EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2026
EMADOC-1829012207-53402
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Icotyde

International non-proprietary name: Icotrokinra hydrochloride

Procedure No. EMEA/H/C/006730/0000

Note

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

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List of abbreviations

3HP	Short-course preventive therapy for latent tuberculosis infection comprising Isoniazid (INH) and Rifapentine (RPT).
AE	Adverse Event
AEIRs	Adverse Event Incidence Rates
ADA	Anti-Drug Antibodies
ADME	Administration, Distribution, Metabolism, Excretion
ADR	Adverse Drug Reaction
ADI	Acceptable daily intake
AMER, EU, APAC	Americas, Europe, Asia-Pacific
ARAs	Acid-Reducing Agents
AS	Axial Spondyloarthritis
ATP	Adenosine triphosphate
AUC	Area Under The Curve
BID	Twice A Day
BCS	Biopharmaceutics Classification System
BLQ	Below The Limit Of Quantification
BMI	Body Mass Index
BSA	Body Surface Area
C_{max}, t_{max}	Maximum Plasma Concentration And Time To C_{max}
CAT	Committee For Advanced Therapies
CD	Crohn's Disease
CHMP	Committee For Medicinal Products For Human Use
ChP	Chinese Pharmacopoeia
CL	Clearance
ClinROs / PROs	Clinician And Patient Reported Outcomes
CM	Continuous manufacture
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CQA	Critical Quality Attribute
C-SSRS	Columbia-Suicide Severity Rating Scale
CVD	Cardiovascular Disease
CXCL13	Chemokine Cxc Ligand 13
DB	Double-Blind
DLQI	Dermatological Life Quality Index

DOE	Design of experiment
DP	Diversion point
DSC	Differential Scanning Calorimetry
E-R analysis	Exposure-Response Analysis
EAIR	Exposure-Adjusted Incidence Rate
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
ECLA	Electro-Chemiluminescence Assay
EDTA	Ethylenediaminetetraacetic Acid
EFD	Embryo-Foetal Development
EMA	European Medicines Agency
FEED	Fertility And Early Embryonic Development
FIH / RI studies	First-In-Human / Renal Impairment Studies
f-PGA	Fingernail PGA
Fu	Fraction Unbound
GC	Gas chromatography
GenPs-SFQ	Genital Psoriasis Sexual Frequency Questionnaire
GI	Gastrointestinal Tract
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
GPSS	Genital Psoriasis Symptoms Scale
GvHD	Graft vs Host Disease
HDPE	High-density polyethylene
hERG	Human Ether-À-Go-Go-Related Gene
hf-PGA	PGA Of Hands And Feet
HR	Hazard Ratio
HR-MS	High-resolution mass spectrometry
hs-CRP	High-Sensitivity C-Reactive Protein
ICE	Intercurrent Event
ICH	International Council for Harmonisation
IFNγ	Interferon Gamma
IGRA	Interferon-Gamma Release Assay
IGA	Investigator's Global Assessment
IIV	Inter-Individual Variability
IPC	In-process control
IR	Immediate Release
ISO	International Organization for Standardization

ISR	Incurred Sample Reproducibility
IWRS	Interactive Web Response System
JP	Japanese Pharmacopoeia
JSFA	Japanese Standards of Food Additives
K_p	Tissue-To-Plasma Partition Coefficient
K_a	Absorption Rate Constant
KF	Karl Fischer titration
KLH	Keyhole Limpet Hemocyanin
LCMS/MS	Liquid Chromatography With Tandem Mass Spectrometry
LDPE	Low-density polyethylene
LLOQ – ULOQ	Lower/Upper Limit Of Quantification
LSC	Liquid Scintillation Counting
LTBI	Latent M. Tuberculosis Infection
LTE	Long-Term Extension
MACE	Major Adverse Cardiovascular Events
MAD	Multiple Ascending Dose
MCP-Mod	Multiple Comparison Procedures With Modeling Techniques
MI	Multiple Imputation
mNAPSI	Modified Nail Psoriasis Severity Index
MnPCEs	Micronucleated Polychromatic Erythrocytes
MMRM	Mixed-Model For Repeated Measures
mNAPSI	Modified Nail Psoriasis Severity Index
NAb/NDA	Neutralising Anti-Drug Antibodies
NIR	Near infrared spectroscopy
NMR	Nuclear magnetic resonance
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NRS	Numeric Rating Scale
PAR	Proven acceptable range
PASI	Psoriasis Area And Severity Index
PAT	Process analytical technology
PBMCs	Peripheral Blood Mononuclear Cells
pcVPCs	Prediction-Corrected Visual Predictive Checks
PD	Pharmacodynamics
PDE4	Phosphodiesterase 4
Pen	Penicillamine
%RSE	Percent Relative Standard Error

PGA	Physician's Global Assessment
PGP (MDR1 or ABCB1)	P-Glycoprotein
PhV	Pharmacovigilance
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PPB	Plasma Protein Binding
PPND	Pre- And Postnatal Development
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic Arthritis
PsO	Psoriasis
PSSD	Psoriasis Signs Symptoms Diary
PSSI	Psoriasis Scalp Severity Index
PT	Preferred Term
QbD	Quality by design
QC	Quality control
QD	Once Daily
QTPP	Quality target product profile
QWBA	Quantitative Whole-Body Autoradiography
R^2_{adj}	Adjusted R-Squared
RA	Rheumatois Arthritis
RH	Relative humidity
RMP	Risk Management Plan
RTD	Residence time distribution
RTRT	Real-time release testing
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAR	Structure-activity relationship
SD	Standard Deviation
SIR	Standardised Incidence Ratio
SM	Synthesis/manufacturing route
SmPC	Summary Of Product Characteristics
SOC	System Organ Class
sPGA-G	Static Physician's Global Assessment Of Genitalia
ssIGA (ssIGAQ)	Scalp Specific Iga
TB	Tuberculosis
TEAEs	Treatment Emergent Adverse Events

