (0.7) 4	357.0	1.1	3 (2.9) 3	84.3	3.6
Nervous system disorders	56 (8.7) 68	517.3	10.8	22 (3.7) 25	350.8	6.3	22 (21.0) 29	73.1	30.1
Headache	23 (3.6) 27	533.6	4.3	8 (1.3) 8	355.7	2.2	13 (12.4) 15	77.7	16.7
Dizziness	9 (1.4) 11	545.0	1.7	2 (0.3) 2	357.7	0.6	4 (3.8) 5	84.7	4.7
Migraine	2 (0.3) 2	548.2	0.4	0	358.3	0	3 (2.9) 3	84.3	3.6
Skin and subcutaneous tissue disorders	101 (15.7) 129	488.5	20.7	76 (12.7) 89	328.6	23.1	11 (10.5) 13	80.3	13.7
Rash	21 (3.3) 22	535.2	3.9	9 (1.5) 9	354.9	2.5	1 (1.0) 1	85.0	1.2
Acne	15 (2.3) 15	538.9	2.8	19 (3.2) 20	350.6	5.4	1 (1.0) 1	84.9	1.2
Metabolism and nutrition disorders	72 (11.2) 98	507.5	14.2	57 (9.5) 68	336.8	16.9	21 (20.0) 30	74.5	28.2

Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/100 P-Y
Hyperlipidaemia	18 (2.8) 18	538.1	3.3	11 (1.8) 11	354.0	3.1	2 (1.9) 3	84.7	2.4
Hyperuricaemia	12 (1.9) 16	542.0	2.2	14 (2.3) 15	353.0	4.0	5 (4.8) 7	82.2	6.1
Hypertriglyceridaemia	11 (1.7) 11	542.0	2.0	3 (0.5) 3	357.1	0.8	4 (3.8) 4	84.3	4.7
Hypercholesterolaemia	9 (1.4) 10	544.1	1.7	9 (1.5) 9	354.5	2.5	4 (3.8) 4	83.5	4.8
Investigations	70 (10.9) 93	510.3	13.7	54 (9.0) 81	337.4	16.0	13 (12.4) 17	79.4	16.4
Blood creatine phosphokinase increased	15 (2.3) 18	542.0	2.8	16 (2.7) 18	352.5	4.5	0	85.8	0
Musculoskeletal and connective tissue disorders	82 (12.7) 122	507.6	16.2	61 (10.2) 80	336.0	18.2	21 (20.0) 39	75.5	27.8
Psoriatic arthropathy	15 (2.3) 16	544.1	2.8	18 (3.0) 20	352.6	5.1	7 (6.7) 7	83.8	8.4
Arthralgia	12 (1.9) 14	544.2	2.2	7 (1.2) 8	355.9	2.0	3 (2.9) 6	84.2	3.6
Back pain	8 (1.2) 10	544.8	1.5	10 (1.7) 10	354.2	2.8	3 (2.9) 5	84.5	3.6
Blood and lymphatic system disorders	32 (5.0) 42	534.4	6.0	11 (1.8) 16	353.1	3.1	5 (4.8) 5	83.1	6.0
Anaemia	14 (2.2) 15	542.3	2.6	6 (1.0) 7	355.6	1.7	2 (1.9) 2	84.9	2.4
General disorders and administration site conditions	44 (6.8) 52	522.5	8.4	26 (4.3) 29	348.0	7.5	7 (6.7) 10	82.4	8.5
Fatigue	13 (2.0) 15	540.5	2.4	4 (0.7) 4	356.7	1.1	3 (2.9) 4	83.5	3.6
Pyrexia	13 (2.0) 16	541.1	2.4	7 (1.2) 7	355.4	2.0	1 (1.0) 1	84.8	1.2
Psychiatric disorders	25 (3.9) 30	535.6	4.7	8 (1.3) 9	355.3	2.3	7 (6.7) 9	82.0	8.5
Insomnia	7 (1.1) 7	546.0	1.3	1 (0.2) 1	357.7	0.3	3 (2.9) 3	83.4	3.6
Respiratory, thoracic and mediastinal disorders	39 (6.1) 49	530.5	7.4	23 (3.8) 26	349.8	6.6	10 (9.5) 11	82.1	12.2
Cough	5 (0.8) 5	547.0	0.9	6 (1.0) 6	355.5	1.7	4 (3.8) 4	83.7	4.8
Cardiac disorders	14 (2.2) 17	542.6	2.6	12 (2.0) 16	353.2	3.4	5 (4.8) 8	83.0	6.0
Palpitations	4 (0.6) 4	547.6	0.7	0	358.3	0	3 (2.9) 4	84.2	3.6

Includes events with a start date between first dose and the Week 52 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055.
Source: Table 14.3.1.1.1.2

▪ *Cumulative DEUC period-phase 3 safety pool*

The Table 53 presents common treatment emergent adverse events in the cumulative phase 3 safety pool DEUC period:

Table 53. AEs Reported in ≥ 2% of Patients by SOC and PT Terms: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool - Treated Population)

	DEUC 6 mg N = 1312			
System Organ Class Preferred Term	n (%)	m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	1005 (76.6)	4151	532.3	188.8
Infections and infestations	696 (53.0)	1531	860.6	80.9
Upper respiratory tract infection	175 (13.3)	268	1378.3	12.7
Nasopharyngitis	154 (11.7)	200	1386.1	11.1
COVID-19	128 (9.8)	142	1380.9	9.3
Bronchitis	58 (4.4)	69	1489.6	3.9
Pharyngitis	51 (3.9)	65	1473.4	3.5
Urinary tract infection	48 (3.7)	57	1486.3	3.2
Sinusitis	38 (2.9)	47	1497.3	2.5
Gastroenteritis	36 (2.7)	42	1499.7	2.4
Tonsillitis	36 (2.7)	50	1490.5	2.4
Influenza	34 (2.6)	34	1497.4	2.3
Gastrointestinal disorders	265 (20.2)	446	1271.9	20.8
Diarrhoea	58 (4.4)	60	1478.5	3.9
Mouth ulceration	41 (3.1)	61	1479.9	2.8
Nausea	34 (2.6)	37	1490.1	2.3
Skin and subcutaneous tissue disorders	214 (16.3)	276	1333.5	16.0
Rash	40 (3.0)	43	1486.4	2.7
Acne	38 (2.9)	40	1494.7	2.5
Musculoskeletal and connective tissue disorders	207 (15.8)	314	1351.6	15.3
Psoriatic arthropathy	47 (3.6)	59	1492.6	3.1
Arthralgia	28 (2.1)	32	1510.7	1.9
Back pain	28 (2.1)	31	1502.0	1.9

	DEUC 6 mg N = 1312			
System Organ Class Preferred Term	n (%)	m	P-Y	IR/ 100 P-Y
Metabolism and nutrition disorders	188 (14.3)	265	1384.4	13.6
Hyperlipidaemia	42 (3.2)	47	1490.2	2.8
Hyperuricaemia	36 (2.7)	45	1501.9	2.4
Hypercholesterolaemia	33 (2.5)	37	1502.0	2.2
Investigations	159 (12.1)	249	1386.8	11.5
Blood creatine phosphokinase increased	34 (2.6)	40	1498.4	2.3
Nervous system disorders	111 (8.5)	142	1431.5	7.8
Headache	38 (2.9)	42	1494.1	2.5
Vascular disorders	108 (8.2)	119	1438.2	7.5
Hypertension	77 (5.9)	85	1466.6	5.3

Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055. (Safety Cutoff Date = 10-10-2024, 07-11-2024).
Source: Table 14.3.1.1.1.3

Treatment related adverse events

▪ *All PsA safety Pool-placebo-controlled period (week 0-16)*

The Table 54 presents treatment related adverse events from the All PsA safety pool-placebo-controlled period pool-52-week period:

Table 54. Treatment Related Adverse Events Reported in ≥ 1% of Patients Summary Placebo-Controlled Period All PsA Safety Pool Treated Population

Preferred Term [n (%) m]	DEUC 6 mg N = 714	PBO N = 710	APR 30 mg N = 105	Total N = 1529
Mouth ulceration	15 (2.1) 15	0	0	15 (1.0) 15
Headache	14 (2.0) 14	6 (0.8) 8	4 (3.8) 4	24 (1.6) 26
Rash	13 (1.8) 13	3 (0.4) 3	1 (1.0) 1	17 (1.1) 17
Upper respiratory tract infection	13 (1.8) 16	7 (1.0) 7	2 (1.9) 2	22 (1.4) 25
Acne	11 (1.5) 11	0	1 (1.0) 1	12 (0.8) 12
Diarrhoea	9 (1.3) 9	7 (1.0) 7	9 (8.6) 10	25 (1.6) 26
Nausea	9 (1.3) 9	4 (0.6) 4	6 (5.7) 8	19 (1.2) 21
Dizziness	6 (0.8) 7	2 (0.3) 2	4 (3.8) 5	12 (0.8) 14
Bronchitis	4 (0.6) 4	1 (0.1) 1	2 (1.9) 2	7 (0.5) 7
Dyspepsia	1 (0.1) 1	0	2 (1.9) 2	3 (0.2) 3
Hypertriglyceridaemia	1 (0.1) 1	0	2 (1.9) 2	3 (0.2) 3
Somnolence	1 (0.1) 1	0	2 (1.9) 2	3 (0.2) 3
Migraine	0	0	2 (1.9) 2	2 (0.1) 2

Includes events with a start date between first dose and the Week 16 visit date.
Includes data from IM011054, IM011055 and IM011084 Part A.
Cutoff is applied prior to rounding PT percentage to 1 decimal for display.
n = number of subjects; m = number of events.
MedDRA Version: 27.1
Program Path: BMS GBS\IM011\IM011 INTEGRATED\Biostatistics\Production\Tables\ISS ISE
Program Name: rt-ae-relclae1.sas 29JAN2025:11:45:29

▪ *Phase 3 safety pool-52-week period*

The Table 55 presents treatment related adverse events from the Phase 3 safety pool – 52-week period:

Table 55. Treatment Related Adverse Events Reported in ≥1% of Patients Summary 52-Week Period Phase 3 Safety Pool Treated Population

Preferred Term [n (%) m]	DEUC 6 mg-DEUC 6 mg N = 644	PBO-DEUC 6 mg N = 598	APR 30 mg-APR 30 mg N = 105	Total N = 1347
Upper respiratory tract infection	29 (4.5) 45	20 (3.3) 24	5 (4.8) 5	54 (4.0) 74
Mouth ulceration	16 (2.5) 21	10 (1.7) 15	0	26 (1.9) 36
Headache	14 (2.2) 14	1 (0.2) 1	5 (4.8) 5	20 (1.5) 20
Acne	11 (1.7) 11	11 (1.8) 12	1 (1.0) 1	23 (1.7) 24
Rash	10 (1.6) 11	3 (0.5) 3	1 (1.0) 1	14 (1.0) 15
Diarrhoea	9 (1.4) 9	2 (0.3) 2	12 (11.4) 14	23 (1.7) 25
Urinary tract infection	9 (1.4) 10	3 (0.5) 3	2 (1.9) 3	14 (1.0) 16
Nasopharyngitis	8 (1.2) 12	10 (1.7) 10	1 (1.0) 1	19 (1.4) 23
Nausea	8 (1.2) 8	2 (0.3) 2	6 (5.7) 8	16 (1.2) 18
Aphthous ulcer	7 (1.1) 8	1 (0.2) 1	0	8 (0.6) 9
Bronchitis	7 (1.1) 7	3 (0.5) 3	2 (1.9) 2	12 (0.9) 12
Hyperlipidaemia	7 (1.1) 7	6 (1.0) 6	1 (1.0) 1	14 (1.0) 14
Oral herpes	7 (1.1) 7	2 (0.3) 3	1 (1.0) 1	10 (0.7) 11
Respiratory tract infection	7 (1.1) 7	6 (1.0) 9	0	13 (1.0) 16
Tonsillitis	7 (1.1) 9	0	0	7 (0.5) 9
Dizziness	5 (0.8) 6	1 (0.2) 1	4 (3.8) 5	10 (0.7) 12
Hyperuricaemia	2 (0.3) 4	6 (1.0) 6	2 (1.9) 3	10 (0.7) 13
Sinusitis	2 (0.3) 2	0	2 (1.9) 4	4 (0.3) 6
Hypertriglyceridaemia	1 (0.2) 1	0	2 (1.9) 2	3 (0.2) 3
Somnolence	1 (0.2) 1	0	2 (1.9) 3	3 (0.2) 4
Dyspepsia	0	0	3 (2.9) 3	3 (0.2) 3
Migraine	0	0	2 (1.9) 2	2 (0.1) 2

Includes events with a start date between first dose and the Week 52 visit date.
Includes data from IM011054 and IM011055.
Cutoff is applied prior to rounding PT percentage to 1 decimal for display.
n = number of subjects; m = number of events.
MedDRA: 27.1
Program Path: BMS GBS\IM011\IM011 INTEGRATED\Biostatistics\Production\Tables\ISS ISE
Program Name: rt-ae-relclae2.sas 29JAN2025:11:46:17

▪ *Cumulative DEUC period–phase 3 safety pool*

In the Cumulative DEUC Period, the most frequently reported treatment-related AEs, based on EAIR/100 PY) by SOC were "Infections and infestations" (EAIR= 18.1/100 P-Y), "Skin and subcutaneous tissue disorders" (EAIR= 7.1/100 P-Y), and 'Gastrointestinal disorders" (EAIR= 6.4/100 P-Y). The most common treatment-related AEs by PT were mouth ulceration (EAIR= 61.9 /100 P-Y), upper respiratory tract infection (EAIR= 4.1/100 P-Y), acne (EAIR= 1.7/100 P-Y), nasopharyngitis (EAIR= 1.5 /100 P-Y), and rash (EAIR= 1.3 / 100 P-Y).

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

▪ *All PsA safety Pool-placebo-controlled period*

The Table 56 displays Serious AEs from All PsA safety pool-placebo-controlled period:

Table 56. Serious Adverse Event Summary: Placebo-Controlled Period (Week 0-16) (All PsA Safety Pool - Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	12 (1.7) 12	210.3	5.7	12 (1.7) 18	208.1	5.8	4 (3.8) 5	28.9	13.8
Infections and infestations	8 (1.1) 8	210.8	3.8	1 (0.1) 1	209.9	0.5	1 (1.0) 2	29.1	3.4
Pneumonia	2 (0.3) 2	211.4	0.9	0	209.9	0	0	29.1	0
Appendicitis	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Cellulitis	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Erysipelas	1 (0.1) 1	211.2	0.5	0	209.9	0	0	29.1	0
Respiratory tract infection	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Urinary tract infection	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Vulval cellulitis	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Diverticulitis intestinal perforated	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Peritonitis	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Soft tissue infection	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Injury, poisoning and procedural complications	2 (0.3) 2	211.2	0.9	0	209.9	0	0	29.1	0
Limb injury	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Wrist fracture	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Eye disorders	1 (0.1) 1	211.3	0.5	1 (0.1) 1	209.8	0.5	0	29.1	0
Optic ischaemic neuropathy	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Iridocyclitis	0	211.5	0	1 (0.1) 1	209.8	0.5	0	29.1	0
Gastrointestinal disorders	1 (0.1) 1	211.5	0.5	1 (0.1) 1	209.7	0.5	0	29.1	0
Gastric ulcer	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Small intestinal obstruction	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0
Cardiac disorders	0	211.5	0	2 (0.3) 3	209.7	1.0	0	29.1	0
Atrial fibrillation	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Myocardial infarction	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Sinus node dysfunction	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0
Metabolism and nutrition disorders	0	211.5	0	0	209.9	0	1 (1.0) 1	29.0	3.5
Dehydration	0	211.5	0	0	209.9	0	1 (1.0) 1	29.0	3.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Adenocarcinoma	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Nervous system disorders	0	211.5	0	2 (0.3) 2	209.3	1.0	0	29.1	0
Migraine	0	211.5	0	1 (0.1) 1	209.6	0.5	0	29.1	0
Transient ischaemic attack	0	211.5	0	1 (0.1) 1	209.6	0.5	0	29.1	0
Psychiatric disorders	0	211.5	0	1 (0.1) 1	209.8	0.5	0	29.1	0
Major depression	0	211.5	0	1 (0.1) 1	209.8	0.5	0	29.1	0
Renal and urinary disorders	0	211.5	0	2 (0.3) 2	209.7	1.0	1 (1.0) 1	29.0	3.4
Acute kidney injury	0	211.5	0	1 (0.1) 1	209.8	0.5	0	29.1	0
Calculus urinary	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0
Ureterolithiasis	0	211.5	0	0	209.9	0	1 (1.0) 1	29.0	3.4
Reproductive system and breast disorders	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0
Vaginal haematoma	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0
Skin and subcutaneous tissue disorders	0	211.5	0	2 (0.3) 4	209.8	1.0	0	29.1	0
Eczema	0	211.5	0	1 (0.1) 3	209.8	0.5	0	29.1	0
Psoriasis	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Vascular disorders	0	211.5	0	2 (0.3) 2	209.7	1.0	0	29.1	0
Deep vein thrombosis	0	211.5	0	2 (0.3) 2	209.7	1.0	0	29.1	0

Includes events with a start date between first dose and the Week 16 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054, IM011055 and IM011084 Part A.
Source: Table 14.3.2.2.1

The Table 57 displays serious <u>treatment related AEs</u> from All PsA safety pool-placebo-controlled period:

Table 57. Treatment Related Serious Adverse Event Summary Exposure Adjusted Incidence Rate All PsA Safety Pool Placebo-Controlled Period Treated Population

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	2 (0.3) 2	211.4	0.9	3 (0.4) 6	209.8	1.4	1 (1.0) 1	29.1	3.4
Infections and infestations	2 (0.3) 2	211.4	0.9	1 (0.1) 1	209.9	0.5	1 (1.0) 1	29.1	3.4
Urinary tract infection	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Vulval cellulitis	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Diverticulitis intestinal perforated	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Soft tissue infection	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Skin and subcutaneous tissue disorders	0	211.5	0	2 (0.3) 4	209.8	1.0	0	29.1	0
Eczema	0	211.5	0	1 (0.1) 3	209.8	0.5	0	29.1	0
Psoriasis	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Vascular disorders	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Deep vein thrombosis	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0

Includes events with a start date between first dose and the Week 16 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054, IM011055 and IM011084 Part A.
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▪ *<u>Phase 3 safety pool-52-week period</u>*

The Table 58 displays Serious AEs from Phase 3 safety pool-52-week period (week 0-52):

Table 58. Serious Adverse Event Summary: 52-Week Period (Week 0-52) (Phase 3 Safety Pool – Treated Population)

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/100 P-Y
TOTAL SUBJECTS WITH AN EVENT	36 (5.6) 39	536.6	6.7	28 (4.7) 34	350.2	8.0	10 (9.5) 11	81.8	12.2
Infections and infestations	10 (1.6) 10	545.1	1.8	9 (1.5) 11	355.6	2.5	2 (1.9) 3	85.7	2.3
Appendicitis	2 (0.3) 2	548.4	0.4	0	358.3	0	0	85.8	0
Pneumonia	2 (0.3) 2	548.5	0.4	3 (0.5) 3	357.5	0.8	0	85.8	0
Cellulitis	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Erysipelas	1 (0.2) 1	548.3	0.2	0	358.3	0	0	85.8	0
Respiratory tract infection	1 (0.2) 1	548.6	0.2	0	358.3	0	0	85.8	0
Salpingitis	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Urinary tract infection	1 (0.2) 1	548.5	0.2	0	358.3	0	1 (1.0) 1	85.7	1.2
Vulval cellulitis	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Bronchitis	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
COVID-19 pneumonia	0	549.2	0	1 (0.2) 1	357.9	0.3	0	85.8	0
Diverticulitis intestinal perforated	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Gastroenteritis	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
Hepatitis infectious mononucleosis	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Herpes zoster disseminated	0	549.2	0	1 (0.2) 1	357.8	0.3	0	85.8	0
Oral candidiasis	0	549.2	0	1 (0.2) 1	357.9	0.3	0	85.8	0
Otitis media	0	549.2	0	1 (0.2) 2	357.7	0.3	0	85.8	0
Peritonitis	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Injury, poisoning and procedural complications	7 (1.1) 7	547.2	1.3	3 (0.5) 4	357.8	0.8	0	85.8	0
Meniscus injury	2 (0.3) 2	549.0	0.4	1 (0.2) 1	358.3	0.3	0	85.8	0
Limb injury	1 (0.2) 1	548.4	0.2	0	358.3	0	0	85.8	0
Radius fracture	1 (0.2) 1	548.7	0.2	0	358.3	0	0	85.8	0
Spinal compression fracture	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Tibia fracture	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Wrist fracture	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Hand fracture	0	549.2	0	1 (0.2) 2	358.3	0.3	0	85.8	0
Traumatic fracture	0	549.2	0	1 (0.2) 1	357.8	0.3	0	85.8	0
Gastrointestinal disorders	5 (0.8) 5	547.9	0.9	3 (0.5) 3	357.0	0.8	1 (1.0) 1	85.4	1.2
Gastric ulcer	1 (0.2) 1	548.5	0.2	0	358.3	0	0	85.8	0
Gastrointestinal haemorrhage	1 (0.2) 1	549.1	0.2	0	358.3	0	0	85.8	0
Gastrointestinal perforation	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Inguinal hernia	1 (0.2) 1	548.7	0.2	0	358.3	0	1 (1.0) 1	85.4	1.2
Large intestine polyp	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Anal fissure	0	549.2	0	1 (0.2) 1	357.6	0.3	0	85.8	0

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/100 P-Y
Gastric dysplasia	0	549.2	0	1 (0.2) 1	358.0	0.3	0	85.8	0
Hiatus hernia	0	549.2	0	1 (0.2) 1	357.9	0.3	0	85.8	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.6) 4	548.5	0.7	2 (0.3) 2	358.0	0.6	1 (1.0) 1	85.8	1.2
Glioblastoma	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Lung adenocarcinoma	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Prostate cancer	1 (0.2) 1	549.1	0.2	0	358.3	0	0	85.8	0
Renal oncocytoma	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Adenocarcinoma	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Endometrial cancer stage 0	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Papillary thyroid cancer	0	549.2	0	1 (0.2) 1	358.0	0.3	0	85.8	0
Musculoskeletal and connective tissue disorders	3 (0.5) 4	547.7	0.5	2 (0.3) 2	357.4	0.6	2 (1.9) 2	85.0	2.4
Osteonecrosis	1 (0.2) 2	548.6	0.2	0	358.3	0	0	85.8	0
Psoriatic arthropathy	1 (0.2) 1	548.7	0.2	0	358.3	0	0	85.8	0
Spinal stenosis	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Back pain	0	549.2	0	1 (0.2) 1	357.6	0.3	0	85.8	0
Osteoarthritis	0	549.2	0	1 (0.2) 1	358.1	0.3	1 (1.0) 1	85.5	1.2
Spondylolisthesis	0	549.2	0	0	358.3	0	1 (1.0) 1	85.3	1.2
Nervous system disorders	3 (0.5) 3	548.3	0.5	1 (0.2) 1	358.3	0.3	0	85.8	0
Cerebral haemorrhage	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Headache	1 (0.2) 1	548.7	0.2	0	358.3	0	0	85.8	0
Spinal claudication	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Embolic stroke	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Blood and lymphatic system disorders	1 (0.2) 1	549.1	0.2	1 (0.2) 1	357.7	0.3	0	85.8	0
Lymphadenitis	1 (0.2) 1	549.1	0.2	0	358.3	0	0	85.8	0
Anaemia	0	549.2	0	1 (0.2) 1	357.7	0.3	0	85.8	0
Cardiac disorders	1 (0.2) 1	548.9	0.2	3 (0.5) 3	357.2	0.8	1 (1.0) 1	85.2	1.2
Atrial fibrillation	1 (0.2) 1	548.9	0.2	1 (0.2) 1	358.1	0.3	0	85.8	0
Acute myocardial infarction	0	549.2	0	1 (0.2) 1	357.8	0.3	1 (1.0) 1	85.2	1.2
Angina unstable	0	549.2	0	1 (0.2) 1	357.8	0.3	0	85.8	0
Eye disorders	1 (0.2) 1	548.3	0.2	0	358.3	0	0	85.8	0
Optic ischaemic neuropathy	1 (0.2) 1	548.3	0.2	0	358.3	0	0	85.8	0

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/100 P-Y
Hepatobiliary disorders	1 (0.2) 1	549.0	0.2	1 (0.2) 1	357.6	0.3	0	85.8	0
Alcoholic liver disease	1 (0.2) 1	549.0	0.2	0	358.3	0	0	85.8	0
Cholecystitis acute	0	549.2	0	1 (0.2) 1	357.6	0.3	0	85.8	0
Psychiatric disorders	1 (0.2) 1	549.2	0.2	1 (0.2) 2	358.3	0.3	0	85.8	0
Panic attack	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Hallucination	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Psychotic disorder	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Renal and urinary disorders	1 (0.2) 1	548.5	0.2	1 (0.2) 1	357.9	0.3	2 (1.9) 2	84.5	2.4
Hypertonic bladder	1 (0.2) 1	548.5	0.2	0	358.3	0	0	85.8	0
Ureterolithiasis	0	549.2	0	0	358.3	0	2 (1.9) 2	84.5	2.4
Urinary incontinence	0	549.2	0	1 (0.2) 1	357.9	0.3	0	85.8	0
Immune system disorders	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
Drug hypersensitivity	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
Metabolism and nutrition disorders	0	549.2	0	1 (0.2) 1	357.8	0.3	1 (1.0) 1	85.0	1.2
Dehydration	0	549.2	0	0	358.3	0	1 (1.0) 1	85.0	1.2
Diabetic metabolic decompensation	0	549.2	0	1 (0.2) 1	357.8	0.3	0	85.8	0
Respiratory, thoracic and mediastinal disorders	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
Nasal septum deviation	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0

Includes events with a start date between first dose and the Week 52 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055.
Source: Table 14.3.2.2.2

The Table 59 displays serious treatment related AEs from the phase 3 safety pool-52-week period:

Table 59. Treatment Related Serious Adverse Event Summary Exposure Adjusted Incidence Rate Phase 3 Safety Pool 52-Week Period Treated Population

System Organ Class Preferred Term	DEUC 6 mg–DEUC 6 mg N = 644 n (%) m	P-Y	IR/ 100 P-Y	PBO–DEUC 6 mg N = 598 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg–APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	5 (0.8) 5	548.4	0.9	6 (1.0) 6	357.0	1.7	1 (1.0) 1	85.8	1.2
Infections and infestations	3 (0.5) 3	548.4	0.5	5 (0.8) 5	357.1	1.4	1 (1.0) 1	85.8	1.2
Appendicitis	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Urinary tract infection	1 (0.2) 1	548.5	0.2	0	358.3	0	0	85.8	0
Vulval cellulitis	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Diverticulitis intestinal perforated	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Hepatitis infectious mononucleosis	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Herpes zoster disseminated	0	549.2	0	1 (0.2) 1	357.8	0.3	0	85.8	0
Oral candidiasis	0	549.2	0	1 (0.2) 1	357.9	0.3	0	85.8	0
Pneumonia	0	549.2	0	2 (0.3) 2	357.9	0.6	0	85.8	0
Gastrointestinal disorders	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Gastrointestinal perforation	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Psychiatric disorders	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Panic attack	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Immune system disorders	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
Drug hypersensitivity	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0

Includes events with a start date between first dose and the Week 52 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055.
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- *Cumulative DEUC period-phase 3 safety pool*

The Table 60 displays Serious AEs from Cumulative phase 3 safety

Table 60. Serious Adverse Event Summary: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool - Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	103 (7.9) 124	1464.9	7.0
Infections and infestations	26 (2.0) 28	1509.2	1.7
Pneumonia	7 (0.5) 7	1522.9	0.5
Appendicitis	2 (0.2) 2	1525.5	0.1
Bronchitis	1 (0.1) 1	1527.1	0.1
Cellulitis	1 (0.1) 1	1527.2	0.1
COVID-19 pneumonia	1 (0.1) 1	1525.6	0.1
Erysipelas	1 (0.1) 1	1526.2	0.1
Gastroenteritis	1 (0.1) 1	1527.1	0.1
Hepatitis E	1 (0.1) 1	1525.6	0.1
Hepatitis infectious mononucleosis	1 (0.1) 1	1527.2	0.1
Herpes zoster	1 (0.1) 1	1526.6	0.1
Herpes zoster disseminated	1 (0.1) 1	1526.2	0.1
Intervertebral discitis	1 (0.1) 1	1527.2	0.1
Oral candidiasis	1 (0.1) 1	1526.4	0.1
Osteomyelitis	1 (0.1) 1	1527.2	0.1
Otitis media	1 (0.1) 2	1526.6	0.1
Respiratory tract infection	1 (0.1) 1	1526.5	0.1
Salpingitis	1 (0.1) 1	1525.0	0.1
Urinary tract infection	1 (0.1) 1	1525.4	0.1
Vestibular neuronitis	1 (0.1) 1	1527.0	0.1
Vulval cellulitis	1 (0.1) 1	1527.2	0.1
Injury, poisoning and procedural complications	14 (1.1) 15	1517.4	0.9
Meniscus injury	4 (0.3) 4	1523.8	0.3
Limb injury	2 (0.2) 2	1525.4	0.1
Tibia fracture	2 (0.2) 2	1526.4	0.1
Hand fracture	1 (0.1) 2	1527.2	0.1
Post procedural complication	1 (0.1) 1	1526.4	0.1
Radius fracture	1 (0.1) 1	1525.4	0.1
Spinal compression fracture	1 (0.1) 1	1527.1	0.1
Traumatic fracture	1 (0.1) 1	1526.4	0.1
Wrist fracture	1 (0.1) 1	1526.8	0.1

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
Cardiac disorders	10 (0.8) 11	1521.3	0.7
Atrial fibrillation	3 (0.2) 3	1526.1	0.2
Acute myocardial infarction	2 (0.2) 2	1525.7	0.1
Angina unstable	1 (0.1) 1	1526.7	0.1
Arteriosclerosis coronary artery	1 (0.1) 1	1527.2	0.1
Atrioventricular block second degree	1 (0.1) 1	1527.2	0.1
Cardiac failure	1 (0.1) 1	1526.4	0.1
Coronary artery disease	1 (0.1) 1	1525.9	0.1
Coronary artery insufficiency	1 (0.1) 1	1525.6	0.1
Musculoskeletal and connective tissue disorders	9 (0.7) 10	1518.9	0.6
Osteoarthritis	3 (0.2) 3	1525.3	0.2
Back pain	1 (0.1) 1	1524.8	0.1
Chondropathy	1 (0.1) 1	1526.7	0.1
Osteonecrosis	1 (0.1) 2	1526.2	0.1
Psoriatic arthropathy	1 (0.1) 1	1526.2	0.1
Spinal osteoarthritis	1 (0.1) 1	1526.1	0.1
Spinal stenosis	1 (0.1) 1	1526.6	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (0.7) 9	1524.2	0.6
Prostate cancer	2 (0.2) 2	1527.0	0.1
Endometrial cancer stage 0	1 (0.1) 1	1527.2	0.1
Glioblastoma	1 (0.1) 1	1527.2	0.1
Lung adenocarcinoma	1 (0.1) 1	1526.8	0.1
Papillary thyroid cancer	1 (0.1) 1	1526.8	0.1
Renal oncocytoma	1 (0.1) 1	1525.2	0.1
Renal perivascular epithelioid cell tumour	1 (0.1) 1	1527.1	0.1
Transitional cell carcinoma	1 (0.1) 1	1527.1	0.1
Nervous system disorders	9 (0.7) 10	1524.1	0.6
Cerebral haemorrhage	1 (0.1) 1	1527.2	0.1
Nervous system disorders			
Cerebral infarction	1 (0.1) 1	1527.2	0.1
Embolic stroke	1 (0.1) 1	1527.2	0.1
Guillain-Barre syndrome	1 (0.1) 1	1527.2	0.1
Headache	1 (0.1) 1	1526.6	0.1
Intracranial pressure increased	1 (0.1) 2	1527.2	0.1
Lacunar infarction	1 (0.1) 1	1526.1	0.1
Spinal claudication	1 (0.1) 1	1526.6	0.1
Transient ischaemic attack	1 (0.1) 1	1526.2	0.1
Gastrointestinal disorders	8 (0.6) 8	1524.0	0.5
Anal fissure	1 (0.1) 1	1526.6	0.1
Gastric dysplasia	1 (0.1) 1	1527.0	0.1
Gastric ulcer	1 (0.1) 1	1526.0	0.1
Gastrointestinal haemorrhage	1 (0.1) 1	1527.1	0.1
Gastrointestinal perforation	1 (0.1) 1	1527.2	0.1
Hiatus hernia	1 (0.1) 1	1526.8	0.1
Inguinal hernia	1 (0.1) 1	1526.6	0.1
Large intestine polyp	1 (0.1) 1	1527.1	0.1
Metabolism and nutrition disorders	4 (0.3) 4	1524.7	0.3
Obesity	2 (0.2) 2	1526.2	0.1
Diabetes mellitus	1 (0.1) 1	1527.2	0.1
Metabolism and nutrition disorders			

Diabetic metabolic decompensation	1 (0.1)	1	1525.7	0.1
Eye disorders	3 (0.2)	4	1524.8	0.2
Cataract diabetic	1 (0.1)	2	1526.8	0.1
Optic ischaemic neuropathy	1 (0.1)	1	1525.5	0.1
Rhegmatogenous retinal detachment	1 (0.1)	1	1526.9	0.1
Hepatobiliary disorders	3 (0.2)	3	1525.9	0.2
Alcoholic liver disease	1 (0.1)	1	1527.0	0.1
Cholecystitis acute	1 (0.1)	1	1526.4	0.1
Hepatic cyst	1 (0.1)	1	1526.9	0.1
Psychiatric disorders	3 (0.2)	4	1527.0	0.2
Depression	1 (0.1)	1	1527.0	0.1
Hallucination	1 (0.1)	1	1527.2	0.1
Panic attack	1 (0.1)	1	1527.2	0.1
Psychotic disorder	1 (0.1)	1	1527.2	0.1
Renal and urinary disorders	3 (0.2)	3	1524.1	0.2
Hypertonic bladder	1 (0.1)	1	1526.2	0.1
Ureterolithiasis	1 (0.1)	1	1527.2	0.1
Urinary incontinence	1 (0.1)	1	1525.1	0.1
Blood and lymphatic system disorders	2 (0.2)	2	1526.6	0.1
Anaemia	1 (0.1)	1	1526.7	0.1
Lymphadenitis	1 (0.1)	1	1527.1	0.1
Congenital, familial and genetic disorders	2 (0.2)	3	1526.3	0.1
Bicuspid aortic valve	1 (0.1)	1	1526.7	0.1
Corneal dystrophy	1 (0.1)	2	1526.8	0.1
General disorders and administration site conditions	2 (0.2)	2	1526.4	0.1
Non-cardiac chest pain	1 (0.1)	1	1526.4	0.1
Sudden death	1 (0.1)	1	1527.2	0.1
Reproductive system and breast disorders	2 (0.2)	2	1526.1	0.1
Cystocele	1 (0.1)	1	1527.0	0.1
Varicocele	1 (0.1)	1	1526.3	0.1
Respiratory, thoracic and mediastinal disorders	2 (0.2)	4	1525.2	0.1
Nasal polyps	1 (0.1)	1	1526.8	0.1
Nasal septum deviation	1 (0.1)	1	1525.6	0.1
Nasal septum disorder	1 (0.1)	1	1526.8	0.1
Nasal turbinate hypertrophy	1 (0.1)	1	1526.8	0.1
Ear and labyrinth disorders	1 (0.1)	1	1525.4	0.1
Vertigo	1 (0.1)	1	1525.4	0.1
Immune system disorders	1 (0.1)	1	1527.1	0.1
Drug hypersensitivity	1 (0.1)	1	1527.1	0.1

The Table 61 displays serious treatment related AEs from Cumulative DEUC:

Table 61. Treatment Related Serious Adverse Event Summary Exposure Adjusted Incidence Rate Phase 3 Safety Pool Cumulative DEUC Period Treated Population

	DEUC 6 mg N = 1312			
System Organ Class Preferred Term	n (%)	m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	16 (1.2)	16	1521.5	1.1
Infections and infestations	10 (0.8)	10	1521.7	0.7
Pneumonia	3 (0.2)	3	1525.9	0.2
Appendicitis	1 (0.1)	1	1526.8	0.1
Hepatitis infectious mononucleosis	1 (0.1)	1	1527.2	0.1
Herpes zoster disseminated	1 (0.1)	1	1526.2	0.1
Oral candidiasis	1 (0.1)	1	1526.4	0.1
Urinary tract infection	1 (0.1)	1	1525.4	0.1
Vestibular neuronitis	1 (0.1)	1	1527.0	0.1
Vulval cellulitis	1 (0.1)	1	1527.2	0.1
Cardiac disorders	1 (0.1)	1	1527.2	0.1
Arteriosclerosis coronary artery	1 (0.1)	1	1527.2	0.1
Gastrointestinal disorders	1 (0.1)	1	1527.2	0.1
Gastrointestinal perforation	1 (0.1)	1	1527.2	0.1
Immune system disorders	1 (0.1)	1	1527.1	0.1
Drug hypersensitivity	1 (0.1)	1	1527.1	0.1

Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055. (Safety Cutoff Date = 10-10-2024, 07-11-2024).
Program Path: BMS GBS\IM011\IM011 INTEGRATED\Biostatistics\Production\Tables\ISS ISE
Program Name: rt-ae-relsae3.sas 28JAN2025:05:23:24

Deaths

No deaths were reported during the Placebo-Controlled Period or the 52-Week Period. One death occurred during the Cumulative DEUC Period beyond 52 weeks; the reason was adjudicated as sudden cardiac death and assessed as not related to study treatment by the investigator. No autopsy was performed.