TK	Toxicokinetics
TLAG	Lag Time
TNBS	2,4,6-Trinitrobenzene Sulfonic Acid
TNFα	Tumour Necrosis Factor Alfa
UC	Ulcerative colitis
UHPLC	Ultra-high performance liquid chromatography
USP/NF	United States Pharmacopeia/National Formulary
Vc	Central Volume Of Distribution
VTE	Venous Thromboembolism
WHO	World Health Organisation
WoE	Weight-Of-Evidence
XRPD	X-ray powder diffraction

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Icotyde
Active substance	icotrokinra hydrochloride
INN or common name	icotrokinra hydrochloride
Applicant	Janssen-Cilag International N.V. Turnhoutseweg 30 Beerse 2340 Antwerp BELGIUM
EMA product number	EMEA/H/C/006730
ATC code and pharmacotherapeutic group	L04AC28 Immunosuppressants, interleukin inhibitors
Pharmaceutical form(s) and strength (s)	Film-coated tablet 200 mg
Packaging	blister (alu/alu) and bottle (HDPE)
Package size(s)	28 x 1 tablets (unit dose), 7 x 1 tablets (unit dose), 84 x 1 (3 x 28 x 1) tablets (unit dose) (multipack) and 30 tablets
Route of administration	Oral use
Device or diagnostic	Not applicable
Orphan designation	N
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Icotyde is indicated for the treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy.
New active substance status	Granted

1.2. Scientific advice

In the past the CHMP Scientific Advice has been provided for icotrokinra:

Table 1. Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
16 September 2021	quality, non-clinical	EMA/SA/0000060737	The Scientific advice pertained to the following aspects: The control strategy for the proposed non-compendial absorption enhancer excipient; the adequacy of the non-clinical safety programme for JNJ 77242113; the adequacy of non-clinical safety of and clinical experience with the proposed absorption enhancer to support the Phase 2b clinical study and a marketing authorization application.
24 March 2022	non-clinical	EMA/SA/0000079068	The Scientific advice pertained to the following aspects: 2-year rat carcinogenicity study
15 September 2022	clinical	EMA/SA/0000095290	The Scientific advice pertained to the following aspects: Need for a human mass-balance study, renal and hepatic impairment studies, drug-drug interaction studies and a formal QT/QTc prolongation assessment
22 June 2023	non-clinical, clinical	EMA/SA/0000131317	The Scientific advice pertained to the following aspects: - proposed safety pharmacology and toxicology studies - Adequacy of the proposed clinical pharmacology program and the overall clinical program; anti-drug antibody (ADA) investigation strategy; design of the phase 3 clinical trials; dose selection; statistical analysis; safety database; and management of latent TB infections
25 January 2024	quality	EMA/SA/0000156074	The Scientific advice pertained to the following aspects:

			comparability of active substance produced with two different methods of synthesis
19 September 2024	quality	EMA/SA/0000180079	The Scientific advice pertained to the following aspects: starting materials
14 November 2024	quality	EMA/SA/0000225900	The Scientific advice pertained to the following aspects: bridging strategy for a titanium-free coating formulation, and the method for controlling the dissolution rate.

1.3. Eligibility to the centralised procedure

The applicant Janssen-Cilag International N.V. submitted on 10 September 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Icotyde (icotrokinra hydrochloride), through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 January 2025.

The applicant applied for the following indication:

Adult plaque psoriasis

Icotyde is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Paediatric plaque psoriasis

Icotyde is indicated for the treatment of moderate to severe plaque psoriasis in adolescents 12 years of age and older and weighing at least 40 kg who are candidates for systemic therapy.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision EMA/PE/0000183329 on the agreement of a paediatric investigation plan (PIP), for the treatment of psoriasis.

At the time of submission of the application, the PIP EMA/PE/0000183329 had not been completed as some measures had been deferred.

The PDCO issued on 25 July 2025 a positive partial compliance check for PIP EMA/PE/0000183329, in

relation to:

Agreed studies/measures (study identifier)	Description
Study 2	Stability studies to support the dispersion of the tablet formulation.
Study 3 (77242113PSO3001)	Double-blind randomised placebo-controlled trial to evaluate pharmacokinetics, safety, efficacy of 77242113 in children years to less than 18 years of age (and adults) with moderate to severe plaque psoriasis.
Study 5 (initiation only)	Modelling and simulation dose finding study

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

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

1.7. Applicant's requests for consideration

1.7.1. New active substance status

The applicant requested the active substance icotrokinra hydrochloride contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.1.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that icotrokinra hydrochloride is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. Patients experience data

Table 2. Patients experience data relevant to the application

Patient experience data submitted with this application				*Section where discussed (if applicable)*
☒	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		☒	Patient-reported outcomes (PRO)	Section 5
		☐	Other	

Patient experience data submitted with this application			Section where discussed (if applicable)
	☐	Patient preference studies	
	☒	Observational studies/RWD designed to capture patient experience data	Section 5
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)	
	☐	Other (please specify)	
☒	Other patient experience data not submitted by the applicant but considered in this evaluation:		
	☐	Input informed from participation in meetings or public hearings with patient stakeholders	
	☒	CHMP early dialogue with patient organisations	Section 5
	☐	Third party interventions from patients and patient groups	
	☐	Other (e.g. medical literature, summaries/analysis from patient engagement activities - please specify)	

1.9. Steps taken for the assessment of the product

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

rapporteur:	Peter Mol
Co-rapporteur:	Martin Mengel

The application was received by the EMA on	10 September 2025
The procedure started on	2 October 2025
The CHMP rapporteur's first assessment report was received on	18 December 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	19 December 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	6 January 2026
The Quality working party agreed on the Assessment Overview during their meeting on	20 January 2026
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	29 January 2026
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 March 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	28 April 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 May 2026

The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	21 May 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	22 June 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	8 July 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Icotyde on	23 July 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	23 July 2026

1.10. CHMP outcome

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

In this procedure, the CHMP reviewed the available data from the studies conducted in accordance with the agreed PIP EMA/PE/0000183329, namely study ICONIC-LEAD, ICONIC-TOTAL. The results of these studies are reflected in sections 4.2, 4.8, 5.1, 5.2 of the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. Further, these results were pivotal in supporting this application.