Adverse events of special interest

Skin toxicity

In non-clinical and clinical studies, DEUC has been associated with certain skin events, i.e., acne and folliculitis. In clinical studies, these skin events were not severe or serious, resolved spontaneously or with topical or oral antimicrobial treatments, and rarely led to treatment discontinuation. The mechanism responsible for these skin events is unclear. Based on the data in the Phase 3 clinical trials in PsO, acneiform rash and folliculitis are adverse reactions with DEUC.

The Table 62, Table 63 and Table 64 present AEs related skin toxicity during the three periods, placebo-controlled period, 0-52 week period and cumulative DEUC period.

Table 62. Skin Events Summary: Placebo-Controlled Period (Week 0-16) (All PsA Safety Pool-Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	85 (11.9) 100	194.4	43.7	25 (3.5) 37	205.4	12.2	4 (3.8) 4	28.4	14.1
Skin and subcutaneous tissue disorders	75 (10.5) 87	196.1	38.2	24 (3.4) 36	205.6	11.7	4 (3.8) 4	28.4	14.1
Rash	22 (3.1) 22	206.6	10.7	4 (0.6) 5	209.0	1.9	1 (1.0) 1	29.0	3.4
Acne	15 (2.1) 15	208.1	7.2	0	209.9	0	1 (1.0) 1	28.9	3.5
Dermatitis acneiform	8 (1.1) 9	209.5	3.8	2 (0.3) 2	209.8	1.0	0	29.1	0
Dermatitis	5 (0.7) 5	210.9	2.4	0	209.9	0	0	29.1	0
Urticaria	5 (0.7) 8	210.8	2.4	2 (0.3) 2	209.7	1.0	0	29.1	0
Dermatitis allergic	4 (0.6) 4	211.0	1.9	1 (0.1) 1	209.7	0.5	0	29.1	0
Eczema	4 (0.6) 5	210.8	1.9	2 (0.3) 10	209.5	1.0	1 (1.0) 1	28.9	3.5
Pruritus	4 (0.6) 4	210.7	1.9	6 (0.8) 7	208.8	2.9	1 (1.0) 1	28.8	3.5
Rosacea	4 (0.6) 4	210.7	1.9	0	209.9	0	0	29.1	0
Rash papular	2 (0.3) 2	210.9	0.9	0	209.9	0	0	29.1	0
Rash vesicular	2 (0.3) 2	211.3	0.9	0	209.9	0	0	29.1	0
Dermatitis atopic	1 (0.1) 2	211.3	0.5	1 (0.1) 1	209.7	0.5	0	29.1	0
Intertrigo	1 (0.1) 1	211.2	0.5	0	209.9	0	0	29.1	0
Prurigo	1 (0.1) 2	211.2	0.5	1 (0.1) 1	209.9	0.5	0	29.1	0
Rash macular	1 (0.1) 1	211.2	0.5	1 (0.1) 1	209.6	0.5	0	29.1	0
Rash maculo-papular	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Dermatitis contact	0	211.5	0	1 (0.1) 1	209.6	0.5	0	29.1	0
Neurodermatitis	0	211.5	0	1 (0.1) 1	209.6	0.5	0	29.1	0
Rash erythematous	0	211.5	0	1 (0.1) 1	209.6	0.5	0	29.1	0
Rash pruritic	0	211.5	0	1 (0.1) 2	209.7	0.5	0	29.1	0
Senile pruritus	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0

Table 63. Skin Events Summary: 52-Week Period (Week 0-52) (Phase 3 Safety Pool-Treated Population)

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	94 (14.6) 116	493.3	19.1	67 (11.2) 81	330.9	20.2	9 (8.6) 9	81.8	11.0
Skin and subcutaneous tissue disorders	81 (12.6) 96	500.8	16.2	59 (9.9) 66	334.6	17.6	9 (8.6) 9	81.8	11.0
Rash	21 (3.3) 22	535.2	3.9	9 (1.5) 9	354.9	2.5	1 (1.0) 1	85.0	1.2
Acne	15 (2.3) 15	538.9	2.8	19 (3.2) 20	350.6	5.4	1 (1.0) 1	84.9	1.2
Urticaria	9 (1.4) 12	546.8	1.6	3 (0.5) 3	357.8	0.8	0	85.8	0
Dermatitis	6 (0.9) 7	545.8	1.1	2 (0.3) 2	357.5	0.6	1 (1.0) 1	85.8	1.2
Dermatitis acneiform	6 (0.9) 7	545.7	1.1	4 (0.7) 4	356.4	1.1	0	85.8	0
Pruritus	6 (0.9) 6	546.1	1.1	5 (0.8) 5	355.8	1.4	1 (1.0) 1	84.8	1.2
Dermatitis allergic	5 (0.8) 5	546.5	0.9	3 (0.5) 3	358.1	0.8	1 (1.0) 1	85.8	1.2
Eczema	5 (0.8) 7	545.7	0.9	3 (0.5) 4	357.0	0.8	1 (1.0) 1	84.9	1.2
Rash papular	3 (0.5) 3	547.5	0.5	0	358.3	0	0	85.8	0
Rosacea	3 (0.5) 3	546.7	0.5	2 (0.3) 2	357.3	0.6	1 (1.0) 1	85.6	1.2
Dermatitis atopic	1 (0.2) 2	548.3	0.2	1 (0.2) 1	357.8	0.3	0	85.8	0
Dyshidrotic eczema	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Prurigo	1 (0.2) 2	548.3	0.2	0	358.3	0	0	85.8	0
Pustular psoriasis	1 (0.2) 1	548.5	0.2	0	358.3	0	0	85.8	0
Rash maculo-papular	1 (0.2) 1	549.2	0.2	2 (0.3) 2	357.1	0.6	0	85.8	0
Rash vesicular	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Urticaria papular	1 (0.2) 1	548.7	0.2	0	358.3	0	0	85.8	0
Intertrigo	0	549.2	0	2 (0.3) 2	357.3	0.6	0	85.8	0
Neurodermatitis	0	549.2	0	0	358.3	0	1 (1.0) 1	85.6	1.2
Perioral dermatitis	0	549.2	0	1 (0.2) 1	358.0	0.3	0	85.8	0
Photosensitivity reaction	0	549.2	0	1 (0.2) 1	357.8	0.3	0	85.8	0
Rash erythematous	0	549.2	0	1 (0.2) 3	357.9	0.3	0	85.8	0
Rash macular	0	549.2	0	1 (0.2) 1	358.2	0.3	0	85.8	0
Rash pruritic	0	549.2	0	2 (0.3) 2	357.3	0.6	0	85.8	0
Seborrhoeic dermatitis	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Skin ulcer	0	549.2	0	1 (0.2) 1	357.6	0.3	0	85.8	0

Table 64. Skin Events Summary: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool-Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	196 (14.9) 248	1349.7	14.5
Skin and subcutaneous tissue disorders	169 (12.9) 201	1377.1	12.3
Rash	40 (3.0) 43	1486.4	2.7
Acne	38 (2.9) 40	1494.7	2.5
Urticaria	15 (1.1) 18	1521.4	1.0
Eczema	12 (0.9) 17	1513.9	0.8
Pruritus	12 (0.9) 12	1518.1	0.8
Dermatitis acneiform	10 (0.8) 11	1519.4	0.7
Dermatitis	9 (0.7) 10	1521.2	0.6
Dermatitis allergic	9 (0.7) 9	1519.6	0.6
Rosacea	6 (0.5) 6	1520.6	0.4
Rash papular	5 (0.4) 5	1522.4	0.3
Rash maculo-papular	3 (0.2) 3	1523.7	0.2
Rash pruritic	3 (0.2) 3	1524.7	0.2
Dermatitis atopic	2 (0.2) 3	1525.7	0.1
Dyshidrotic eczema	2 (0.2) 2	1527.0	0.1
Intertrigo	2 (0.2) 2	1523.7	0.1
Perioral dermatitis	2 (0.2) 2	1525.9	0.1
Blister	1 (0.1) 1	1526.8	0.1
Dermatitis contact	1 (0.1) 1	1526.9	0.1
Photosensitivity reaction	1 (0.1) 1	1524.8	0.1
Prurigo	1 (0.1) 2	1526.2	0.1
Pustular psoriasis	1 (0.1) 1	1526.2	0.1
Rash erythematous	1 (0.1) 3	1526.8	0.1
Rash macular	1 (0.1) 1	1526.3	0.1
Rash vesicular	1 (0.1) 1	1527.2	0.1
Seborrhoeic dermatitis	1 (0.1) 1	1526.0	0.1
Skin exfoliation	1 (0.1) 1	1526.9	0.1
Skin ulcer	1 (0.1) 1	1525.8	0.1
Urticaria papular	1 (0.1) 1	1526.1	0.1

Infections

AEs of herpes zoster, herpes simplex, influenza, opportunistic infection, TB, and COVID-19 were specified as infection AESIs in the Phase 3 studies. All infection AESIs were reviewed by an independent, blinded Infection Adjudication Committee who classified events as herpes viral

infections (zoster or simplex), influenza, COVID-19, TB (pulmonary or extrapulmonary), and opportunistic infections (fungal, bacterial, viral, parasitic, or other). Table 65, Table 66 and Table 67 present AEs related to infections and infestations that occurred during the three periods, placebo-controlled period, 0–52-week period and cumulative DEUC period.

Table 65. Summary of Infection Adverse Events - Placebo-Controlled Period (Week 0-16) (All PsA Pool –Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
Infections and infestations	224 (31.4) 312	170.4	131.5	155 (21.8) 195	184.3	84.1	34 (32.4) 43	24.2	140.6
Upper respiratory tract infection	40 (5.6) 47	204.4	19.6	23 (3.2) 25	206.0	11.2	4 (3.8) 5	28.7	13.9
COVID-19	31 (4.3) 31	206.5	15.0	24 (3.4) 25	205.8	11.7	7 (6.7) 7	27.6	25.4
Nasopharyngitis	31 (4.3) 33	205.1	15.1	38 (5.4) 39	204.1	18.6	4 (3.8) 4	28.3	14.1
Pharyngitis	16 (2.2) 17	208.8	7.7	4 (0.6) 4	209.2	1.9	1 (1.0) 1	28.9	3.5
Urinary tract infection	11 (1.5) 12	210.2	5.2	11 (1.5) 12	207.3	5.3	2 (1.9) 2	29.0	6.9
Bronchitis	9 (1.3) 9	210.5	4.3	5 (0.7) 6	209.0	2.4	3 (2.9) 3	28.5	10.5
Oral herpes	9 (1.3) 9	209.5	4.3	3 (0.4) 3	209.4	1.4	2 (1.9) 2	29.0	6.9
Respiratory tract infection	9 (1.3) 10	209.9	4.3	4 (0.6) 4	209.2	1.9	0	29.1	0
Tonsillitis	9 (1.3) 10	209.6	4.3	2 (0.3) 2	209.8	1.0	0	29.1	0
Gastroenteritis	8 (1.1) 8	210.3	3.8	8 (1.1) 8	208.4	3.8	2 (1.9) 2	29.0	6.9
Influenza	7 (1.0) 7	210.2	3.3	4 (0.6) 4	209.2	1.9	1 (1.0) 1	29.1	3.4
Folliculitis	6 (0.8) 7	210.5	2.8	0	209.9	0	0	29.1	0
Sinusitis	6 (0.8) 7	210.4	2.9	4 (0.6) 6	209.0	1.9	1 (1.0) 1	29.1	3.4
Gastroenteritis viral	5 (0.7) 5	211.0	2.4	0	209.9	0	0	29.1	0
Pharyngotonsillitis	5 (0.7) 5	210.5	2.4	0	209.9	0	0	29.1	0
Tinea pedis	5 (0.7) 5	210.3	2.4	0	209.9	0	0	29.1	0
Gingivitis	4 (0.6) 4	211.3	1.9	0	209.9	0	0	29.1	0
Pneumonia	4 (0.6) 5	211.0	1.9	4 (0.6) 4	209.7	1.9	0	29.1	0
Ear infection	3 (0.4) 3	210.8	1.4	1 (0.1) 1	209.8	0.5	0	29.1	0
Laryngitis	3 (0.4) 3	210.9	1.4	1 (0.1) 1	209.8	0.5	0	29.1	0
Oral candidiasis	3 (0.4) 3	210.9	1.4	0	209.9	0	1 (1.0) 1	29.1	3.4
Pulpitis dental	3 (0.4) 3	211.4	1.4	1 (0.1) 1	209.9	0.5	1 (1.0) 1	28.8	3.5
Pustule	3 (0.4) 3	211.0	1.4	0	209.9	0	0	29.1	0
Tooth abscess	3 (0.4) 4	211.2	1.4	1 (0.1) 1	209.9	0.5	0	29.1	0
Acute sinusitis	2 (0.3) 2	211.2	0.9	3 (0.4) 3	209.4	1.4	0	29.1	0
Cellulitis	2 (0.3) 3	211.5	0.9	0	209.9	0	1 (1.0) 1	28.9	3.5
Conjunctivitis	2 (0.3) 3	211.1	0.9	3 (0.4) 3	209.5	1.4	0	29.1	0
Erysipelas	2 (0.3) 3	211.0	0.9	1 (0.1) 1	209.6	0.5	0	29.1	0
Fungal foot infection	2 (0.3) 3	210.9	0.9	0	209.9	0	0	29.1	0
Fungal skin infection	2 (0.3) 2	210.9	0.9	0	209.9	0	0	29.1	0
Furuncle	2 (0.3) 2	211.0	0.9	0	209.9	0	1 (1.0) 1	29.0	3.5
Herpes simplex	2 (0.3) 2	211.0	0.9	2 (0.3) 2	209.6	1.0	0	29.1	0
Herpes zoster	2 (0.3) 2	211.4	0.9	3 (0.4) 3	209.6	1.4	0	29.1	0
Oral infection	2 (0.3) 3	211.1	0.9	0	209.9	0	0	29.1	0
Paronychia	2 (0.3) 2	211.2	0.9	0	209.9	0	0	29.1	0
Rhinitis	2 (0.3) 2	211.0	0.9	2 (0.3) 2	209.7	1.0	0	29.1	0
Tooth infection	2 (0.3) 2	211.3	0.9	2 (0.3) 2	209.7	1.0	0	29.1	0
Tracheobronchitis	2 (0.3) 2	211.1	0.9	1 (0.1) 1	209.7	0.5	0	29.1	0
Viral infection	2 (0.3) 3	211.1	0.9	5 (0.7) 6	209.3	2.4	1 (1.0) 1	29.0	3.5
Appendicitis	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Conjunctivitis viral	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Cystitis	1 (0.1) 1	211.5	0.5	3 (0.4) 4	209.4	1.4	0	29.1	0
Gastrointestinal viral infection	1 (0.1) 1	211.3	0.5	1 (0.1) 1	209.7	0.5	1 (1.0) 1	28.9	3.5
Genital infection	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Groin abscess	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Herpes ophthalmic	1 (0.1) 1	211.2	0.5	0	209.9	0	0	29.1	0
Lyme disease	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Lymphangitis	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Onychomycosis	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Otitis media	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Periodontitis	1 (0.1) 1	211.4	0.5	1 (0.1) 1	209.8	0.5	0	29.1	0
Pharyngitis bacterial	1 (0.1) 1	211.2	0.5	0	209.9	0	0	29.1	0
Pharyngitis streptococcal	1 (0.1) 1	211.4	0.5	1 (0.1) 1	209.7	0.5	0	29.1	0
Post procedural infection	1 (0.1) 1	211.3	0.5	1 (0.1) 2	209.8	0.5	0	29.1	0
Skin bacterial infection	1 (0.1) 1	211.2	0.5	0	209.9	0	0	29.1	0
Suspected COVID-19	1 (0.1) 1	211.3	0.5	2 (0.3) 2	209.8	1.0	0	29.1	0
Tinea versicolour	1 (0.1) 1	211.2	0.5	0	209.9	0	0	29.1	0
Upper respiratory tract infection bacterial	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Vaginal infection	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Viral pharyngitis	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Viral skin infection	1 (0.1) 1	211.3	0.5	0	209.9	0	0	29.1	0
Viral upper respiratory tract infection	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0
Vulval cellulitis	1 (0.1) 2	211.4	0.5	0	209.9	0	0	29.1	0
Vulvovaginal candidiasis	1 (0.1) 1	211.4	0.5	0	209.9	0	0	29.1	0

Table 66. Summary of Infection Adverse Events: 52-Week Period (Week 0-52) (Phase 3 Safety Pool –Treated Population

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%)	m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%)	m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%)	m	P-Y	IR/ 100 P-Y
Infections and infestations	335 (52.0)	651	351.9	95.2	246 (41.1)	412	257.0	95.7	54 (51.4)	94	52.7	102.5
Upper respiratory tract infection	78 (12.1)	109	505.8	15.4	53 (8.9)	67	338.7	15.6	11 (10.5)	13	81.0	13.6
COVID-19	64 (9.9)	66	515.0	12.4	37 (6.2)	38	344.9	10.7	13 (12.4)	15	77.0	16.9
Nasopharyngitis	63 (9.8)	88	516.9	12.2	58 (9.7)	64	335.4	17.3	8 (7.6)	8	80.6	9.9
Urinary tract infection	28 (4.3)	31	535.5	5.2	12 (2.0)	14	351.8	3.4	7 (6.7)	8	83.2	8.4
Pharyngitis	27 (4.2)	30	533.8	5.1	13 (2.2)	16	352.9	3.7	1 (1.0)	1	85.0	1.2
Tonsillitis	20 (3.1)	24	537.3	3.7	8 (1.3)	9	354.8	2.3	0		85.8	0
Gastroenteritis	19 (3.0)	21	538.5	3.5	9 (1.5)	12	356.1	2.5	2 (1.9)	2	85.0	2.4
Bronchitis	17 (2.6)	19	541.9	3.1	14 (2.3)	17	354.6	3.9	4 (3.8)	4	83.4	4.8
Sinusitis	15 (2.3)	18	541.7	2.8	11 (1.8)	11	355.3	3.1	3 (2.9)	5	84.4	3.6
Influenza	14 (2.2)	14	540.6	2.6	10 (1.7)	10	354.4	2.8	3 (2.9)	3	84.6	3.5
Oral herpes	14 (2.2)	16	542.0	2.6	4 (0.7)	6	357.5	1.1	2 (1.9)	2	84.3	2.4
Respiratory tract infection	13 (2.0)	17	542.1	2.4	8 (1.3)	12	354.1	2.3	0		85.8	0
Folliculitis	8 (1.2)	9	544.7	1.5	7 (1.2)	9	355.6	2.0	0		85.8	0
Herpes simplex	8 (1.2)	9	545.4	1.5	3 (0.5)	4	357.2	0.8	1 (1.0)	1	85.2	1.2
Pharyngotonsillitis	7 (1.1)	7	546.0	1.3	6 (1.0)	6	356.6	1.7	0		85.8	0
Pneumonia	7 (1.1)	8	545.8	1.3	5 (0.8)	10	356.8	1.4	1 (1.0)	1	85.4	1.2
Tinea pedis	7 (1.1)	7	544.3	1.3	1 (0.2)	1	357.7	0.3	0		85.8	0
Herpes zoster	6 (0.9)	6	547.2	1.1	5 (0.8)	5	356.2	1.4	1 (1.0)	1	85.3	1.2
Pulpitis dental	6 (0.9)	7	546.5	1.1	1 (0.2)	1	358.2	0.3	3 (2.9)	4	83.8	3.6
Gastroenteritis viral	5 (0.8)	5	546.5	0.9	5 (0.8)	5	356.7	1.4	0		85.8	0
Gingivitis	5 (0.8)	5	547.7	0.9	0		358.3	0	0		85.8	0
Rhinitis	5 (0.8)	5	547.2	0.9	1 (0.2)	1	357.7	0.3	0		85.8	0
Viral infection	5 (0.8)	7	546.1	0.9	3 (0.5)	4	357.1	0.8	2 (1.9)	2	85.0	2.4
Cellulitis	4 (0.6)	5	548.2	0.7	4 (0.7)	4	356.9	1.1	1 (1.0)	1	84.9	1.2
Conjunctivitis	4 (0.6)	5	547.2	0.7	3 (0.5)	3	357.1	0.8	0		85.8	0
Pustule	4 (0.6)	4	546.6	0.7	4 (0.7)	4	356.4	1.1	0		85.8	0
Tooth abscess	4 (0.6)	4	548.4	0.7	0		358.3	0	0		85.8	0
Cystitis	3 (0.5)	4	548.4	0.5	1 (0.2)	2	357.7	0.3	1 (1.0)	1	85.1	1.2
Dengue fever	3 (0.5)	3	548.3	0.5	2 (0.3)	2	357.9	0.6	0		85.8	0
Ear infection	3 (0.5)	3	547.0	0.5	5 (0.8)	5	357.3	1.4	0		85.8	0
Fungal skin infection	3 (0.5)	3	547.2	0.5	0		358.3	0	0		85.8	0
Laryngitis	3 (0.5)	3	547.6	0.5	3 (0.5)	3	356.6	0.8	0		85.8	0
Paronychia	3 (0.5)	3	548.5	0.5	2 (0.3)	2	357.7	0.6	0		85.8	0
Periodontitis	3 (0.5)	3	548.5	0.5	0		358.3	0	0		85.8	0
Pharyngitis bacterial	3 (0.5)	3	548.0	0.5	1 (0.2)	2	357.8	0.3	0		85.8	0
Viral upper respiratory tract infection	3 (0.5)	3	548.5	0.5	4 (0.7)	4	357.5	1.1	0		85.8	0
Acute sinusitis	2 (0.3)	2	547.8	0.4	0		358.3	0	1 (1.0)	1	85.4	1.2

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%)	m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%)	m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%)	m	P-Y	IR/ 100 P-Y
Appendicitis	2 (0.3)	2	548.4	0.4	0		358.3	0	0		85.8	0
Erysipelas	2 (0.3)	3	547.4	0.4	1 (0.2)	1	358.0	0.3	0		85.8	0
Febrile infection	2 (0.3)	2	548.6	0.4	2 (0.3)	3	357.6	0.6	1 (1.0)	1	85.7	1.2
Fungal foot infection	2 (0.3)	4	547.4	0.4	0		358.3	0	0		85.8	0
Furuncle	2 (0.3)	2	548.0	0.4	2 (0.3)	2	357.2	0.6	1 (1.0)	1	85.5	1.2
Gastrointestinal infection	2 (0.3)	2	549.0	0.4	5 (0.8)	5	357.6	1.4	0		85.8	0
Onychomycosis	2 (0.3)	2	548.0	0.4	0		358.3	0	0		85.8	0
Oral candidiasis	2 (0.3)	2	547.9	0.4	4 (0.7)	5	356.9	1.1	1 (1.0)	1	85.1	1.2
Oral infection	2 (0.3)	3	547.4	0.4	1 (0.2)	1	357.6	0.3	0		85.8	0
Otitis externa	2 (0.3)	3	548.2	0.4	0		358.3	0	2 (1.9)	2	84.2	2.4
Otitis media	2 (0.3)	2	548.8	0.4	2 (0.3)	3	357.0	0.6	1 (1.0)	1	85.7	1.2
Skin infection	2 (0.3)	2	549.0	0.4	0		358.3	0	0		85.8	0
Tooth infection	2 (0.3)	2	548.0	0.4	2 (0.3)	2	357.8	0.6	0		85.8	0
Tracheobronchitis	2 (0.3)	2	547.4	0.4	0		358.3	0	0		85.8	0
Viral pharyngitis	2 (0.3)	2	548.4	0.4	0		358.3	0	0		85.8	0
Asymptomatic bacteriuria	1 (0.2)	1	548.8	0.2	2 (0.3)	2	358.0	0.6	0		85.8	0
Borrelia infection	1 (0.2)	1	548.9	0.2	0		358.3	0	0		85.8	0
Conjunctivitis bacterial	1 (0.2)	1	549.0	0.2	0		358.3	0	0		85.8	0
Conjunctivitis viral	1 (0.2)	1	548.8	0.2	0		358.3	0	0		85.8	0
Dermatophytosis	1 (0.2)	1	548.7	0.2	0		358.3	0	0		85.8	0
Diverticulitis	1 (0.2)	1	548.9	0.2	0		358.3	0	1 (1.0)	1	85.8	1.2
Fungal infection	1 (0.2)	1	549.2	0.2	0		358.3	0	1 (1.0)	1	85.7	1.2
Gastrointestinal viral infection	1 (0.2)	1	548.4	0.2	1 (0.2)	1	357.9	0.3	1 (1.0)	1	85.6	1.2
Genital infection	1 (0.2)	1	548.3	0.2	0		358.3	0	0		85.8	0
Gingival abscess	1 (0.2)	1	548.6	0.2	0		358.3	0	1 (1.0)	1	85.1	1.2
Groin abscess	1 (0.2)	1	548.8	0.2	0		358.3	0	0		85.8	0
Helicobacter gastritis	1 (0.2)	1	548.6	0.2	1 (0.2)	1	357.7	0.3	0		85.8	0
Herpes ophthalmic	1 (0.2)	1	548.8	0.2	1 (0.2)	2	357.8	0.3	0		85.8	0
Infected cyst	1 (0.2)	1	548.7	0.2	0		358.3	0	0		85.8	0
Infection parasitic	1 (0.2)	1	548.8	0.2	0		358.3	0	0		85.8	0
Lower respiratory tract infection	1 (0.2)	1	548.9	0.2	0		358.3	0	0		85.8	0
Lyme disease	1 (0.2)	1	549.0	0.2	0		358.3	0	1 (1.0)	1	85.5	1.2
Lymphangitis	1 (0.2)	1	549.2	0.2	0		358.3	0	0		85.8	0
Oral fungal infection	1 (0.2)	1	548.6	0.2	0		358.3	0	0		85.8	0
Otitis media acute	1 (0.2)	1	548.7	0.2	1 (0.2)	1	357.9	0.3	0		85.8	0
Pharyngitis streptococcal	1 (0.2)	1	548.4	0.2	0		358.3	0	0		85.8	0
Post procedural infection	1 (0.2)	1	548.9	0.2	0		358.3	0	0		85.8	0
Rash pustular	1 (0.2)	1	549.2	0.2	0		358.3	0	0		85.8	0
Respiratory tract infection viral	1 (0.2)	1	548.7	0.2	0		358.3	0	0		85.8	0

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%)	m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%)	m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%)	m	P-Y	IR/ 100 P-Y
Salpingitis	1 (0.2)	1	548.9	0.2	0		358.3	0	0		85.8	0
Skin bacterial infection	1 (0.2)	1	548.5	0.2	0		358.3	0	0		85.8	0
Sporotrichosis	1 (0.2)	1	548.6	0.2	0		358.3	0	0		85.8	0
Superinfection	1 (0.2)	1	549.0	0.2	0		358.3	0	0		85.8	0
Superinfection bacterial	1 (0.2)	1	548.6	0.2	0		358.3	0	0		85.8	0
Suspected COVID-19	1 (0.2)	1	548.4	0.2	1 (0.2)	1	358.0	0.3	0		85.8	0
Tinea cruris	1 (0.2)	1	549.0	0.2	0		358.3	0	0		85.8	0
Tinea versicolour	1 (0.2)	1	548.2	0.2	0		358.3	0	0		85.8	0
Tonsillitis bacterial	1 (0.2)	1	548.7	0.2	1 (0.2)	3	358.1	0.3	0		85.8	0
Upper respiratory tract infection bacterial	1 (0.2)	1	548.5	0.2	0		358.3	0	0		85.8	0
Vaginal infection	1 (0.2)	1	549.0	0.2	1 (0.2)	1	357.7	0.3	0		85.8	0
Viral skin infection	1 (0.2)	1	548.4	0.2	0		358.3	0	0		85.8	0
Vulval cellulitis	1 (0.2)	2	549.2	0.2	0		358.3	0	0		85.8	0
Vulvovaginal candidiasis	1 (0.2)	1	548.5	0.2	2 (0.3)	2	357.1	0.6	1 (1.0)	1	85.7	1.2
Vulvovaginal mycotic infection	1 (0.2)	1	548.8	0.2	0		358.3	0	0		85.8	0

Table 67. Summary of Infection Adverse Events - Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool –Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
Infections and infestations	696 (53.0) 1531	860.6	80.9
Upper respiratory tract infection	175 (13.3) 268	1378.3	12.7
Nasopharyngitis	154 (11.7) 200	1386.1	11.1
COVID-19	128 (9.8) 142	1380.9	9.3
Bronchitis	58 (4.4) 69	1489.6	3.9
Pharyngitis	51 (3.9) 65	1473.4	3.5
Urinary tract infection	48 (3.7) 57	1486.3	3.2
Sinusitis	38 (2.9) 47	1497.3	2.5
Gastroenteritis	36 (2.7) 42	1499.7	2.4
Tonsillitis	36 (2.7) 50	1490.5	2.4
Influenza	34 (2.6) 34	1497.4	2.3
Oral herpes	25 (1.9) 29	1508.8	1.7
Respiratory tract infection	25 (1.9) 37	1502.9	1.7
Pneumonia	21 (1.6) 27	1513.4	1.4
Folliculitis	17 (1.3) 21	1511.0	1.1
Herpes zoster	17 (1.3) 18	1513.0	1.1
Pharyngotonsillitis	16 (1.2) 17	1512.5	1.1
Conjunctivitis	14 (1.1) 15	1514.3	0.9
Herpes simplex	14 (1.1) 18	1512.8	0.9
Dengue fever	13 (1.0) 13	1521.1	0.9
Ear infection	12 (0.9) 12	1517.3	0.8
Latent tuberculosis	12 (0.9) 12	1522.7	0.8
Viral infection	12 (0.9) 15	1515.3	0.8
Pulpitis dental	11 (0.8) 13	1516.7	0.7
Pustule	11 (0.8) 14	1517.8	0.7
Gastroenteritis viral	10 (0.8) 10	1520.7	0.7
Tinea pedis	10 (0.8) 10	1518.0	0.7
Cellulitis	9 (0.7) 10	1522.1	0.6
Rhinitis	9 (0.7) 9	1520.9	0.6
Laryngitis	8 (0.6) 8	1517.5	0.5
Oral candidiasis	8 (0.6) 9	1523.3	0.5
Otitis media	8 (0.6) 9	1521.6	0.5
Cystitis	7 (0.5) 9	1520.7	0.5
Gastrointestinal infection	7 (0.5) 8	1519.3	0.5
Viral upper respiratory tract infection	7 (0.5) 8	1525.2	0.5
Furuncle	6 (0.5) 6	1521.3	0.4
Gingivitis	6 (0.5) 6	1523.1	0.4
Helicobacter infection	6 (0.5) 6	1523.8	0.4
Paronychia	6 (0.5) 6	1523.2	0.4
Tooth infection	6 (0.5) 6	1522.9	0.4
Febrile infection	5 (0.4) 6	1519.8	0.3
Pharyngitis bacterial	5 (0.4) 6	1522.3	0.3
Erysipelas	4 (0.3) 5	1523.6	0.3
Herpes virus infection	4 (0.3) 6	1522.6	0.3
Oral infection	4 (0.3) 5	1523.6	0.3
Periodontitis	4 (0.3) 4	1525.6	0.3
Tooth abscess	4 (0.3) 4	1526.0	0.3
Vulvovaginal candidiasis	4 (0.3) 4	1524.9	0.3
Acute sinusitis	3 (0.2) 3	1523.9	0.2
Asymptomatic bacteriuria	3 (0.2) 3	1526.5	0.2
Fungal foot infection	3 (0.2) 6	1523.7	0.2
Fungal skin infection	3 (0.2) 3	1523.7	0.2
Otitis externa	3 (0.2) 4	1525.7	0.2
Viral pharyngitis	3 (0.2) 4	1524.5	0.2
Appendicitis	2 (0.2) 2	1525.5	0.1
Bacterial vaginosis	2 (0.2) 2	1526.4	0.1
Candida infection	2 (0.2) 2	1523.7	0.1
Chronic sinusitis	2 (0.2) 2	1526.3	0.1

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
Conjunctivitis bacterial	2 (0.2) 2	1524.7	0.1
Gastrointestinal viral infection	2 (0.2) 2	1524.9	0.1
Helicobacter gastritis	2 (0.2) 2	1525.1	0.1
Hepatitis E	2 (0.2) 2	1525.7	0.1
Herpes ophthalmic	2 (0.2) 3	1525.5	0.1
Laryngopharyngitis	2 (0.2) 2	1524.2	0.1
Onychomycosis	2 (0.2) 2	1525.8	0.1
Otitis media acute	2 (0.2) 2	1526.2	0.1
Pharyngitis streptococcal	2 (0.2) 2	1525.8	0.1
Salpingitis	2 (0.2) 2	1525.4	0.1
Skin infection	2 (0.2) 2	1526.6	0.1
Suspected COVID-19	2 (0.2) 2	1525.4	0.1
Tinea cruris	2 (0.2) 2	1526.4	0.1
Tonsillitis bacterial	2 (0.2) 4	1525.8	0.1
Tracheobronchitis	2 (0.2) 2	1523.1	0.1
Vaginal infection	2 (0.2) 2	1526.0	0.1
Beta haemolytic streptococcal infection	1 (0.1) 1	1526.6	0.1
Borrelia infection	1 (0.1) 1	1526.8	0.1
Bronchitis bacterial	1 (0.1) 1	1525.3	0.1
Conjunctivitis viral	1 (0.1) 1	1526.7	0.1
COVID-19 pneumonia	1 (0.1) 1	1525.6	0.1
Cystitis klebsiella	1 (0.1) 1	1527.3	0.1
Dental sepsis	1 (0.1) 1	1527.2	0.1
Dermatophytosis	1 (0.1) 1	1526.6	0.1
Dermatophytosis of nail	1 (0.1) 1	1526.1	0.1
Diverticulitis	1 (0.1) 1	1526.7	0.1
Enterococcal infection	1 (0.1) 1	1527.3	0.1
Erythema infectiosum	1 (0.1) 1	1526.5	0.1
Erythema migrans	1 (0.1) 1	1526.9	0.1
Eyelid infection	1 (0.1) 1	1526.2	0.1
Fungal infection	1 (0.1) 1	1526.6	0.1
Genital infection	1 (0.1) 1	1526.2	0.1
Gingival abscess	1 (0.1) 1	1524.8	0.1
Groin abscess	1 (0.1) 1	1526.8	0.1
Helminthic infection	1 (0.1) 1	1526.4	0.1
Hepatitis infectious mononucleosis	1 (0.1) 1	1527.2	0.1
Herpes zoster disseminated	1 (0.1) 1	1526.2	0.1
Hordeolum	1 (0.1) 1	1527.2	0.1
Infected cyst	1 (0.1) 1	1526.4	0.1
Infection parasitic	1 (0.1) 1	1526.7	0.1
Intervertebral discitis	1 (0.1) 2	1527.1	0.1
Klebsiella infection	1 (0.1) 1	1527.3	0.1
Localised infection	1 (0.1) 2	1526.7	0.1
Lower respiratory tract infection	1 (0.1) 1	1526.8	0.1
Lyme disease	1 (0.1) 1	1527.0	0.1
Lymphangitis	1 (0.1) 1	1527.1	0.1
Nail infection	1 (0.1) 1	1527.2	0.1
Nasal herpes	1 (0.1) 1	1526.5	0.1
Oral fungal infection	1 (0.1) 1	1526.5	0.1
Osteomyelitis	1 (0.1) 3	1527.2	0.1
Otitis media bacterial	1 (0.1) 1	1527.1	0.1
Pertussis	1 (0.1) 1	1526.4	0.1
Pneumonia mycoplasmal	1 (0.1) 1	1526.9	0.1
Pneumonia viral	1 (0.1) 1	1526.2	0.1
Post procedural infection	1 (0.1) 1	1526.9	0.1
Post-acute COVID-19 syndrome	1 (0.1) 1	1526.4	0.1
Rash pustular	1 (0.1) 1	1527.2	0.1
Respiratory syncytial virus infection	1 (0.1) 1	1526.0	0.1
Respiratory tract infection viral	1 (0.1) 1	1525.9	0.1

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
Salpingo-oophoritis	1 (0.1) 1	1526.4	0.1
Septic shock	1 (0.1) 1	1527.3	0.1
Sinobronchitis	1 (0.1) 1	1526.6	0.1
Skin bacterial infection	1 (0.1) 1	1526.5	0.1
Skin candida	1 (0.1) 1	1527.1	0.1
Soft tissue infection	1 (0.1) 1	1526.2	0.1
Sporotrichosis	1 (0.1) 1	1526.6	0.1
Streptococcal infection	1 (0.1) 1	1526.9	0.1
Superinfection	1 (0.1) 1	1526.9	0.1
Superinfection bacterial	1 (0.1) 1	1525.7	0.1
Tinea capitis	1 (0.1) 1	1526.7	0.1
Tinea versicolour	1 (0.1) 1	1524.5	0.1
Tracheitis	1 (0.1) 1	1527.1	0.1
Upper respiratory tract infection bacterial	1 (0.1) 1	1525.4	0.1
Vaginitis gardnerella	1 (0.1) 1	1526.5	0.1
Varicella	1 (0.1) 1	1526.6	0.1
Vestibular neuronitis	1 (0.1) 2	1527.0	0.1
Viral skin infection	1 (0.1) 1	1525.1	0.1
Viral tonsillitis	1 (0.1) 1	1526.4	0.1
Vulval cellulitis	1 (0.1) 2	1527.1	0.1
Vulvovaginal mycotic infection	1 (0.1) 1	1526.7	0.1

Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054 and IM011055. (Safety Cutoff Date = 10-10-2024, 07-11-2024).
Source: Table 14.3.1.1.1.3

Malignancies

Chronic inflammation has been shown to be a significant risk factor for the development of cancer and plays a prominent role in promoting tumor progression including the development of metastatic disease. The risk for malignancy in PsA compared to the general population is not well defined and may be influenced by treatment. An increased risk of malignancies has been associated with certain immunomodulatory and immunosuppressive therapies. Table 68 and Table 69 present AEs related to infections and infestations that occurred during the Phase 3 safety pool-52 -week period (week 0-52) and the cumulative DEUC period. During the Placebo-Controlled Period, there were no malignancies in the DEUC group. In the placebo group, 1 patient experienced small intestine carcinoma and 1 patient had basal cell carcinoma and Bowen's disease.