EMA has deferred the paediatric development of this medicinal product. The relevant paediatric statement has been included in Section 5.1 of the SmPC.

1.10.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.10.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Icotyde is favourable in the following indication(s):

Icotyde is indicated for the treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.10.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.10.5. Other conditions and requirements of the marketing authorisation

1.10.5.1. Periodic safety update reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.10.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.10.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Psoriasis is a relatively common chronic inflammatory skin disease, that may exhibit a variety of clinical manifestations. Overall, it affects approximately 1% to 4% of the adult population and up to 1% of children worldwide (Armstrong AW 2021; Parisi 2013, 2020).

Plaque psoriasis (psoriasis vulgaris) is the most common clinical sub form, and is characterised by the presence of well-demarcated, erythematous plaques with overlying silvery scales. These plaques may be asymptomatic, but pruritis is common. Patients with plaque psoriasis can have a heterogenous disease expression, with different degrees of severity and/or special site involvement (scalp, genitals, nails, hand/feet); the latter are considered difficult to treat (Armstrong 2022; Merola 2018). Patients with chronic plaque psoriasis, regardless of area of involvement or age, report significant debilitation in social, psychological, and health-related quality of life.

The treatment goal is to achieve a clear or almost clear skin status and improve quality of life (Nast 2023). Topical therapies are generally the first-line treatment for plaque psoriasis across all ages, with phototherapy or systemic treatments used when topicals are inadequate or impractical. Conventional oral systemic therapies, including cyclosporine, methotrexate, or oral retinoids, may provide variable

efficacy but have dose-limiting toxicities. Biologic therapies approved for use in adults with moderate to severe plaque psoriasis include injectable therapies targeting specific cytokines, such as TNFα inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors, with fewer options available for adolescents (TNFα inhibitors, an IL-12/23 inhibitor and IL-17 inhibitors). The efficacy of biologics varies, with particularly anti-IL-17 and most anti-IL-23 therapies, showing greater effectiveness compared to others such as ustekinumab, several anti-TNF agents, and deucravacitinib (Sbidian et al. 2023). Further, biologics have specific adverse effects, including an increased risk of serious infections such as tuberculosis, and an increased risk for malignancies. Across multiple classes, common adverse reactions include infections, hypersensitivity reactions, and injection site reactions. Currently available advanced oral systemic therapies for psoriasis include small molecules such as PDE4 inhibitors and selective TYK2 inhibitors. These treatments provide clinically meaningful efficacy but may be limited in some patients by safety and tolerability.

Despite the variety of treatment options, there remains an unmet need for oral therapies that are safe, highly effective, convenient, and capable of providing long-term control of moderate to severe plaque psoriasis across diverse patient populations.

2.2. Aspects of development

The Phase 3 program of icotrokinra consists of 4 randomised, controlled studies, designed to assess the safety, efficacy, PK, and immunogenicity of icotrokinra 200 mg orally once daily (QD) in participants with plaque psoriasis who are candidates for phototherapy or systemic therapy. All 4 studies evaluated the effect of treatment with icotrokinra versus placebo (through week 16) on the signs and symptoms of psoriasis, including special area psoriasis.

Studies of moderate to severe plaque psoriasis (defined as BSA ≥10%, PASI ≥12, and IGA ≥3):

- **PSO3001** (ICONIC-LEAD) included adults and adolescents (weighing ≥40 kg) and incorporated a randomised withdrawal period for adult responders to provide evidence for the durability of response.
- **PSO3002** (ADVANCE-1) and **PSO3004** (ADVANCE-2) included adult participants only; included an active-comparator arm to demonstrate superiority to (oral) deucravacitinib 6 mg QD.

Study of plaque psoriasis with at least moderate special area (scalp, genital, and/or hand/foot) involvement (defined as overall BSA ≥1%, IGA score ≥2, and at least one of the following: ss IGA ≥3, sPGA G ≥3, and/or hf PGA ≥3):

- **PSO3003** (ICONIC-TOTAL) included adults and adolescents (weighing ≥40 kg) to provide evidence of the effectiveness of icotrokinra in this patient population with special site psoriasis.

Efficacy data from PSO3001 and PSO3003 through Week 52, PSO3002 through Week 44, and PSO3004 through Week 24 were included at the time of submission, as well as safety data through each study's specified safety data cut-off date (see safety section). A total of 2,500 participants were enrolled in the Phase 3 studies, including 72 adolescents. All 4 Phase 3 studies are ongoing to collect efficacy and safety data for up to 3 years of icotrokinra exposure.

The icotrokinra psoriasis clinical program also includes completed Phase 2 dose-ranging studies PSO2001 and its LTE (PSO2002), which evaluated 5 doses of icotrokinra for up to 1 year of continuous treatment in adult participants with moderate to severe plaque psoriasis. In addition, supportive data are available from 7 completed Phase 1 studies (PN-235-01, PSO1002, PSO1003, PSO1004, PSO1006, PSO1007, PSO1009) including healthy and renally impaired participants, and 1 completed Phase 2a

study using a formulation of icotrokinra with a tablet formulation which is different from the claimed formulation (PSO2003).

2.3. Description of the product

Icotrokinra, also known as JNJ-77242113, is a first-in-class, orally administered synthetic peptide that selectively binds to the IL-23 receptor to competitively antagonise the binding of IL-23. This results in inhibition of proximal IL-23R signalling and downstream effector functions (e.g., cytokine secretion).

The initially proposed therapeutic indication for icotrokinra was as follows:

Adult Plaque Psoriasis

TRADENAME is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Paediatric Plaque Psoriasis

TRADENAME is indicated for the treatment of moderate to severe plaque psoriasis in adolescents 12 years of age and older and weighing at least 40 kg who are candidates for systemic therapy."