Table 68. Malignancy Events Summary: 52-Week Period (Week 0-52) (Phase 3 Safety Pool-Treated Population)

	DEUC 6 mg-DEUC 6 mg N = 644			PBO-DEUC 6 mg N = 598			APR 30 mg-APR 30 mg N = 105		
System Organ Class Preferred Term	n (%)	m	P-Y	IR/ 100 P-Y	n (%)	m	P-Y	IR/ 100 P-Y	n (%)	m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	3 (0.5)	3	546.8	0.5	2 (0.3)	2	358.0	0.6	1 (1.0)	1	85.8	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.5)	3	546.8	0.5	2 (0.3)	2	358.0	0.6	1 (1.0)	1	85.8	1.2
Glioblastoma	1 (0.2)	1	549.2	0.2	0		358.3	0	0		85.8	0
Lung adenocarcinoma	1 (0.2)	1	548.9	0.2	0		358.3	0	0		85.8	0
Prostate cancer	1 (0.2)	1	549.1	0.2	0		358.3	0	0		85.8	0
Adenocarcinoma	0		549.2	0	0		358.3	0	1 (1.0)	1	85.8	1.2
Endometrial cancer stage 0	0		549.2	0	1 (0.2)	1	358.3	0.3	0		85.8	0
Papillary thyroid cancer	0		549.2	0	1 (0.2)	1	358.0	0.3	0		85.8	0

Includes events with a start date between first dose and the Week 52 visit date.
Includes data from IM011054 and IM011055.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
AE = Adverse Event (Treatment Emergent).
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Source: Table 14.3.2.4.1.26

Table 69. Malignancy Events Summary: Cumulative DEUC Period (Week 0- Safety Data Cutoff) (Phase 3 Safety Pool-Treated Population)

	DEUC 6 mg N = 1312			
System Organ Class Preferred Term	n (%)	m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	8 (0.6)	8	1525.6	0.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (0.6)	8	1525.6	0.5
Prostate cancer	2 (0.2)	2	1527.0	0.1
Basal cell carcinoma	1 (0.1)	1	1526.6	0.1
Endometrial cancer stage 0	1 (0.1)	1	1527.2	0.1
Glioblastoma	1 (0.1)	1	1527.2	0.1
Lung adenocarcinoma	1 (0.1)	1	1526.8	0.1
Papillary thyroid cancer	1 (0.1)	1	1526.8	0.1
Transitional cell carcinoma	1 (0.1)	1	1527.1	0.1

Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
Includes data from IM011054 and IM011055. (Safety Cutoff Date = 10-10-2024, 07-11-2024).
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
AE = Adverse Event (Treatment Emergent).
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Source: Table 14.3.2.4.1.27

Cardiovascular events (MACE, extended MACE, arterial thromboembolic events, venous thromboembolic events, other CV events)

PsA is a chronic disorder which may result in health consequences beyond joint function, such as CV disease associated with increased morbidity and mortality. The Adjudication Committee defined MACE as non-fatal myocardial infarction, non-fatal stroke, or CV death; extended MACE also included unstable angina requiring hospitalisation.

The Table 70, Table 71, and Table 72 present AEs related to cardiovascular toxicity that occurred during the Phase 3 safety pool-52 -week period (week 0-52) and the cumulative DEUC period

○ *MACE and extended MACE*

Table 70. Adjudicated Cardiovascular AE Summary: Placebo-Controlled Period (Week 0-16) (All PsA Safety Pool-Treated Population)

Adjudicated Cardiovascular Category Adjudicated Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH A MACE	0	211.5	0	1 (0.1) 2	209.9	0.5	0	29.1	0
Non-Fatal Cardiovascular-Related Event	0	211.5	0	1 (0.1) 2	209.9	0.5	0	29.1	0
Myocardial infarction, ST Elevation	0	211.5	0	1 (0.1) 2	209.9	0.5	0	29.1	0
TOTAL SUBJECTS WITH AN EXTENDED MACE	0	211.5	0	1 (0.1) 2	209.9	0.5	0	29.1	0
Non-Fatal Cardiovascular-Related Event	0	211.5	0	1 (0.1) 2	209.9	0.5	0	29.1	0
Myocardial infarction, ST Elevation	0	211.5	0	1 (0.1) 2	209.9	0.5	0	29.1	0
TOTAL SUBJECTS WITH OTHER CV EVENTS	18 (2.5) 19	208.9	8.6	18 (2.5) 21	206.7	8.7	8 (7.6) 9	27.9	28.6
Non-Fatal, Non-Cardiovascular Event	18 (2.5) 19	208.9	8.6	17 (2.4) 17	207.1	8.2	8 (7.6) 9	27.9	28.6
Arrythmia Not Associated with Ischemia	0	211.5	0	1 (0.1) 2	209.6	0.5	0	29.1	0
Other Cardiovascular Event	0	211.5	0	1 (0.1) 1	209.7	0.5	0	29.1	0
Transient Ischemic Attack	0	211.5	0	1 (0.1) 1	209.6	0.5	0	29.1	0

Includes events with a start date between first dose and the Week 16 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
MACE = Major Adverse Cardiovascular Event; CV = Cardiovascular; Extended MACE = MACE + unstable angina requiring hospitalization;
Includes data from IM011054, IM011055 and IM011084 Part A.
A unique event may be counted more than once (m) if adjudicated into multiple categories.
Source: Table 14.3.2.4.2.1

○ *Arterial Thromboembolic Events (ATE) and venous thromboembolic events (VTE)*

No adjudicated ATEs were reported during the Placebo-Controlled Period, the- 52-Week Period, and the Cumulative DEUC Period. Likewise, there were no adjudicated VTEs in the DEUC group. Two patients who were receiving placebo experienced events with the PT of deep vein thrombosis that were confirmed as deep vein thrombosis by the Adjudication Committee.

○ *MACE and extended MACE*

Table 71. Adjudicated Cardiovascular AE Summary: 52-Week Period (Week 0-52) (Phase 3 Safety Pool-Treated Population)

Adjudicated Cardiovascular Category Adjudicated Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH A MACE	2 (0.3) 2	548.9	0.4	2 (0.3) 2	357.8	0.6	1 (1.0) 1	85.2	1.2
Non-Fatal Cardiovascular-Related Event	2 (0.3) 2	548.9	0.4	2 (0.3) 2	357.8	0.6	1 (1.0) 1	85.2	1.2
Stroke Hemorrhagic	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Stroke Ischemic	1 (0.2) 1	548.9	0.2	1 (0.2) 1	358.3	0.3	0	85.8	0
Myocardial infarction, Non-ST Elevation	0	549.2	0	1 (0.2) 1	357.8	0.3	1 (1.0) 1	85.2	1.2
TOTAL SUBJECTS WITH AN EXTENDED MACE	2 (0.3) 2	548.9	0.4	2 (0.3) 2	357.8	0.6	1 (1.0) 1	85.2	1.2
Non-Fatal Cardiovascular-Related Event	2 (0.3) 2	548.9	0.4	2 (0.3) 2	357.8	0.6	1 (1.0) 1	85.2	1.2
Stroke Hemorrhagic	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Stroke Ischemic	1 (0.2) 1	548.9	0.2	1 (0.2) 1	358.3	0.3	0	85.8	0
Myocardial infarction, Non-ST Elevation	0	549.2	0	1 (0.2) 1	357.8	0.3	1 (1.0) 1	85.2	1.2
TOTAL SUBJECTS WITH OTHER CV EVENTS	42 (6.5) 49	528.6	7.9	23 (3.8) 26	347.0	6.6	8 (7.6) 9	80.8	9.9
Non-Fatal, Non-Cardiovascular Event	42 (6.5) 48	528.6	7.9	20 (3.3) 23	348.3	5.7	8 (7.6) 9	80.8	9.9
Arrythmia Not Associated with Ischemia	1 (0.2) 1	548.9	0.2	1 (0.2) 1	357.9	0.3	0	85.8	0
Insufficient Information to Adjudicate	0	549.2	0	2 (0.3) 2	357.3	0.6	0	85.8	0

Includes events with a start date between first dose and the Week 52 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
MACE = Major Adverse Cardiovascular Event; CV = Cardiovascular; Extended MACE = MACE + unstable angina requiring hospitalization; Includes data from IM011054 and IM011055.
A unique event may be counted more than once (m) if adjudicated into multiple categories.
Source: Table 14.3.2.4.2.2

Table 72. Adjudicated Cardiovascular AE Summary: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool-Treated Population)

Adjudicated Cardiovascular Category Adjudicated Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH A MACE	8 (0.6) 8	1521.6	0.5
Non-Fatal Cardiovascular-Related Event	7 (0.5) 7	1521.6	0.5
Stroke Ischemic	3 (0.2) 3	1524.7	0.2
Myocardial infarction, Non-ST Elevation	2 (0.2) 2	1525.7	0.1
Myocardial infarction, ST Elevation	1 (0.1) 1	1525.6	0.1
Stroke Hemorrhagic	1 (0.1) 1	1527.2	0.1
Fatal Event, Death	1 (0.1) 1	1527.2	0.1
Sudden Cardiac Death	1 (0.1) 1	1527.2	0.1
TOTAL SUBJECTS WITH AN EXTENDED MACE	8 (0.6) 8	1521.6	0.5
Non-Fatal Cardiovascular-Related Event	7 (0.5) 7	1521.6	0.5
Stroke Ischemic	3 (0.2) 3	1524.7	0.2
Myocardial infarction, Non-ST Elevation	2 (0.2) 2	1525.7	0.1
Myocardial infarction, ST Elevation	1 (0.1) 1	1525.6	0.1
Stroke Hemorrhagic	1 (0.1) 1	1527.2	0.1
Fatal Event, Death	1 (0.1) 1	1527.2	0.1
Sudden Cardiac Death	1 (0.1) 1	1527.2	0.1

Adjudicated Cardiovascular Category Adjudicated Term	DEUC 6 mq N = 1312 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH OTHER CV EVENTS	79 (6.0) 98	1445.7	5.5
Non-Fatal, Non-Cardiovascular Event	76 (5.8) 91	1450.1	5.2
Arrythmia Not Associated with Ischemia	3 (0.2) 3	1524.8	0.2
Insufficient Information to Adjudicate	2 (0.2) 2	1523.3	0.1
Coronary Revascularization	1 (0.1) 1	1525.9	0.1
Heart Failure	1 (0.1) 1	1526.4	0.1

Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
MACE = Major Adverse Cardiovascular Event; CV = Cardiovascular; Extended MACE = MACE + unstable angina requiring hospitalization;
Includes data from IM011054 and IM011055. (Safety Cutoff Date = 10-10-2024, 07-11-2024).
A unique event may be counted more than once (m) if adjudicated into multiple categories.
Source: Table 14.3.2.4.2.3

Depression and suicidal ideation or behaviour (SIB)

Patients with chronic illnesses, including PsA, may be prone to depression and be at risk for suicide, due to the disease manifestations and symptoms. Depression is an ADR reported for APR. Based on the inclusion of APR in Study IM011055, events of depression and SIB were evaluated as AESIs.

No SIB events were reported in any analysis period [Placebo-Controlled Period], [52-Week Period], [Cumulative DEUC Period]). Additionally, no events in Study IM011055 were adjudicated as SIB by the SIB adjudication committee [Placebo-Controlled Period], [52-week Period]).

Overall, 15 cases of depression have been reported of which three pertain to cases identified during a more recent cut-off date.

Three cases were considered related and further described:

i/ First was a 40-year-old female. At Day 54 after DEUC initiation, the patient was diagnosed with non-serious moderate depression. The patient had a medical history of chronic depression which had worsened. The patient also experienced severe insomnia. The patient received treatment with escitalopram for depression and trazodone for insomnia. On Day 115, the study therapy was discontinued due to depression with the last dose received on Day 114. On Day 169, depression resolved.

ii/ Second was a 63-year-old female. On Day 2, the patient experienced mild non-serious diarrhoea (verbatim: diarrhoea, related to the study drug). No other action was taken. On an unknown date, the patient was diagnosed with moderate non-serious depression (verbatim: worsening depression, related to the study drug). No other action was taken. On Day 56, the study therapy was discontinued due to depression and persistent diarrhoea, with the last dose received on Day 55. On Day 57, diarrhoea resolved. On Day 63, depression resolved.

These two cases appear to be compelling but rather insufficient to conclude on any causal association with DEUC. As a matter of fact, in the first case, the patient medical history is a major limit and, in the second case, the event of diarrhoea and perhaps no effect yet of DEUC on PsA during this short exposure may have also contribute to the event of depression.

iii/The third case was a 57-year-old male at the time of enrolment. On an unknown day, the subject consulted primary care physician and was diagnosed with nonserious, moderate depression (related). The subject was treated with amitriptyline. The study therapy was discontinued due to depression, with the last dose taken on Day 229. This case was considered

related but the information was limited and could not allow an adequate appraisal of DEUC causality.

Laboratory findings

Haematology

Overall, there were no substantial differences in the incidence of haematology abnormalities observed versus placebo. Over time, some patients experienced abnormalities; these can be attributed to normal variability and considered not adverse given the low frequency of AEs reported for these laboratory parameters.

Hepatic biochemistry

During the placebo-controlled period, there were no clinically relevant mean changes from baseline in ALT, AST, ALP or bilirubin over time in all 3 treatment groups. With longer exposure on DEUC in the 52-Week Period and Cumulative DEUC Period, findings were consistent with the Placebo-Controlled Period.

During Placebo-Controlled Period, the incidence of worst toxicity values of CTCAE Grade 3 in hepatic parameters was low across treatment groups, with notably lower frequency in DEUC as compared to placebo. There were no Grade 4 events in any treatment group. With longer exposure on DEUC treatment in the 52-Week Period and Cumulative DEUC Period, the incidence of worst toxicity values of CTCAE Grade 3 for hepatic parameters remained low. Grade 4 events occurred infrequently in the DEUC-DEUC group, and none were reported in the PBO-DEUC or APR-APR groups. The majority of patients had Grade 0 hepatic parameters at baseline and remained within the normal range (Grade 0) postbaseline in all 3 treatment groups. No shifts in chemistry parameters of > 2 CTC grades occurred with DEUC, and they were infrequent in the other treatment groups.

Renal biochemistry

There were no clinically meaningful mean changes from baseline observed in creatinine and eGFR during the Placebo-Controlled Period in the DEUC group compared with the placebo. With longer exposure on DEUC through 52 weeks and beyond 52 weeks in the Cumulative DEUC Period, findings were consistent with the Placebo-Controlled Period.

Overtime, during the Placebo-controlled Period, there were no clinically meaningful increases from baseline in mean CPK values in the DEUC group compared with the PBO and APR groups. With longer exposure on DEUC in the 52-Week Period and Cumulative DEUC Period, findings with DEUC were consistent with the Placebo-controlled Period and no notable trends were observed.

Cholesterol

During the Placebo-controlled Period, there were no clinically relevant changes from baseline in mean values for total cholesterol, HDL, or LDL (fasting) in the DEUC group compared with patients in the placebo and APR groups. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, findings were generally consistent with the Placebo-controlled- Period and not progressive over time. During the Placebo-controlled Period, no Grade 3 events were reported in the DEUC or APR groups, and there was 1 event (high cholesterol) in the PBO group. There were no Grade 4 events in any treatment group. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, findings of cholesterol increase remained low (with exception of 1 Grade 3 event of high cholesterol in the DEUC-DEUC group during the 52-Week Period, and another in the Cumulative DEUC Period) and consistent with the Placebo-controlled Period.

During the Placebo-controlled Period, most patients had cholesterol levels of Grade 0 or 1 at baseline and almost all remained Grade 0 or 1 post baseline. No patients had a shift in cholesterol levels of > 2 CTC grades from baseline. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, cholesterol level findings were consistent with the Placebo-controlled Period. During the Placebo-controlled Period, AEs related to cholesterol increase (blood cholesterol increased and hypercholesterolaemia) occurred infrequently across treatment groups. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, AE findings (as EAIR) related to cholesterol increase were generally consistent with the Placebo-controlled Period. There were no SAEs or AEs related to cholesterol increase that led to treatment discontinuation across treatment periods.

Triglycerides

Laboratory Values Over Time: During the Placebo-controlled Period, there were no clinically meaningful increases from baseline in fasting triglyceride levels in patients in the DEUC group compared with patients in the placebo and APR groups. In the 52-Week Period and in the Cumulative DEUC Period, findings were generally consistent with the Placebo-controlled Period and indicating a small increase from baseline in patients receiving DEUC. With long-term treatment with DEUC in the Cumulative DEUC Period, the mean triglyceride levels trended towards baseline levels.

Worst Toxicity Grade by CTC Post-Baseline: During Placebo-controlled Period, high triglyceride (fasting) levels of ≥ Grade 3 occurred infrequently across treatment groups. With longer term exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, the incidence of toxicity Grade 3 events post baseline remained low, and a few additional patients had Grade 3 events of high triglycerides compared with the Placebo-controlled Period. Grade 4 events were reported infrequently with DEUC, there was 1 additional Grade 4 event in the Cumulative DEUC Period beyond Week 52.

Shifts from Baseline Grade to Worst Post Baseline Grade by CTC: During the Placebo-controlled Period, the majority of patients had Grade 0 or 1 triglyceride values at baseline and remained in that range post-baseline. The incidence of shifts of > 2 CTC grades was reported infrequently in the DEUC group (1 patient, 0.2% [Grade 0 to 3], and 1 patient, 0.2% [Grade 1 to 4]) and none were reported in the placebo and APR groups. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, findings were consistent with the Placebo-controlled Period, and no new trends were observed.

AEs related to lipid parameters, during the Placebo-controlled Period, AEs related to lipid parameters (that included blood triglycerides increased, hypertriglyceridemia, hyperlipidaemia, and dyslipidaemia) occurred infrequently across treatment groups. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, AE findings (as EAIR) were generally consistent with the Placebo-controlled Period. There were no SAEs or AEs related to lipid parameters that led to treatment discontinuation in any treatment period.

Serum immunoglobulins

During the Placebo-controlled Period, the only AE term related to immunoglobulins was blood immunoglobulin E increased reported in the PBO group. With longer exposure on DEUC in the 52-Week Period beyond Week 16, there were 2 AEs related to immunoglobulins (blood immunoglobulin A increased and blood immunoglobulin E increased both reported in the PBO-DEUC group). In the Cumulative DEUC Period beyond Week 52, there were no new AEs related to immunoglobulins. There were no SAEs or AEs related to immunoglobulins that led to treatment discontinuation in any analysis period.

Haemoglobin A1C

There were no clinically relevant changes from baseline in mean haemoglobin A1C levels in the Placebo-controlled Period, 52-Week Period, or Cumulative DEUC Period.

C-Reactive Protein (CRP)

C-reactive protein levels at baseline were similar across treatment groups during the Placebo-controlled Period. There was a trend towards a decrease in mean C-reactive protein levels across treatment groups through Week 16, and was higher in the DEUC and APR groups compared with the PBO group. With longer exposure on DEUC in the 52-Week Period, C reactive-protein levels continued to decrease with DEUC from baseline through Week 52 (DEUC-DEUC: -4.163 mg/L, and PBO-DEUC: -4.907 mg/L), and the reduction was higher compared with the APR-APR group (-2.965 mg/L). In the Cumulative DEUC Period, mean change in C-reactive protein levels with DEUC was consistent with the 52-Week Period. These results demonstrating a reduction in C-reactive protein levels are expected given the MOA of DEUC and reflect meaningful decreases in inflammation.

Urinalysis

There were no clinically relevant changes from baseline or cumulative trends noted for mean levels of urinalysis parameters (Specific Gravity and pH) across the Placebo-controlled Period, 52-Week Period and Cumulative DEUC Period.

Vital signs:

No clinically meaningful changes from baseline in vital signs or in markedly abnormal vital signs were observed in the Placebo-controlled Period, 52-Week Period, or Cumulative DEUC Period. AEs related to vital signs in the SOC of investigations (that included blood pressure increased, weight increased, and weight decreased) occurred infrequently across treatment groups. With longer exposure on DEUC in the 52-Week Period and in the Cumulative DEUC Period, AE findings (as EAIR) in vitals did not increase with DEUC compared with the Placebo-controlled Period. There were no SAEs or AEs related to vital signs that led to treatment discontinuation in any treatment period.

Electrocardiogram

The electrocardiogram evaluations were consistent with previously reported findings with DEUC 6 mg QD in PsO. No clinically relevant changes from baseline in mean values for PR, QRS, QTcB, or QTcF intervals were observed with DEUC treatment. The incidence of markedly abnormal ECG results was low and generally comparable across treatment groups with no notable trends in the Placebo-controlled Period, 52-Week Period, and Cumulative DEUC Period.

Safety in special populations

Intrinsic Factors

Age: In the All PsA Safety Pool, the majority of patients (around 64%) were in the age group of 40 to < 65 years, approximately 22% were aged < 40 years, around 12% were aged between 65 to < 75 years, and around 2% were aged ≥ 75 years. In the Placebo-Controlled Period, the incidence of AEs, SAEs, and AEs leading to treatment discontinuation did not reveal any clinically relevant concerns with DEUC treatment in any age group compared with placebo and APR. Across all age groups, the most common SOC was infections and infestations, and the most common AEs were generally similar across age groups. With longer exposure on DEUC during the 52-Week Period, the incidence (based on EAIR) of AEs, SAEs, and AEs leading to treatment discontinuation across the age subgroups were consistent with the Placebo-Controlled Period with no discernible trends.

Gender: In the All PsA Safety Pool, the ratio of males to females was almost equal (49.2% vs. 50.8%). In the Placebo-Controlled Period, the incidence of AEs was higher in females compared with males in all 3 treatment groups. The incidence of SAEs was low and comparatively higher in females versus males in all 3 treatment groups. The incidence of AEs leading to discontinuation was low and comparatively higher in females versus males in the DEUC and APR groups, while in the placebo group, the incidence was higher in males compared with females. With additional exposure to DEUC in the 52-Week Period, the incidence (based on EAIR) of AEs, SAEs, and AEs leading to treatment discontinuation across the sex subgroups were consistent with the Placebo-DEUC Period except that SAEs were higher in males than females in the DEUC-DEUC group.

Ethnic groups: In the All PsA Safety Pool, approximately 78% of patients were mainly white and 10.7% Asian. Therefore, comparisons between subgroups should be interpreted with caution due to the small sample size of subgroups of non-white races relative to the white subgroup. During the Placebo-DEUC Period, there was a higher incidence of AEs in the Asian subgroup compared with the white subgroup in the DEUC and placebo groups (Asian: 81.8%, 696.5/100 p-y [DEUC] and 64.4%, 375.6 [Placebo] vs White: 58.3%, 324.8/100 p-y [DEUC] and 48.8%, 238.5/100 p-y [Placebo]), and similar incidence in subgroups in the APR group (71.4%, 516.6/100 p-y [Asian] vs 72.3%, 462.5/100 p-y [White]). The incidence of AEs in the white subgroup was higher in the DEUC compared with the placebo group and lower than APR group (58.3%, 324.8/100 p-y [DEUC], 48.8%, 238.5/100 p-y [Placebo], and 72.3%, 462.5/100 p-y [APR]). The SAEs and AEs leading to treatment discontinuation mostly occurred in single patients across treatment groups with no discernible trends by race subgroups. With longer exposure on DEUC in the 52-Week Period, the incidence (based on EAIR) of AEs, SAEs, and AEs leading to treatment discontinuation across the race subgroups were consistent with the Placebo-Controlled Period with no discernible trends.

Weight: In the All PsA Safety Pool, there were more patients in the body weight category of < 90 kg versus≥ 90 kg category (63.2% vs 36.8%) and this difference was observed across treatment groups (DEUC: 62.6% and 37.4%; placebo: 63.9% and 36.1%; and APR: 62.9% and 37.1%). In the Placebo-Controlled Period, there were no differences observed in incidences of AEs across body weight subgroups. The incidence of SAEs and AEs leading to discontinuation was low, and similar across body weight subgroups. With longer exposure on DEUC through Week 52 in the 52-Week Period, the incidence (based on EAIR) of AEs, SAEs, and AEs leading to discontinuation between the body weight subgroups were consistent with the Placebo-Controlled Period with no discernible trends.

BMI: In the All PsA Safety Pool at baseline, the proportion of patients in the body weight categories was: 33.6% in the 25 to <30 kg/m^2, 26.9% in the 30 to <35 kg/m^2, 21.3% in the < 25 kg/m^2, and 18.1% in the ≥ 35 kg/m^2 category. In the Placebo-Controlled Period, the incidence of AEs, SAEs, and AEs leading to treatment discontinuation was not clinically meaningful with DEUC treatment in any BMI category. Similar findings were observed in the placebo and APR groups. With longer exposure on DEUC in the 52-Week Period, the incidence (based on EAIR) of AEs, SAEs, and AEs leading to treatment discontinuation across the BMI categories were consistent with the Placebo-Controlled Period.

Extrinsic factors

Prior TNF Inhibitor Use at Baseline: In the All PsA Safety Pool, 48.7% of patients were TNFi naive, and 7.8% were TNFi-experienced. Comparisons between subgroups should be interpreted with caution given the small sample size of TNFi-experienced participants. In the Placebo-Controlled Period, the incidence of AEs among patients who were TNFi naive was comparable with the TNFi-experienced across treatment groups. The incidence of SAEs and AEs leading to discontinuation

was low and occurred mostly in single patients across treatment groups and did not reveal any clinically relevant concerns with DEUC and TNFi use.

With longer exposure on DEUC in the 52-Week Period, based on EAIR, the incidence of AEs, SAEs and AEs leading to discontinuation by TNFi use were consistent with the Placebo-Controlled Period with no discernible trends.

In the Cumulative-DEUC Period, the overall EAIR (per 100 p-y) of SAEs was higher in patients who were TNFi naive compared to those with TNFi experienced (7.4 and 5.4, respectively).

Baseline Non-biologic DMARD Use: In the All PsA Safety Pool, the majority of patients reported use of non-biologic DMARD at baseline (66.1%), and 33.9% did not use non-biologic DMARDs. In the Placebo-Controlled Period, the incidence of AEs in the DEUC and placebo groups was comparable among patients who had non-biologic DMARD use compared to those without nonbiologic DMARD use; in the APR group, the incidence was higher in the subgroup with nonbiologic DMARD use compared to those without non-biologic DMARD use. The incidence of SAEs and AEs leading to discontinuation with DEUC was higher among patients without nonbiologic DMARD treatment use. With longer exposure on DEUC in the 52-Week Period, based on EAIR, the incidence of AEs, SAEs, and AEs leading to discontinuation between the subgroups were consistent with the Placebo-Controlled Period with no discernible trends.

In the Cumulative-DEUC Period, the EAIR (per 100 p-y) of SAEs was low and comparable in patients with non-biologic DMARD use to those without non-biologic DMARD use (7.5 and 6.0, respectively).

Baseline MTX Use: In the All PsA Safety Pool, 56.0% of patients reported use of MTX at baseline (vs 44.0% who did not use MTX). In the Placebo-Controlled Period, the incidence of AEs among patients who received MTX was comparable with those who did not receive MTX across treatment groups. The incidence of SAEs and AEs leading to treatment discontinuation was low and was higher compared to those who did not use MTX in the DEUC and placebo groups.

With longer exposure on DEUC through Week 52 in the 52-Week Period, based on EAIR, the incidence of AEs, SAEs, and AEs leading to discontinuation between the subgroups were consistent with the Placebo-Controlled Period with no discernible trends.

Baseline NSAID Use: In the All PsA Safety Pool, the majority patients reported use of NSAIDs at baseline (61.9% vs 38.1% who did not use NSAIDs). In the Placebo-Controlled Period, the incidence of AEs, SAEs, and AEs leading to treatment discontinuation among patients who received NSAIDs was comparable with those who did not receive NSAIDs in the DEUC and placebo groups. In the APR group, the incidence of AEs was higher among patients who did not receive NSAIDs.

With longer exposure on DEUC through Week 52, the differences in AEs, SAEs, and AEs leading to discontinuation between the subgroups in the 52-Week Period were consistent with the Placebo-Controlled Period with no discernible trends.

Baseline Glucocorticoid Use: In the All PsA Safety Pool, 18.1% of patients reported use of glucocorticoids at baseline (vs 81.9% who did not use glucocorticoids). In the Placebo-Controlled Period, the overall incidence of AEs was higher among patients who have received glucocorticoids compared to those who did not use glucocorticoids in the DEUC (443.6 vs 349.5/100p-y) and APR (936.5 vs 447.9/100 p-y) groups. In the placebo group, the incidence of AEs in the subgroups was comparable (243.0 vs 255.6/100 p-y). The incidence of SAEs was lower in patients with glucocorticoids use in the DEUC group (3.0 vs 6.2/100 p-y), and was higher in the placebo and APR groups (Placebo: 9.5 vs 4.8/100 p-y, and APR: 18.0 vs 12.9/100 p-y). The incidence of AEs leading to discontinuation in the subgroups was comparable in the DEUC (9.0 vs 8.5/100 p-y) and placebo

(4.7 vs 5.4/100 p-y) groups, and was higher in the APR group in patients with glucocorticoids use (55.5 vs 34.2/100 p-y). With longer exposure on DEUC in the 52-Week Period, the differences in AEs, SAEs, and AEs leading to discontinuation between the subgroups were consistent with the Placebo-Controlled Period with no discernible trends.

With long-term exposure to DEUC beyond Week 52 in the Cumulative DEUC Period, the EAIR (per 100 p-y) of SAEs in the subgroups with or without glucocorticoids use was low and was higher with glucocorticoids use compared with those without glucocorticoids use (9.6 and 6.5, respectively).

Duration of disease: In the All PsA Safety Pool, the overall median duration of disease was 4.02 years. In the Placebo-Controlled Period, the overall incidence of AEs was comparable among patients with disease duration of ≥ 4.02 years or < 4.02 years in all 3 treatment groups. In the DEUC and APR groups, SAE rates were higher among patients with disease duration of < 4.02 years whereas AEs leading to discontinuation rates were higher among patients with disease duration of ≥ 4.02 years.

With longer exposure on DEUC through Week 52, the differences in AEs, SAEs, AEs leading to discontinuation between the subgroups in the 52-Week Period were consistent with the Placebo-Controlled Period with no discernible trends. *Use in Pregnancy and Lactation:* There were no pregnancies reported for patients in the PsA studies of DEUC as of the safety data cutoff date. Pregnant and lactating women were excluded from the study population and throughout the clinical development program. In the PsA studies, female patients of reproductive potential were required to use a highly effective method of contraception.

Discontinuation due to adverse events

Table 73, Table 74 and Table 75 present AEs leading to discontinuation during the three periods:

Table 73. Adverse Events Leading to Discontinuation of Study Treatment Summary: Placebo-Controlled Period (Week 0-16) (All PsA Safety Pool - Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 714 n (%) m	P-Y	IR/ 100 P-Y	PBO N = 710 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	18 (2.5) 19	211.0	8.5	11 (1.5) 12	209.8	5.2	11 (10.5) 19	28.8	38.2
Skin and subcutaneous tissue disorders	5 (0.7) 5	211.3	2.4	4 (0.6) 4	209.9	1.9	0	29.1	0
Rash	2 (0.3) 2	211.4	0.9	0	209.9	0	0	29.1	0
Acne	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Rash vesicular	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Rosacea	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Eczema	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Psoriasis	0	211.5	0	2 (0.3) 2	209.9	1.0	0	29.1	0
Urticaria	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Infections and infestations	3 (0.4) 3	211.5	1.4	1 (0.1) 1	209.9	0.5	2 (1.9) 2	29.1	6.9
Bronchitis	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Cellulitis	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Herpes zoster	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Diverticulitis intestinal perforated	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Osteomyelitis	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Soft tissue infection	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Immune system disorders	2 (0.3) 2	211.5	0.9	0	209.9	0	0	29.1	0
Drug hypersensitivity	2 (0.3) 2	211.5	0.9	0	209.9	0	0	29.1	0
Investigations	2 (0.3) 2	211.5	0.9	2 (0.3) 2	209.8	1.0	0	29.1	0
Glomerular filtration rate abnormal	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Glomerular filtration rate decreased	1 (0.1) 1	211.5	0.5	1 (0.1) 1	209.8	0.5	0	29.1	0
Transaminases increased	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Musculoskeletal and connective tissue disorders	2 (0.3) 2	211.4	0.9	0	209.9	0	0	29.1	0
Psoriatic arthropathy	2 (0.3) 2	211.4	0.9	0	209.9	0	0	29.1	0
Blood and lymphatic system disorders	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Eosinophilia	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Gastrointestinal disorders	1 (0.1) 1	211.5	0.5	3 (0.4) 3	209.9	1.4	8 (7.6) 10	28.8	27.7
Abdominal pain upper	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Abdominal discomfort	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Abdominal distension	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Abdominal pain	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Diarrhoea	0	211.5	0	1 (0.1) 1	209.9	0.5	2 (1.9) 2	29.0	6.9
Dyspepsia	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Gastrointestinal disorder	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Lip oedema	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Nausea	0	211.5	0	0	209.9	0	3 (2.9) 3	29.0	10.3
Vomiting	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Nervous system disorders	1 (0.1) 1	211.5	0.5	1 (0.1) 1	209.9	0.5	3 (2.9) 3	29.0	10.3
Dizziness	1 (0.1) 1	211.5	0.5	0	209.9	0	2 (1.9) 2	29.0	6.9
Headache	0	211.5	0	1 (0.1) 1	209.9	0.5	1 (1.0) 1	29.1	3.4
Psychiatric disorders	1 (0.1) 1	211.3	0.5	0	209.9	0	1 (1.0) 1	29.0	3.5
Depression	1 (0.1) 1	211.3	0.5	0	209.9	0	1 (1.0) 1	29.0	3.5
Renal and urinary disorders	1 (0.1) 1	211.5	0.5	0	209.9	0	1 (1.0) 1	29.1	3.4
Renal impairment	1 (0.1) 1	211.5	0.5	0	209.9	0	0	29.1	0
Urinary bladder polyp	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	211.5	0	0	209.9	0	1 (1.0) 2	29.1	3.4
Adenocarcinoma	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Colorectal adenoma	0	211.5	0	0	209.9	0	1 (1.0) 1	29.1	3.4
Vascular disorders	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0
Deep vein thrombosis	0	211.5	0	1 (0.1) 1	209.9	0.5	0	29.1	0

Includes events with a start date between first dose and the Week 16 visit date.
n = number of subjects; m = number of events; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time in days for the selected AE under each treatment.
MedDRA: 27.1
Includes data from IM011054, IM011055 and IM011084 Part A.
Source: Table 14.3.2.3.1

Table 74. Adverse Events Leading to Discontinuation of Study Treatment Summary: 52-Week Period (Week 0- 52) (Phase 3 Safety Pool - Treated Population)

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	29 (4.5) 30	548.0	5.3	16 (2.7) 17	357.3	4.5	13 (12.4) 21	85.5	15.2
Skin and subcutaneous tissue disorders	5 (0.8) 5	549.1	0.9	3 (0.5) 3	358.2	0.8	0	85.8	0
Acne	2 (0.3) 2	549.2	0.4	0	358.3	0	0	85.8	0
Rash	1 (0.2) 1	549.2	0.2	1 (0.2) 1	358.2	0.3	0	85.8	0
Rash vesicular	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Urticaria	1 (0.2) 1	549.2	0.2	1 (0.2) 1	358.2	0.3	0	85.8	0
Dermatitis allergic	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Infections and infestations	4 (0.6) 4	549.2	0.7	3 (0.5) 3	358.3	0.8	2 (1.9) 2	85.8	2.3
Bronchitis	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Cellulitis	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Herpes zoster	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Rash pustular	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Diverticulitis intestinal perforated	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Oral herpes	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Osteomyelitis	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Pneumonia	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Tonsillitis bacterial	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.6) 4	548.7	0.7	1 (0.2) 1	358.0	0.3	1 (1.0) 2	85.8	1.2
Glioblastoma	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Leiomyoma	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Lung adenocarcinoma	1 (0.2) 1	548.9	0.2	0	358.3	0	0	85.8	0
Prostate cancer	1 (0.2) 1	549.1	0.2	0	358.3	0	0	85.8	0
Adenocarcinoma	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Colorectal adenoma	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Papillary thyroid cancer	0	549.2	0	1 (0.2) 1	358.0	0.3	0	85.8	0
Investigations	3 (0.5) 3	549.2	0.5	2 (0.3) 2	358.2	0.6	0	85.8	0
Glomerular filtration rate decreased	2 (0.3) 2	549.2	0.4	0	358.3	0	0	85.8	0
Glomerular filtration rate abnormal	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Aspartate aminotransferase increased	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0
Hepatic enzyme increased	0	549.2	0	1 (0.2) 1	358.3	0.3	0	85.8	0