The recommended dosage of icotrokinra is 200 mg orally once daily (QD).

No dose adjustments are proposed for elderly patients or patients with renal or hepatic impairment.

icotrokinra has been approved by the FDA in 2026 (17 March 2026).

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

A routine GCP inspection of the 77242113PSO3004 (ICONIC ADVANCE 2) trial was adopted at the October 2025 CHMP meeting.

3. Quality aspects

3.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg of icotrokinra active substance (as hydrochloride salt).

Other ingredients are:

Tablet core: crospovidone (E1202), magnesium stearate (E572), silica colloidal anhydrous (E551), silicified microcrystalline cellulose (silica colloidal anhydrous and microcrystalline cellulose).

Film-coating: glyceryl monocaprylocaprate (E471), iron oxide yellow (E172), macrogol polyvinyl alcohol graft copolymer (E1209), polyvinyl alcohol partially hydrolysed (E1203), talc (E553b), titanium dioxide (E171)

The product is available in aluminium/aluminium foil perforated unit dose blisters, or HDPE bottle with a silica gel desiccant and a child resistant polypropylene closure, as described in section 6.5 of the SmPC.

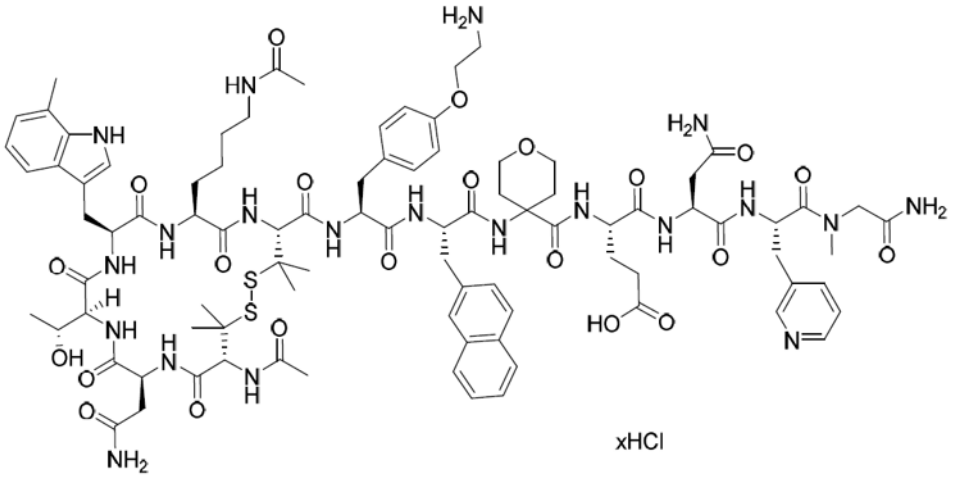
3.2. Active substance

3.2.1. General information

The name of the active substance is icotrokinra (INN) hydrochloride. Full details of manufacture are submitted by the applicant as part of the application.

The chemical name of icotrokinra hydrochloride is (4S)-4-[([4-[(2S)-2-[(2S)-2-[([(4R,7S,10S,13S,16S,19R)-19-acetamido-7-(4-acetamidobutyl)-16-(2-amino-2-oxoethyl)-13-[(1R)-1-hydroxyethyl]-3,3,20,20-tetramethyl-10-[(7-methyl-1H-indol-3-yl)methyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-4-yl]carbonyl)amino]-3-[4-(2-aminoethoxy)phenyl]propanamido]-3-(2-naphthyl)propanamido]tetrahydro-2H-pyran-4-yl]carbonyl)amino]-5-[[(2S)-4-amino-1-[[(2S)-1-[(2-amino-2-oxoethyl)(methyl)amino]-1-oxo-3-(pyridin-3-yl)propan-2-yl]amino]-1,4-dioxobutan-2-yl]amino]-5-oxopentanoic acid hydrochloride corresponding to the molecular formula $C_{90}H_{120}N_{20}O_{22}S_2$.xHCl. It has a relative molecular mass of 1898.17 + x36.46 and the following structure:

Figure 1. Active substance structure



icotrokinra hydrochloride is a white to almost white powder. It is hygroscopic and shows high solubility under acidic and strongly basic conditions whereas low solubility is observed between pH 5 to 9. The active substance is classified as a BCS Class IV compound.

icotrokinra comprises 13 amino acids of which 9 are non-natural. It has 12 chiral centres and exists as a single enantiomer. icotrokinra is isolated as a non-stoichiometric crystalline HCl salt with polymorphic form 1.

3.2.2. Manufacture, process controls and process development

Description of manufacturing process and process controls

The active substance is manufactured at Janssen Pharmaceutica NV, Janssen Pharmaceuticalaan 3, B-2440 Geel, Belgium. Satisfactory evidence of GMP compliance has been presented for the manufacturing of icotrokinra.

Full details of manufacture are submitted by the applicant as part of the application.

icotrokinra hydrochloride is synthesised using well-defined starting materials with acceptable specifications.

The active substance manufacturing process has been adequately described. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria are described for critical steps only. The active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information concerning the starting materials used in the active substance manufacturing process has been submitted. The proposed starting materials are suitably justified in accordance with ICH Q11, and all other materials or reagents proposed for use are adequately described and controlled.

Control of critical steps and intermediates

The active substance manufacturing process was systematically evaluated using quality risk management tools as per ICH Q9 guideline to determine which process steps, process parameters, and material attributes have an impact on the critical quality attributes (CQAs) of the active substance. A summary is given of this criticality analysis along with the control strategy for critical steps in the active substance manufacturing process and it is considered acceptable.

Adequate in-process controls are applied during the synthesis and critical steps have been suitably defined. The specifications and analytical procedures for intermediate products have been presented. A detailed discussion of impurities and their purging in relevant process intermediates is given, and it is considered adequate.