System Organ Class Preferred Term	DEUC 6 mg-DEUC 6 mg N = 644 n (%) m	P-Y	IR/ 100 P-Y	PBO-DEUC 6 mg N = 598 n (%) m	P-Y	IR/ 100 P-Y	APR 30 mg-APR 30 mg N = 105 n (%) m	P-Y	IR/ 100 P-Y
Musculoskeletal and connective tissue disorders	3 (0.5) 3	548.8	0.5	2 (0.3) 2	358.2	0.6	1 (1.0) 1	85.8	1.2
Psoriatic arthropathy	3 (0.5) 3	548.8	0.5	2 (0.3) 2	358.2	0.6	1 (1.0) 1	85.8	1.2
Gastrointestinal disorders	2 (0.3) 2	549.2	0.4	1 (0.2) 1	358.2	0.3	9 (8.6) 11	85.5	10.5
Abdominal pain upper	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Gastrointestinal perforation	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Abdominal discomfort	0	549.2	0	1 (0.2) 1	358.2	0.3	1 (1.0) 1	85.8	1.2
Abdominal distension	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Diarrhoea	0	549.2	0	0	358.3	0	2 (1.9) 2	85.7	2.3
Dyspepsia	0	549.2	0	0	358.3	0	2 (1.9) 2	85.8	2.3
Gastrointestinal disorder	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Nausea	0	549.2	0	0	358.3	0	3 (2.9) 3	85.7	3.5
Vomiting	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2
Immune system disorders	2 (0.3) 2	549.2	0.4	1 (0.2) 1	358.2	0.3	0	85.8	0
Drug hypersensitivity	2 (0.3) 2	549.2	0.4	1 (0.2) 1	358.2	0.3	0	85.8	0
Nervous system disorders	2 (0.3) 2	549.2	0.4	2 (0.3) 3	358.1	0.6	3 (2.9) 3	85.7	3.5
Cerebral haemorrhage	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Dizziness	1 (0.2) 1	549.2	0.2	1 (0.2) 1	358.3	0.3	2 (1.9) 2	85.8	2.3
Headache	0	549.2	0	1 (0.2) 1	358.3	0.3	1 (1.0) 1	85.8	1.2
Nerve compression	0	549.2	0	1 (0.2) 1	358.1	0.3	0	85.8	0
Psychiatric disorders	2 (0.3) 2	549.1	0.4	1 (0.2) 1	358.1	0.3	1 (1.0) 1	85.7	1.2
Depression	1 (0.2) 1	549.1	0.2	1 (0.2) 1	358.1	0.3	1 (1.0) 1	85.7	1.2
Panic attack	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Blood and lymphatic system disorders	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Eosinophilia	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Injury, poisoning and procedural complications	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Spinal compression fracture	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Renal and urinary disorders	1 (0.2) 1	549.2	0.2	0	358.3	0	1 (1.0) 1	85.8	1.2
Renal impairment	1 (0.2) 1	549.2	0.2	0	358.3	0	0	85.8	0
Urinary bladder polyp	0	549.2	0	0	358.3	0	1 (1.0) 1	85.8	1.2

Table 75. Adverse Events Leading to Discontinuation of Study Treatment Summary: Cumulative DEUC Period (Week 0-Safety Data Cutoff) (Phase 3 Safety Pool - Treated Population)

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	62 (4.7) 66	1523.7	4.1
Infections and infestations	11 (0.8) 11	1527.2	0.7
Herpes zoster	2 (0.2) 2	1527.2	0.1
Bronchitis	1 (0.1) 1	1527.2	0.1
Cellulitis	1 (0.1) 1	1527.2	0.1
Intervertebral discitis	1 (0.1) 1	1527.2	0.1
Latent tuberculosis	1 (0.1) 1	1527.2	0.1
Oral herpes	1 (0.1) 1	1527.2	0.1
Osteomyelitis	1 (0.1) 1	1527.2	0.1
Pneumonia	1 (0.1) 1	1527.2	0.1
Rash pustular	1 (0.1) 1	1527.2	0.1
Tonsillitis bacterial	1 (0.1) 1	1527.2	0.1
Skin and subcutaneous tissue disorders	10 (0.8) 10	1526.8	0.7
Rash	3 (0.2) 3	1526.9	0.2
Urticaria	3 (0.2) 3	1527.2	0.2
Acne	2 (0.2) 2	1527.1	0.1
Dermatitis allergic	1 (0.1) 1	1527.2	0.1
Rash vesicular	1 (0.1) 1	1527.2	0.1
Musculoskeletal and connective tissue disorders	8 (0.6) 8	1526.2	0.5
Psoriatic arthropathy	6 (0.5) 6	1526.4	0.4
Arthritis	1 (0.1) 1	1527.0	0.1
Tenosynovitis	1 (0.1) 1	1527.1	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.5) 8	1526.2	0.5
Prostate cancer	2 (0.2) 2	1527.0	0.1
Glioblastoma	1 (0.1) 1	1527.2	0.1
Leiomyoma	1 (0.1) 1	1527.1	0.1
Lung adenocarcinoma	1 (0.1) 1	1526.8	0.1

System Organ Class Preferred Term	DEUC 6 mg N = 1312 n (%) m	P-Y	IR/ 100 P-Y
Papillary thyroid cancer	1 (0.1) 1	1526.8	0.1
Renal perivascular epithelioid cell tumour	1 (0.1) 2	1527.1	0.1
Investigations	6 (0.5) 6	1527.0	0.4
Glomerular filtration rate decreased	2 (0.2) 2	1527.2	0.1
Aspartate aminotransferase increased	1 (0.1) 1	1527.2	0.1
Glomerular filtration rate abnormal	1 (0.1) 1	1527.2	0.1
Hepatic enzyme increased	1 (0.1) 1	1527.2	0.1
Hepatitis B DNA assay positive	1 (0.1) 1	1527.1	0.1
Nervous system disorders	6 (0.5) 7	1527.0	0.4
Dizziness	2 (0.2) 2	1527.2	0.1
Cerebral haemorrhage	1 (0.1) 1	1527.2	0.1
Cerebral infarction	1 (0.1) 1	1527.2	0.1
Guillain-Barre syndrome	1 (0.1) 1	1527.2	0.1
Headache	1 (0.1) 1	1527.2	0.1
Nerve compression	1 (0.1) 1	1527.0	0.1
Gastrointestinal disorders	4 (0.3) 4	1526.9	0.3
Abdominal discomfort	1 (0.1) 1	1527.2	0.1
Abdominal pain upper	1 (0.1) 1	1527.2	0.1
Gastrointestinal perforation	1 (0.1) 1	1527.2	0.1
Oral mucosal blistering	1 (0.1) 1	1526.9	0.1
Immune system disorders	3 (0.2) 3	1527.1	0.2
Drug hypersensitivity	3 (0.2) 3	1527.1	0.2
Psychiatric disorders	3 (0.2) 3	1526.8	0.2
Depression	2 (0.2) 2	1526.8	0.1
Panic attack	1 (0.1) 1	1527.2	0.1
Injury, poisoning and procedural complications	2 (0.2) 2	1527.2	0.1
Incision site haemorrhage	1 (0.1) 1	1527.2	0.1
Spinal compression fracture	1 (0.1) 1	1527.2	0.1
Blood and lymphatic system disorders	1 (0.1) 1	1527.2	0.1
Eosinophilia	1 (0.1) 1	1527.2	0.1
Cardiac disorders	1 (0.1) 1	1527.2	0.1
Acute myocardial infarction	1 (0.1) 1	1527.2	0.1
General disorders and administration site conditions	1 (0.1) 1	1527.2	0.1
Sudden death	1 (0.1) 1	1527.2	0.1
Renal and urinary disorders	1 (0.1) 1	1527.2	0.1
Renal impairment	1 (0.1) 1	1527.2	0.1

Post marketing experience

DEUC is authorised in 54 countries worldwide. No new safety concerns or safety signals have been identified by the MAH based on the review of available post-marketing data for DEUC to date.

2.5.1. Discussion on clinical safety

The safety profile of DEUC in PsA patients is based on safety outcomes from the two phase 3 studies, IM011054 and IM011055, and the part A of the phase 2 study IM011084, pooled to the "All PsA Safety Pool-placebo- controlled period (week 0-16)". The safety outcomes from the 2 phase 3 studies, IM011054 and IM011055, were also pooled with two periods: a phase 3 safety pool-52-week period (week 0-52), and cumulative safety data from week 0-52 and including the ongoing open-label extension (OLE) safety outcomes (Cumulative DEUC period) up the data cut-off (IM011054 data cutoff: 10-Oct-2024; IM011055 data cutoff: 07-Nov-2024; IM011084 Part A data cutoff:02-Jul-2020). These safety pools are endorsed.

From the phase 3 safety pools, the median duration of exposure to DEUC in the cumulative DEUC period was 372 days. A total of 1312 patients received at least 1 dose of DEUC, out of them 82.9% and 33.8% received DEUC continuously for at least 16 and 52 weeks, respectively, and their

cumulative exposure with DEUC was 1527.2 P-Y. The size of the safety database was considered acceptable to the CHMP.

Although all patients received at least one dose of DEUC at week 16, continuous long-term exposure appears somewhat limited with one-third of patients who had received continuously DEUC after one year of treatment. Therefore, at the CHMP request, the study IM011194 will be amended to include PsA patients and follow the long-term safety in this population. The MAH committed to submit an updated protocol within 3 months following the approval of the current procedure, which is reassuring.

Common TEAES

▪ From All PsA safety pool-placebo-controlled period, the most frequently reported AEs with a higher incidence in the DEUC group compared with placebo group, belong to the SOC "Infections and infestations", "Gastrointestinal disorders", "Skin and subcutaneous tissue disorders", and "Nervous system disorders". Similar incidence rates were observed in the SOC "Musculoskeletal and tissue disorders" between the DEUC group and the PBO group. In comparison to apremilast, a higher incidence of skin and subcutaneous tissue disorders was reported in DEUC group, and a comparable incidence of infections and infestations.

▪ From the phase 3 safety pool-52-week period, with longer exposure with DEUC, the most frequently reported AEs with a higher incidence in [DEUC-DEUC] group compared with [PBO-DEUC] group, belong to the SOC: "Infections and infestations "Gastrointestinal disorders".

▪ From the phase 3 safety pool-Cumulative DEUC period, with long-term exposure to DEUC beyond week 52, the most frequently reported AEs by SOC in the Cumulative DEUC Period were: "Infections and infestations", "Gastrointestinal disorders", and "Skin and subcutaneous disorders", "Musculoskeletal and connective tissue disorders", "Metabolism and nutrition disorders" and "Investigations". The most frequently reported AEs by PT in the Cumulative DEUC Period were upper respiratory tract infection and nasopharyngitis.

The observed AEs were predominantly mild or moderate in severity. With longer exposure to DEUC, there was no evidence of increased incidence in severe AEs.

Treatment related AES (TRAEs)

▪ In the All PsA safety pool-placebo-controlled period, the Phase 3 safety pool cumulative DEUC period, and the phase 3 safety-pool-52-week period, the most frequently reported treatment-related AEs by SOC in all treatment groups were "Infections and infestations", "Skin and subcutaneous tissue disorders", and "Gastrointestinal disorders".

Overall, the assessment of treatment-related adverse events appears consistent with DEUC safety profile in PsO patient and with the current list of adverse drug reactions displayed under the section 4.8 of Sotyktu SmPC and no update was necessary.

Serious AEs and deaths

▪ *All PsA safety pool-placebo-controlled period:* The incidence of serious AEs was similar between DEUC and placebo group; the incidence of treatment-related SAEs was lower in the DEUC group. The main SOC remains "Infection and infestations".

▪ *Phase 3 safety pool-52-week period:* Across treatment groups in the 52-week period, the incidence of SAEs was lower in the DEUC-DEUC group than in the PBO-DEUC groups. Consistent with the All PsA safety pool-placebo-controlled period, the EAIRs of most frequently reported SAEs, including treatment-related SAEs were in the SOC of "Infections and infestations".

▪ *Cumulative DEUC period-phase 3 safety pool:* The EAIR of SAEs in the Cumulative DEUC Period remained is consistent with the Placebo-Controlled Period. As previously, the most frequently reported SAEs were in the SOC "Infections and infestations"

Adverse events of special interests (AESIs)

Rash papular

In the Placebo-controlled Period of the All PsA Safety Pool, the incidence of rash papular was 0.3% in the DEUC group; no events were reported in either the PBO or APR groups. During the Cumulative DEUC Period 6 events were reported, and one was assessed as related. Across the pooled DEUC clinical trials, 20 events were reported. A total of 45 events were reported in post-marketing. Although the incidence of rash papular has been low across the DEUC clinical program and in marketing experience, rash papular is part of the medical concept of Acneiform Rash, which is an adverse reaction for DEUC in section 4.8 of the approved SmPC. Therefore, the term "rash papular" was added to the footnote that lists the PTs that comprise Acneiform Rash in Table 1 of the SmPC.

Infections and infestations

In all PsA Safety Pool - Placebo-Controlled Period, the incidence of AEs in the SOC of infections and infestations was higher in the DEUC group compared with placebo was consistent with the apremilast group All observed events, except bronchitis (further discussed below), are already listed as ADRs in SmPC section 4.8. Five adverse events of pharyngotonsillitis were reported during the placebo- controlled period in DEUC group and none in placebo and APR groups, and seven other cases during the 52-week period in DEUC-DEUC group, 6 in placebo and none in APR-APR group. Most of them were related to DEUC. The MAH proposed to include pharyngotonsillitis under the PT upper respiratory infections in section 4.8 of the SmPC, this was endorsed by the CHMP.

Similar incidences of infections were reported in Phase 3 Safety Pool in 52-Week Period as well as in Cumulative DEUC Period. SAEs occurred in single subjects, except for pneumonia and appendicitis. 4 events of pneumonia were reported in placebo-controlled period, 7 events in DEUC-DEUC group and 5 events in PBO-DEUC group during 52-week period (almost all events were assessed as serious, and 2 in placebo-controlled period as related). During the Cumulative DEUC Period, 37 events of pneumonia were reported. Of those, 15 were assessed as related. Across the pooled clinical trials for DEUC, 111 events in 91 subjects were reported. In post-marketing 83 events were reported. The MAH stated that cases from clinical studies were confounded with known risk factors such as respiratory comorbidities, age over 65 years, heart or kidney disease. However, submitted cumulative review and analysis of all PT pneumonia cases have revealed few cases without concomitant risk factors, in younger patient populations, with positive dechallenge, including at least 4 cases with positive rechallenge. Therefore, pneumonia was added in section 4.8 of the SmPC with a frequency uncommon.

Bronchitis

In the Placebo-controlled Period of the All PsA Safety Pool, the incidence of bronchitis was 1.3% in the DEUC group, 0.7% in the PBO group, and 2.9% in the APR group. During the Cumulative DEUC Period, 89 events of bronchitis were reported. Of those, 28 were assessed as related. In the pooled DEUC clinical trials across doses and subject populations, 190 subjects experienced 221 AEs of bronchitis. In post-marketing, 37 cases were reported.

Therefore, taking into account that infections are known DEUC risk, 28 bronchitis cases assessed as related in clinical studies, as well as cases without concomitant risk factors and with positive

dechallenge/ rechallenge, the MAH included bronchitis in section 4.8 of the SmPC with a frequency uncommon.

Herpes Simplex

During the Placebo-Controlled Period, the overall incidence of herpes simplex events was higher in DEUC group compared with PBO group and similar to the apremilast group. Of the 9 adjudicated events in the DEUC group, 6 events were reported as oral herpes, 2 events were reported as herpes simplex, and 1 event was reported as herpes ophthalmic. In the 52-Week Period, the overall EAIR of herpes simplex events was 4.3/100 P-Y in the DEUC-DEUC group, 3.1/100 P-Y in the PBO-DEUC group and 4.8/100 P-Y in the APR-APR group. 1 subject in the PBO-DEUC group had 2 events of herpes ophthalmic, both adjudicated as herpes simplex. The MAH proposed to include, under Herpes simplex infections, the term herpes ophthalmic. This was endorsed by the CHMP.

Malignancies

Overall, there were 8 malignancies reported with DEUC. There were no cases of lymphoma or other hematologic malignancies. None of the events were fatal. In addition to PsA, several of the patients had risk factors for malignancies including smoking history and elderly age. The malignancies were assessed as not related to study drug by the investigator except one event of transitional cell carcinoma which was assessed as related.

All patients had confounding factors (i.e. comorbidities, medical history) or limited information that did not allow any causal association with DEUC to be established. Therefore, the assessment of these data did not reveal new safety issues related to the risk of malignancy with DEUC. Malignancies are classified as important potential risks in the safety concerns of the RMP. Additional pharmacovigilance activities are ongoing and planned to further characterise this risk with DEUC. At the CHMP request, the non-interventional study utilising medical records databases and PsO patient registries (IM011194) will be updated by the MAH to include PsA patients.

Cardiovascular events (MACE, extended MACE, arterial thromboembolic events (ATE), venous thromboembolic events (VTE), other CV events)

- MACE, extended MACE (also included unstable angina requiring hospitalisation)

Overall, patients with psoriasis have an increased risk of (MACE) regardless the treatments they received. There were 7 events adjudicated as MACE reported for DEUC. Based on the assessment of the corresponding narratives, it is not possible to establish a causal association with DEUC or to see whether DEUC had or not precipitated the AE of MACE or extended mace. Despite a compatible TTO (time-to-onset), all patients had confounding factors (i.e. associated comorbidities such as hypertension, dyslipidaemia, medical history, smoking). Nonetheless, although in Placebo-Controlled Period, there were no increased number of MACE in patients receiving deucravacitinib, a certain number of MACE events were reported with increased deucravacitinib exposure; particularly in patients who are current or past smokers, and in patients with a history of cardiovascular or cerebrovascular disease. The information included in the SmPC are considered sufficient.

- ATE and VTE

No adjudicated arterial thromboembolic events were reported in any period in the safety analysis.

One patient in the DEUC-DEUC group experienced an event of thrombosis (medical history of vascular insufficiency; current smoker) and 1 patient in the PBO-DEUC group experienced an event of superficial vein thrombosis (current smoker). Both events were adjudicated as deep vein thrombosis. Neither event was classified as serious.

Overall, consistent with the experience with DEUC in PsO, the MAH concluded that there is no evidence of an increased risk of MACE, extended MACE, or VTE associated with DEUC. There was 1 event adjudicated as MACE after the DBL in the DEUC arm during Week 0-16. The patients who experienced the events with DEUC had CV risk factors (e.g., elderly age, hypertension, hyperlipidaemia, obesity, current/former smoker, diabetes) and/or underlying CV disease (coronary artery disease, atherosclerosis). The MAH's conclusion is endorsed.

MACE and VTE (DVT and PE) are classified as important potential risks in the safety concerns of the RMP. Additional pharmacovigilance activities are ongoing and planned to further characterise this risk. At the CHMP's request, the non-interventional study utilising medical records databases and PsO patient registries (IM011194) will be updated by the MAH to include PsA patients.

Depression and suicidal ideation or behaviour

Overall, 15 cases of depression have been reported of which three pertain to cases identified during a more recent cut-off date.

The two cases were compelling but appeared rather insufficient to conclude on any causal association with DEUC. In the first case, the patient medical history was a major limit and, in the second case, the event of diarrhoea and perhaps no effect yet of DEUC on PsA during this short exposure may have also contribute to the event of depression.

The 10 remaining cases that occurred in patients under DEUC treatment had confounding factors (notably medical history) or limited information that did not allow any causal association with DEUC to be established.

No SIB events were reported in any of the three periods.

Overall, the available data, cannot allow a clear relationship to be established between the events of depression and DEUC treatment.

Discontinuation and dose modifications due to adverse events

During the placebo-controlled period, the overall incidence of AEs leading to treatment discontinuation was higher in the DEUC group than in placebo group. Most AEs leading to discontinuation occurred in single patients with DEUC except for rash, drug hypersensitivity, and psoriatic arthropathy, each of which occurred in 2 patients.

From the phase 3 safety pool-52-week period, the most frequently reported AEs leading to treatment discontinuation occurred in the SOC "Skin and subcutaneous tissue disorders". The other most frequently reported AEs that led to discontinuation with DEUC belong to the SOC "Infections and infestations".