Process validation

Process validation data has not been provided in the application which is acceptable for a non-sterile active substance.

Manufacturing process development

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by Design (QbD) such as risk assessment and design of experiment (DOE) studies. Based on these studies, proven acceptable ranges (PARs) have been defined for the critical

steps of the manufacturing process of the active substance. The available development data, the proposed control strategy and batch analysis data support the proposed PARs.

3.2.3. Characterisation and impurities

The chemical structure of icotrokinra was elucidated by a combination of elemental analysis, high-resolution mass spectrometry (HR-MS), infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy (^{1}H NMR, 2D HSQC), ultraviolet (UV) spectroscopy, circular dichroism (CD) spectroscopy and optical rotation.

icotrokinra exhibits stereoisomerism due to the presence of 12 chiral centres and exists as a single enantiomer. The absolute stereochemistry was determined by single X-ray crystallography. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), IR spectroscopy, thermogravimetric analysis (TGA) and dynamic vapour sorption (DVS). The selected polymorphic form is the only one produced by the commercial synthesis process and it does not change upon storage.

The characterisation of the active substance and its impurities are in accordance with EU guideline on chemistry of active substances. Potential and actual impurities are well discussed with regards to their origin and characterised. Mutagenic impurities assessment has been performed for non-peptide impurities in line with ICH M7 guideline.

The initial mutagenic impurities risk assessment was incomplete and the CHMP raised a major objection (MO1) questioning: a) the proposed control strategy for residual reagent, b) purge factor calculations for mutagenic impurities, c) carry-over levels of non-peptide impurities from starting materials, d) incomplete *in silico* structure-activity relationships (SAR) predictions, e & f) mutagenic potential of process reagents. The applicant resolved this MO by: a) substantiating the ICH M7 Option 4 control strategy with analytical data, b) providing detailed purge factor calculations and underlying assumptions to exclude carry-over to the active substance, c) providing batch data on residual levels of non-peptide related impurities, d) submitting updated results from complementary SAR prediction methodologies, e) submitting negative mutagenicity outcomes for and f) submitting evidence of negative *in vivo* carcinogenicity along with batch data for residuals in the active substance.

The initial risk assessment for the presence of nitrosamines in the active substance was incomplete, and the CHMP raised MO questions as part of the overall risk assessment and MO2 raised at the finished product level as discussed in section 3.3.3.

The organic solvents used in the synthesis of icotrokinra hydrochloride are discussed and residual solvents are controlled as recommended by ICH Q3C. No class 1 solvents are used in the manufacture of active substance or starting materials. Benzene can be present as a class 1 solvent impurity in the two solvents used in the final manufacturing step. Therefore, the CHMP raised a major objection (MO3) since benzene was not controlled in the originator solvents nor in the active substance. The applicant resolved this MO by including a routine test for benzene in the originator solvents and the acceptance limit proposed was justified with spiking studies and batch analysis data for the active substance.

3.2.4. Control of active substance

Specifications

The active substance specification includes tests for appearance (visual), identification of icotrokinra (UHPLC-UV, UHPLC-MS) and counter ion (Ph. Eur.), assay (UHPLC-UV), chromatographic purity (UHPLC-UV), chloride content (potentiometric titration), water content (KF, NIR), residual solvents (G:C), residue on ignition (Ph. Eur.), particle size (laser diffraction).

The proposed analytical procedures and corresponding limits are adequate for routine control of the active substance. They are in line with ICH and EMA guidelines, Ph. Eur. requirements, batch release data and stability data.

During the procedure the applicant was requested to tighten the total impurities limit based on release and stability data and this was satisfactorily addressed.

Justifications given for tests not included in the specification are considered acceptable. Given the manufacturing process conditions for the active substance and its packaging, microbial growth is unlikely and this is supported with process validation and stability data.

Analytical procedures and reference standards

The analytical procedures used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis

A comprehensive amount of batch analysis data of the active substance are provided, including 3 primary stability batches representative for the commercial process and 6 registration stability batches using the final proposed commercial manufacturing process. The results are within the specifications and confirm consistency of the manufacturing process.

3.2.5. Stability

The retest period of 30 months in the proposed container is justified by the available stability data.

The commercial active substance is packaged in a low-density polyethylene (LDPE) bag, which complies with Commission Regulation (EU) 10/2011, as amended. The bag is placed in a heat-sealed aluminium laminated bag which is placed in a closed suitable fibreboard or plastic container.

Stability data from three primary batches of the active substance from the proposed commercial manufacturing site and stored in the intended commercial package for up to 9 months at -20°C, 24 months under long term conditions (5 °C/25% RH) and for 6 months under accelerated storage conditions (25 °C /60% RH) were provided.

In addition, stability data are presented from six supportive batches manufactured by the commercial process and stored for 12 months under long term conditions (5 °C/25% RH) and for 6 months under accelerated storage conditions (25 °C /60% RH).

The stability-indicating parameters were tested. No significant changes or trends are observed for any of the stability batches.

Photostability testing following ICH guideline Q1B was performed on two batches (one primary and one commercial batch). Results from forced degradation studies were also provided. The analytical method used for assay and chromatographic purity is stability-indicating.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description the product

The finished product is a yellowish orange to yellowish brown, oval shaped, film-coated tablet of approximately 19 mm length and 9 mm width. The tablet is debossed with “200” on one side and

"JNJ" on the other side. The composition of the finished product is presented.

Pharmaceutical development

The aim of the pharmaceutical development as defined in the quality target product profile (QTTP) was to develop an immediate release (IR) oval shaped film-coated (FC) tablet for oral administration, containing icotrokinra hydrochloride active substance (equivalent to 200 mg icotrokinra free base), with low level of impurities/degradation products/microbial burden, and compliant with ICH stability requirements over a shelf life of minimum 24 months when packaged in bottles or blisters.

The physicochemical properties of the active substance that could influence manufacturability and the *in vivo* performance of the finished product (polymorphism, solubility, particle size distribution) were discussed. The stability of the polymorphic form has been confirmed by XRPD analysis of finished product batches stored in the commercial packaging up to 12 months at ICH long term storage conditions. Suitability of the limits for particle size has been adequately demonstrated.

All excipients are well known pharmaceutical ingredients that are commonly used in solid oral dosage forms, and their quality is compliant with compendial standards except for the commercial coating powder. However, its basic components comply with compendial standards There are no novel excipients used in the formulation. The rationale for selection and function of the various excipients has been acceptably discussed. The critical material attributes have been included in the excipients' specifications, parameters tested and limits applied are sufficiently justified in line with general Ph. Eur. text on functionality-related characteristics of excipients. The suitability of the excipient grades was also confirmed by compatibility studies between excipients and active substance, formulation robustness studies, NIR robustness testing, stability studies, manufacturing experience and prior knowledge with similar products.

The formulation development has been described, which confirm that the formulation is robust towards small changes in the concentrations or material attributes of the excipients. Several formulations and presentations were used throughout development and clinical testing. Changes between those formulations used in previous clinical trials and the proposed commercial IR film-coated tablet formulation were described and the rationale for the changes provided. A relative bioavailability study was conducted to demonstrate the PK equivalence of the proposed commercial formulation with the pivotal clinical formulations. Comparability of the dissolution profiles has been confirmed for tablets manufactured using active substance synthesised.

The development of the dissolution method and dissolution parameters (dissolution medium, volume, pH, paddle apparatus and rotation speed) has been described. The discriminatory power of the dissolution method was investigated using samples with appropriate formulation variables.

Manufacturing process development

The proposed commercial 200 mg film-coated tablet formulation is manufactured using continuous manufacturing (CM) operations and process analytical technology (PAT), with pre-blending being performed in batch mode, material feeding, blending and compression of core tablets being performed by CM, and the film coating being performed again in batch mode.

The manufacturing process development started from the defined QTPP and finished product critical quality attributes (CQAs), and the criticality of the various factors, material attributes and process parameters which can impact CQAs. The CQAs of the finished product are appearance, identification, assay, chromatographic purity, uniformity of dosage units, dissolution, water content and microbial purity. The definition and justification of the critical process parameters and the general control strategy are discussed. The overall approach is considered acceptable.

Early process development and batch manufacture occurred at a development site. At the commercial CM line production site primary stability batches and several pivotal clinical batches have been produced. Furthermore, characterisation and development studies were performed at the commercial site. The CM lines at the development and commercial site have been set up in a comparable configuration. The characterisation batches cover for the entire proposed run time range and include experiments with variations in the process parameters around the target values. The optimisation of each process step is described in detail, and the in-process controls are justified.

Real time release testing (RTRT) is applied for the parameters assay, identity and content uniformity, based on NIR tests performed during the process. This is supported by comparative batch data, as obtained by the reference methods and by the proposed NIR methods, of batches of finished product manufactured according to the commercial process at the extremes of the manufacturing run time range.

The proposed primary packaging materials are common for solid oral dosage forms. Their compatibility with the finished product is confirmed by the results of stability studies. The need for a desiccant in the bottle packaging has been justified by open dish studies, showing a significant increase of impurities in presence of high humidity.

The compatibility of the drug product with drinking water has been investigated, in order to justify the alternative way of administration (tablet can be dispersed in a glass of water and taken as soon as possible) described in the SmPC. The indication to use it as soon as possible has been justified based on the risk for errors and non-compliance to the instructions for use, and this was found acceptable.

3.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory evidence of GMP compliance has been provided including authorisation for continuous manufacturing operations and real-time release testing and the batch release site.

The size of a batch produced by CM is defined as a run time at a defined mass flow rate. The runtime of each batch is documented prior to the start of manufacture. The batch formula has been presented for the minimum and maximum run time.

The manufacturing process consists of six main steps: pre-blending of the active substance with an excipient (in batch mode) followed by continuous feeding of the pre-blend and the remaining excipients, in-line blending (adding the lubricant), and direct compression (all in continuous manufacturing mode), followed by film-coating (in batch mode) and final packaging. The process is considered to be a non-standard manufacturing process.

A summary of the startup, shutdown, pause and restart procedures of the CM process has been described including the events that would trigger a pause or shutdown of the process. The strategy to monitor and maintain the state of control and to manage disturbances, detect, divert and segregate potential non-conforming material has also been described in the manufacturing process description.

Diversion points (DP) in the CM process to detect and segregate non-conform material have been described and justified. The development, description, validation and model maintenance protocol for the reference method for the NIR method for % potency of the powder blend have been provided.

No prolonged holding times are applicable for the pre-blend and the core tablets. A bulk holding time of 12 months in a double LDPE bag in sealed aluminium bag or in or in aluminium lined pack at 15-25°C has been established for the coated tablets.

The manufacturing process has been validated on three batches of commercial size (covering the minimum and maximum run time). The process validation batches are representative of the routine

commercial process. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

3.3.3. Control of Finished Product

Specifications

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form including: description (visual), identification (NIR or UHPLC/UV), assay (NIR or UHPLC), chromatographic purity (UHPLC), uniformity of dosage units (Ph. Eur., NIR or UHPLC/UV), dissolution (UHPLC), water content (KF or NIR) and microbial purity (Ph. Eur.).

Partial real-time release testing is performed for the finished product. RTRT of the core tablets (identity, assay, uniformity of dosage units) is conducted at-line by NIR. Finished product release testing of the film-coated tablets (appearance, chromatographic purity, dissolution, water content, and microbial purity) is conducted in the QC lab. The sampling frequency and sampling size per sampling point are adequately justified and ensure that analytical obtained are representative for the complete batch.

The RTRT approach and its relationship with end-product testing is approvable.