The EAIR of AEs leading to treatment discontinuation was lower in the 52-Week Period compared with the Placebo-Controlled Period. In the Cumulative DEUC Period, the most frequently reported AEs leading to treatment discontinuation were in the SOCs "Skin and subcutaneous tissue disorders" and "Infections and infestations".

No new AEs related to DEUC leading to the drug discontinuation were identified.

Other safety findings

Hepatic enzymes increase was reported with DEUC during the three treatment periods. The study treatment was discontinued for 2 patients (aspartate aminotransferase increased and hepatic enzyme increased) under DEUC treatment beyond Week 16. Of note, no patients met Hy's Law criteria for drug-induced liver injury 2× ULN) in any of the three treatment periods. Seven patients experienced transaminase elevations (6 patients >× 10 and 1 patient ×20 ULN) post-baseline.

Overall, albeit a compatible time-to-onset, most of the patients had confounding factors or contained limited information that cannot allow any causal association with DEUC to be clearly established. Therefore, no update of section 4.4 was warranted. However, hepatic disorders remain a topic under close monitoring in the PSUR.

No trends or new signals emerged from the provided data related to creatinine phosphokinase elevation, serum immunoglobulin, haemoglobin A1C, CRP and urinanalysis.

No safety issues related to age, sex, race, BMI, ethnicity/region has been identified.

Post-marketing

According to the last PSUR a total of 5,977 subjects had been exposed to DEUC in clinical trials. Estimated post marketing exposure for the current reporting period was 8,590 P-Ys (worldwide) and 1,196 P-Ys (EU/EEA). Cumulative post-marketing exposure was 20,286 P-Ys (worldwide). During the reporting period, there were no new validated, ongoing, or closed signals as well as no new significant safety information was identified from PSUR data. Three topics are under close monitoring: rhabdomyolysis, hepatic disorders, depression and suicidal ideation. Following the assessment of data related to these risks, no new significant safety information was identified but a close monitoring of the above-mentioned three safety topics remains in place.

Overall, the safety profile of deucravacitinib was adequately characterised and the available data are considered sufficient to support its use in PsA.

2.5.2. Conclusions on clinical safety

The safety profile of deucravacitinib in PsA patients is consistent with its mechanism of action (MOA) and with the one raised in PsO patients. Safety database in psoriatic arthritis programme is adequate to establish a safety profile of deucravacitinib in this new indication.

Out of the 1312 patients who received at least one dose of DEUC, three-quarters (76.6%) experienced adverse events and in one-third (31%) of patients, the event was related to DEUC.

Due to its immunosuppressant properties related to its MOA, DEUC substantially increases risk of infections notably upper respiratory tract infections and skin disorders. These AEs were mainly mild to moderate in intensity. New safety issues related to infections (i.e. pneumonia and bronchitis) were identified and added in section 4.8 of the SmPC.

Although no clear relationship with DEUC can presently be established, the risk of malignancies, NMSC, MACE and other cardiovascular AEs were thoroughly analysed and discussed by the MAH. Notwithstanding, no new safety signals related to these risks were identified, they remain important potential risks in the safety concerns of the RMP. The non-interventional cohort study protocol (IM011194) will be updated to also follow-up these risks and long-term safety in PsA patients. This is agreed by the CHMP. The SmPC has been updated to reflect the most up-to-date safety profile of deucravacitinib.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable. The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	Serious infections Malignancies MACE VTE (DVT/PE)
Missing information	Use in pregnancy and lactation Long-term safety

Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194) Category 3 Ongoing	To evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting, including subgroup analyses for PsA.	Serious infections, Malignancies, MACE, VTE (DVT/PE), Long-term safety	1. Submission of study protocol 2. Progress updates 3. Interim report submission (1,000 p-y) 4. Final report submission	Q2 2023 PSUR Q4 2026/ Q4 2028 Q4 2032
Randomized, active-controlled clinical trial to evaluate the long-term safety of deucravacitinib in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy (IM0111130)[a] Category 3 Ongoing	To evaluate the long-term safety of deucravacitinib; the trial will be of sufficient size and duration to characterize safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.	Serious infections, Malignancies, MACE, VTE (DVT/PE), Long-term safety	1. Final protocol submission 2. Final report submission	Q4 2024 Dec 2029
Deucravacitinib pregnancy study: a retrospective observational study on the safety of deucravacitinib exposure in pregnant women and their offspring (IM011201)[a] Category 3 Ongoing	To assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to deucravacitinib during pregnancy compared to an unexposed control population.	Use in pregnancy	1. Final protocol submission 2. Progress updates 3. Final report submission	Q4 2024 PSUR Dec 2029

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
An open-label, multi-center extension study to characterize the long-term safety and efficacy of BMS-986165 in subjects with moderate-to-severe plaque psoriasis (IM011075)[b] Category 3 Ongoing	To characterize the safety and tolerability of long-term use of deucravacitinib in subjects with moderate-to-severe plaque psoriasis.	Serious infections, Malignancies, MACE, VTE (DVT/PE), Long-term safety	1. Study protocol finalization 2. Progress updates 3. Final report submission	05-Feb-2019 PSUR Dec-2026

[a] US FDA study commitment.

[b] Extension of the Phase 3 clinical studies IM011046 and IM011047.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	**Routine risk minimisation measures:** SmPC (Sections 4.4 and 4.8); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (IM011194) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
Malignancies	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (IM011194) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
MACE	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (IM011194) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
VTE (DVT/PE)	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (IM011194) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
	Routine risk minimisation measures:	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy and lactation	SmPC (Section 4.6); PL (Section 2)	**signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Pregnancy study (IM011201)
Long-term safety	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (IM011194) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the list of local representatives in the Package Leaflet has been revised.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

PsA is a heterogeneous, immune-mediated inflammatory disease arising from a complex interplay of genetic, immunologic, and environmental factors. It is estimated to affect 0.1–1% of the general population, with onset typically between 40–50 years of age, and carries a burden of disability, impaired quality of life, and psychosocial morbidity comparable to rheumatoid arthritis and axial spondyloarthritis. The pathogenesis involves dysregulation of both innate and adaptive immunity, with central roles for the IL-23/IL-17 axis and TNF-driven inflammation, leading to synovitis, enthesitis, dactylitis, and structural damage.

3.1.2. Available therapies and unmet medical need

The available therapies for PsA target both musculoskeletal and skin manifestations. Systemic therapy, include adjunctive therapies such as NSAIDs and low-dose glucocorticoids, conventional synthetic DMARDs (csDMARDs) such as MTX, biologic DMARDs (bDMARDs) such as TNF inhibitors, and inhibitors of the IL-17 pathway and IL-12/23 or IL-23 inhibitors, and targeted synthetic DMARDs (tsDMARDs) such as apremilast and JAK inhibitors.

Acknowledging the above-mentioned treatments, newer more effective and safer treatments or treatments with a different mechanism of action are desirable to improve quality of life of psoriatic arthritis patients.

3.1.3. Main clinical studies

The deucravacitinib clinical development program in PsA included one Phase 2 dose finding study and two pivotal Phase 3 studies in adults who had PsA with hsCRP ≥ 3 mg/L, ≥ 3 swollen joints and ≥ 3 tender joints. Participants in IM011054 (POETYK PsA-1) had inadequate response or intolerance to at least a csDMARD or an NSAIDs while participants in study IM011055 (POETYK PsA-2) had inadequate response or intolerance to at least a csDMARD or an NSAID or a TNF-inhibitor.

Study IM011054 was a multi-center, randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of deucravacitinib in participants with active psoriatic arthritis who are naïve to biologic disease-modifying anti-rheumatic drugs.

Study IM011055 was a multi-center, randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of deucravacitinib in participants with PsA who are naïve to biologic disease-modifying anti-rheumatic drugs or had previously received TNFα inhibitor treatment.

3.2. Favourable effects

The primary endpoint was met in both Phase 3 studies. Deucravacitinib demonstrated superiority over placebo, as evidenced by statistically significant differences in the proportions of subjects achieving an ACR20 response at Week 16. In Study IM011054, 54.2% of subjects in the deucravacitinib 6 mg arm achieved ACR20 compared with 34.1% in the placebo group, with an estimated difference across groups of 20% [95% CI: 12.7, 27.4]. In Study IM011055, the proportions of responder were respectively 54.2% versus 39.4% with an estimated difference across the groups of 14.8 [95% CI: 7.0, 22.5]. The supplemental and sensitivity analysis were overall consistent with the primary findings.

Significant improvements were observed in HAQ-DI and SF-36 PCS. For HAQ-DI, the adjusted mean change from baseline was –0.3850 for deucravacitinib versus –0.2163 for placebo in Study IM011054, corresponding to a difference of –0.1688 (95% CI: –0.4418, –0.3282). In Study IM011055, the adjusted mean difference versus placebo was –0.1126 (95% CI: –0.1814, –0.0438; p = 0.0013). For SF-36 PCS, in IM011054 the adjusted mean difference of 2.042 (95% CI: 0.980, 3.105) was observed. In Study IM011055, the adjusted mean difference was 2.344 (95% CI: 1.277, 3.411).

Statistically significantly higher proportion of subjects in the deucravacitinib arm achieved PASI 75 response at Week 16. In Study IM011054, 51.9% of deucravacitinib-treated subjects versus 7.1% of placebo-treated subjects achieved PASI 75 (difference: 44.1; 95% CI: 35.4, 52.7; p < 0.0001). In Study IM011055, the corresponding proportions were 40.9% versus 15.4% (difference: 25.6; 95% CI: 15.7, 35.5; p ≤ 0.0001).

In addition, across both pivotal studies, a significantly higher proportion of subjects in the deucravacitinib arm achieved MDA response compared with placebo.

In Study IM011054, the improvements in therapeutic response across joint and skin endpoints were maintained up to week 52 in more than 80% of week 16 responders. The maintenance rates for stricter measures of improvement showed about 71-74% of subjects maintaining their ACR70

and PASI90 response up to week 52. The MDA response was maintained by 89.1% subjects, reflecting sustained overall improvement. In study IM011055, maintenance rates showed about 81-85% of subjects maintaining their initial week 16 ACR20 and MDA response, respectively. Maintenance rates for other endpoints were between 66% for PASI90 and 77% for ACR50.

3.3. Uncertainties and limitations about favourable effects

Apremilast was selected as an active comparator for safety assessment; no efficacy comparisons with apremilast were conducted initially. While according to the EMA PsA guideline, this is not mandatory, comparison with an available active comparator could have been useful to contextualise further deucravacitinib's efficacy. Upon the CHMP's request, efficacy comparisons with apremilast were provided. The results appear to be slightly in favour of deucravacitinib. However, given the exploratory nature of the analysis, these findings should be interpreted with caution.

In the two pivotal study, the 5th pre-specified secondary endpoint: enthesitis resolution assessed by LEI did not demonstrate a statistically significant difference between deucravacitinib and placebo. Consequently, subsequent endpoints in the hierarchical testing sequence, FACIT-fatigue, dactylitis resolution, and DAS28-CRP, were not formally adjusted for multiplicity, and the results should therefore be interpreted with caution and regarded as nominal. Several clinically relevant endpoints were tested only as additional secondary endpoints without multiplicity adjustments (ACR 50/70, PASI 90/100, DAPSA, PASDAS, PsARC, BASDAI, ASDAS-CRP). Nevertheless, their results, although nominal, are considered supportive of the primary outcome.

Deucravacitinib effects on axial disease or structural joint damage cannot be concluded based on available data. Therefore, a statement in section 5.1. of the SmPC, was included to inform prescribers that the number of PsA patients with axial involvement/predominant spondylitis was too small to allow meaningful assessment.

The maintenance of effect after week 16 was evaluated in an uncontrolled manner at week 52 in IM011055 study. Given the exploratory nature of these analyses, the results should be interpreted with caution; nevertheless, they appear consistent with the primary findings. Overall, the majority of week 16 responders maintained their response at Week 52, demonstrating the durability of response achieved with deucravacitinib treatment.

3.4. Unfavourable effects

The safety profile of deucravacitinib in PsA patients remains consistent with the safety data assessed during the initial MAA in PsO patients.

No new major safety concerns have been identified in the PsA clinical programme. However, new safety issues have arisen from this new population. Imbalance in reporting rates between deucravacitinib and placebo groups have been observed for pneumonia and bronchitis, which were not included as ADRs in the previously approved PsO indication. Therefore, these ADRs have been added in section 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Although no clear relationship with deucravacitinib can presently be established, the risk of malignancies, NMSC, MACE and other cardiovascular AEs were thoroughly analysed and discussed by the MAH. Notwithstanding no new safety signals related to these risks were identified, they

remain important potential risks in the safety concerns of the RMP. The non-interventional cohort study (IM011194) will be updated to also follow-up these risks in PsA patients.

Long term safety information remains also limited; therefore, the MAH was asked to update study IM011194 to include PsA patients for follow-up in the post approval setting.

3.6. Effects Table

Table 76. Effects Table for Deucravacitinib in PsA

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ACR20	ACR 20 Response Rate at Week 16	%	54.2	34.1	DEUC showed superior efficacy over placebo across placebo-controlled studies	Study IM011054
		%	54.2	39.4		Study IM011055
HAQ-DI	Change from baseline in HAQ-DI score at Week 16	Adjusted mean change from baseline (SE)	-0.3850 (0.02897)	-0.2163 (0.02888)	DEUC showed superior efficacy over placebo across placebo-controlled studies.	Study IM011054
			-0.3246 (0.03196)	-0.2120 (0.03216)		Study IM011055
PASI 75	PASI 75 Response Rate at Week 16	%	51.9	7.1	DEUC showed superior efficacy over placebo across placebo-controlled studies.	Study IM011054
		%	40.9	15.4		Study IM011055
SF-36 PCS	Change from baseline in SF-36 PCS score at Week 16	Adjusted mean change from baseline (SE)	6.055 (0.4103)	3.711 (0.4086)	DEUC showed superior efficacy over placebo across placebo-controlled studies.	Study IM011054
			5.838 (0.4931)	3.796 (0.4962)		Study IM011055
MDA	Change from baseline in SF-36 PCS score at Week 16	Adjusted mean change from baseline (SE)	6.055 (0.4103)	3.711 (0.4086)	DEUC showed superior efficacy over placebo across placebo-controlled studies.	Study IM011054
			5.838 (0.4931)	3.796 (0.4962)		Study IM011055
Unfavourable Effects:						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Upper respiratory infections [a]	Adult patients ≥18 years	%	DEUC (n=644): 15.1 (n=97)	PBO (n=644): 10.4 (n=67)	Placebo-controlled period: week 0-16	Phase 3 studies: IM011054 and IM011055
Acneiform rash[b]	Adult patients ≥18 years	%	DEUC (n=644): 6.7 (n=43)	PBO (n=644): 0.9 (n=6)	Placebo-controlled period: week 0-16	Phase 3 studies: IM011054 and IM011055
Herpes simplex infections[c]	Adult patients ≥18 years	%	DEUC (n=644): 1.4 (n=9)	PBO (n=644): 0.8 (n=5)	Placebo-controlled period: week 0-16	Phase 3 studies: IM011054 and IM011055
Oral ulcers[d]	Adult patients ≥18 years	%	DEUC (n=644): 5.6 (n=36)	PBO (n=644): 0.2 (n=1)	Placebo-controlled period: week 0-16	Phase 3 studies: IM011054 and IM011055
Folliculitis	Adult patients ≥18 years	%	DEUC (n=644): 0.9 (n=6)	PBO (n=644): 0	Placebo-controlled period: week 0-16	Phase 3 studies: IM011054 and IM011055
Herpes zoster	Adult patients ≥18 years	%	DEUC (n=644): 0.3 (n=2)	PBO (n=644): 0.5 (n=3)	Placebo-controlled period: week 0-16	Phase 3 studies: IM011054 and IM011055

Notes:
[a] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis, acute sinusitis, pharyngotonsillitis, rhinitis, tonsillitis, peritonsillar abscess, laryngitis, tracheitis, and rhinotracheitis.
[b] Acneiform rash includes acne, dermatitis acneiform, rash, rosacea, pustule, rash pustular, rash papular and papule.
[c] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, herpes ophthalmic, and herpes viral infection.
[d] Oral ulcers include aphthous ulcer, mouth ulceration, tongue ulceration, and stomatitis.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The demonstration of the efficacy is supported by two pivotal Phase 3 studies whose similar design and conduct were considered acceptable. Both studies met their primary endpoint with an estimated difference in responder in ACR20 at Week 16 of respectively 20% and 14.3% versus

placebo. These improvements are overall reflected on both joint and skin manifestations of PsA, as well as in PRO related to physical function and quality of life. Some aspects of efficacy, like improvements in axial disease or effects on structural joint damage remain inconclusive. Therefore, a statement in section 5.1. of the SmPC, was included to inform prescribers that the number of PsA patients with axial involvement/predominant spondylitis was too small to allow meaningful assessment.

Overall, the majority of week 16 responders maintained their response at Week 52, demonstrating the durability of response achieved with deucravacitinib treatment.

The recommendation that deucravacitinib could be potentially combined with all cDMARDs was considered insufficiently justified given that the majority of patients treated with concomitant cDMARDs received MTX. Therefore, the indication was amended to use deucravacitinib alone or in combination with methotrexate (MTX), where a clear effect was observed.

The safety profile of deucravacitinib in PsA patients remains consistent with the safety data assessed during the initial MAA in PsO patients. New safety issues related to infections (i.e. pneumonia and, bronchitis) were identified and added in section 4.8 of the SmPC.

Although no clear relationship with deucravacitinib can presently be established, the risk of malignancies, NMSC, MACE and other cardiovascular AEs were thoroughly analysed and discussed by the MAH. Notwithstanding, no new safety signals related to these risks were identified, they remain important potential risks in the safety concerns of the RMP. The non-interventional cohort study (IM011194) will be updated to also follow-up these risks in PsA patients.

3.7.2. Balance of benefits and risks

The demonstration of the efficacy of deucravacitinib in the treatment of active PsA is acceptable. Overall, deucravacitinib demonstrated favourable effects across joint, dermatological, and patient-reported outcomes at Week 16, with maintenance of response observed to Week 52. The overall safety profile observed in patients with PsA is generally consistent with that observed in the previously approved indication in patients with PsO.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Sotyktu is positive in the indication:

Sotyktu, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic (DMARD) therapy (see section 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include, the treatment of active psoriatic arthritis (PsA), alone or in combination with methotrexate (MTX), in adults who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic (DMARD) therapy. This is based on results from the following phase 3 studies: Study IM011054 (POETYK PsA-1); a phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of deucravacitinib in participants with active PsA who are naïve to biologic DMARD, and Study IM011055 (POETYK PsA-2); a multi-center, randomised, double-blind, placebo-controlled phase 3 study to evaluate the efficacy and safety of deucravacitinib in participants with active PsA who are naïve to biologic DMARD or had previously received TNFα inhibitor treatment. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. The updated RMP version 3.2 is acceptable. In addition, the marketing authorisation holder took the opportunity to update the list of local representatives in the Package Leaflet, as well as introduce administrative changes to the product information.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Sotyktu-H-C-5755-II-EMAVR0000282554'

Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) as adopted by the CHMP on 26 March 2026.