In case the NIR test results would not conform to the specification acceptance criteria, no switch will be made to the UHPLC methods for release testing. In case the at-line NIR tool for real time release testing is not operational (e.g. model maintenance or technical issues), the core tablet samples are analysed offline by NIR methodology or UHPLC, the latter is also used as the reference method for the secondary at-line and off-line NIR methods. The methods are shown to be equivalent.

Stability testing of the finished product is performed on the film-coated tablets.

The proposed analytical procedures and corresponding specification limits are adequate for routine control of the finished product at release and shelf life. They are justified with reference to relevant ICH guidelines (ICH Q6A, ICH Q3B, ICH Q3D), Ph. Eur. requirements, batch release and stability data. The average tablet weight and hardness are covered by in-process controls. Therefore, it is acceptable not to include these tests in the release specifications.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed according to the applicable guidance. A risk was identified due to presence of various secondary amines in the active substance synthesis. Experimental test results and purge data for the secondary amine impurities and the corresponding nitrosamines excluded risk for any nitrosamine impurity in the active substance above 10% of the acceptable daily intake (ADI). No additional risk was identified for the finished product. However, the overall risk assessment and conclusion was incomplete and not all suspected root causes were taken into consideration. Therefore an MO was raised by the CHMP to request: a) method validation reports for determination of nitrosamine impurities, b) confirmatory test results known nitrosamines in the finished product, c) general discussion on absence of nitrosating agents in excipients, d) specific discussion for presence of residual nitrite in crospovidone with confirmatory test results on the finished product is risk is ident and e) submission of EMA Step 1 document "Template for the Notification of Step 1 Risk Evaluation Outcome: Confirmation of No Risk Identified" (MO2).

In their responses, the applicant presented an updated risk assessment including validation reports for determination of nitrosamine impurities, background documentation from the excipient suppliers, confirmatory testing on three finished product batches for the known nitrosamines which demonstrate that all results are below 10% of the acceptable intake. Also, the EMA Step 1 Risk Evaluation Outcome has been submitted. Based on the information, there is no risk of nitrosamine impurities in the finished product. Therefore, no specific control measures are deemed necessary and the MO was resolved.

Analytical procedures and reference standards

The analytical procedures used have been adequately described and appropriately validated in accordance with the ICH guidelines, and the EMA Guideline on the use of near infrared spectroscopy.

An alternative method may be used for control of microbiological quality based on adenosine triphosphate (ATP) bioluminescence. The equivalence of the ATP method to the compendial microbial purity test has been shown. In case of a positive result for ATP, the microbial purity test is performed.

For information about the reference standards for testing of the finished product, it is referred to the active substance section, which is acceptable.

Batch analysis

Batch analysis data are provided for all finished product batches used during clinical development and for finished product batches of the commercial strength and formulation (including process validation batches). The results are within the specifications and confirm consistency of the manufacturing process.

3.3.4. Stability of the product

The shelf life of 2 years without any special temperature storage conditions in the proposed container, as stated in the SmPC, is justified by the available stability data. The storage restrictions in the SmPC 'store in the original package to protect from moisture' for the blister and "store in the original package and keep the bottle tightly closed in order to protect from moisture" for the bottle have been justified and are supported.

Container closure system

The two container closure systems described are an aluminium/aluminium foil perforated unit dose blister, and 75 mL HDPE bottle with a silica gel desiccant and a child resistant polypropylene closure with induction seal liner (polyethylene contact layer). Both are considered appropriate for intended storage. Its specifications are acceptable and the material in direct contact with the tablets complies with EC requirements. Compliance with ISO standards for child-resistant closures has also been provided.

Stability data

Stability data from three commercial scale primary stability batches manufactured at the proposed commercial manufacturing site, were provided. The batches were packaged in the two intended commercial containers (blisters and bottles) and stored for 18 months under long term conditions (25 ºC/60% RH) and for 6 months under accelerated conditions (40 ºC/75% RH) according to the ICH guidelines.

The following parameters were tested: appearance, assay, chromatographic purity, dissolution, water content and microbial purity.

The available data of the primary stability studies show no significant change of the stability indicating parameters (appearance, assay, impurities, water content and dissolution) at all tested storage

conditions and in both the proposed commercial packaging configurations. Based on this, and on the principles for extrapolation of guideline ICH Q1E, the proposed shelf life (24 months) is acceptable.

An in-use stability study up to two months storage after first opening of the HDPE bottle, has been performed with one primary batch stored for 12 months. The study is considered an adequate simulation of the routine use of the product in worst case conditions, as the desiccant was removed. Considering the results of the primary stability studies and of the in-use study, along with the additional labelling statement for the HDPE bottles, it is acceptable that no in-use shelf life is stated in the SmPC.

Photostability testing following ICH guideline Q1B was performed on one production scale primary batch. Results from forced degradation studies (acidic, alkaline, oxidative, heat, humidity, metal ions) were also provided.

The finished is not sensitive to light, heat and metal ion conditions tested. The results confirm that the analytical method used for assay and chromatographic purity is stability-indicating.

At least one commercial batch per year manufactured in the primary package type will be placed on long-term storage condition as per the approved stability protocol. In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

3.3.5. Biosimilarity exercise

Not applicable

3.3.6. Post approval change management protocol(s)

Not applicable.

3.3.7. Adventitious agents

No excipients derived from animal or human origin have been used in the formulation of the capsule contents.

3.4. Discussion and conclusions on quality aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner.

During the procedure 3 MOs were raised by the CHMP related to: 1) incomplete assessment of mutagenic potential of impurities and control strategy for potential mutagenic impurities, 2) the incomplete risk assessment and conclusions for nitrosamine impurities in the finished product without taking all suspected root causes into consideration, 3) the control strategy for Class 1 solvent benzene which can be present as impurity in organic solvents used in the final steps of the active substance manufacturing process.

All MOs were satisfactorily resolved by:

1) substantiating the ICH M7 option 4 control strategy with analytical data, explaining purge factor calculations and underlying assumptions to exclude carry-over of impurities to the active substance, providing batch data on residual levels of non-peptide related impurities, submitting updated results from complementary SAR prediction methodologies; submitting negative mutagenicity outcomes for

suspected mutagens, submitting evidence of negative *in vivo* carcinogenicity for residuals along with batch data for residual reagents in the active substance

2) submitting method validation reports for determination of nitrosamine impurities, background documentation from the excipient suppliers and confirmatory testing on three finished product batches for the known nitrosamines, demonstrating that all results are below 10% of the acceptable intake

3) including a routine test for benzene in the originator solvents and justifying the acceptance limit proposed with spiking studies and batch analysis data for the active substance.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The nonclinical program consisted of studies to investigate primary PD, select the pharmacologically relevant species, characterise pharmacokinetics/toxicokinetics and potential immunogenicity, and evaluate potential toxicity. Studies were designed and conducted in accordance with the ICH guidelines on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (ICH M3 [R2] 2009) and associated safety guidelines. The safety pharmacology, repeated dose toxicity, carcinogenicity, reproductive toxicity and *in vitro* and *in vivo* genotoxicity studies were conducted in line with Good Laboratory Practice (GLP) requirements.

4.2. Analytical methods

The bioanalytical methods were developed to support the PK/TK analyses of icotrokinra in rat, mouse, dog, rabbit and monkey plasma. Liquid chromatography with tandem mass spectrometry (LCMS/MS) methods were employed to analyse plasma samples from both GLP and non-GLP nonclinical toxicology studies in rat, rabbit and monkey. In general, plasma (EDTA), after the addition of an internal standard, was deproteinised using acetonitrile, centrifuged and in the supernatant the analyte was analysed. The analytical range (LLOQ – ULOQ) for plasma samples was mostly 0.100 to 200 ng/ml. Methods were validated for sensitivity, selectivity, carryover, linearity, intra-run & inter-run accuracy and precision, repeatability, sample dilution analysis, and long-term sample stability. Incurred sample reproducibility (ISR) for nonclinical sample analysis was conducted once per method per species (rat, monkey).

Radiolabelled profiling studies were performed in rat and monkey. The ^{14}C-label in ^{14}C-icotrokinra was placed on the carbonyl of the acetyl group adjacent to the Penicillamine (Pen). Metabolite profiles were characterised and quantified by HPLC with radioactivity detection and their chemical structures were elucidated by LC-MS/MS. Tissue distribution and excretion (mass balance) studies in rat and monkey were evaluated by measuring ^{14}C-radioactivity in samples of plasma, tissues, and excreta from animals dosed with ^{14}C-icotrokinra using liquid scintillation counting (LSC) and by quantitative whole-body autoradiography (QWBA).

For the detection of antibodies against icotrokinra (ADA) in mouse, rat, rabbit (qualified method only) and monkey, plasma samples were analysed using a qualified or validated bridging Electro-Chemiluminescence Assay (ECLA). The ECLA assays are selective, and samples were considered ADA positive when the signal exceeded the in the method established cut-points.

In addition, qualified non-GLP assays were available for measuring the neutralising effect of the ADAs (NDA) in rat and monkey plasma.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

The release of proinflammatory cytokines involved in the pathogenesis of plaque PsO is mediated by interleukin-23 (IL-23), a heterodimeric cytokine composed of an IL-23p19 subunit and an IL-23/12p40 subunit. These subunits bind to the IL-23R subunit and the IL-12Rβ1 subunit of the IL-23 receptor, respectively. icotrokinra is a 13-amino acid cyclic peptide that targets IL-23R.

In silico, the human IL-23R extracellular domain protein was found to have 95.5%, 72.4%, 76.8%, and 70.5% homology with the monkey, rabbit, rat and mouse receptors, respectively (DD25029). I*n vitro* surface plasmon resonance studies at a physiological temperature (DD23067 and DD21102) showed that icotrokinra bound to human, monkey and rat IL-23R with affinities in the same order of magnitude (K_D of 2-23 pM). Binding affinity for rabbit IL-23R was low and even lower for mouse IL-23R (K_D of 420 and 86000 pM, respectively). The *in vitro* $t_{1/2}$ value of icotrokinra for human IL-23R was 2.5 h. In an enzyme-linked immunosorbent assay, icotrokinra competed with human IL-23 for the binding to monkey IL-23R with an IC_{50} of 1.06 nM (DD20023).

The *in vitro* potency of icotrokinra in inhibiting proximal IL-23R signalling was tested in a PBMC assay (DD20018). icotrokinra blocked IL-23-induced STAT3 phosphorylation in a concentration-dependent manner (IC_{50} of 5.6 pM). The specificity of icotrokinra for IL-23R was tested in the same assay to exclude effects on IL-12Rβ1, which is also a subunit of the IL-12 receptor. icotrokinra did not affect IL-12-induced STAT4 phosphorylation (up to 2 µM). The equilibrium dissociation constant of icotrokinra was determined in an assay of IL-23-induced STAT3 phosphorylation in human diffuse large-cell B-lymphoma cells (DD20021). icotrokinra behaved as a simple competitive antagonist of IL-23 binding to IL-23R with high potency (Kb of 15.1 pM).

icotrokinra showed strong *in vitro* functional efficacy in several assays. IL-23-stimulated IFNγ production by human NK cells was inhibited with an IC_{50} of 18.4 pM (DD20020). In whole blood of healthy subjects and PsO patients, icotrokinra inhibited IL 23-induced IFNγ production (IC_{50} of 11 and 9 pM, respectively) (DD23066). icotrokinra also inhibited IL-23-induced IL-17A release by rat splenocytes (IC_{50} of 260 pM, DD20018) and in rat whole blood (IC_{50} of 54-250 pM, DD21040).

An *ex vivo* study showed dose-dependent inhibition of IL-17A production in IL-23-stimulated blood from rats orally treated with 1-100 mg/kg icotrokinra (IC_{50} of 32-270 pM, DD21040). The extent of inhibition was reduced at higher IL-23 concentrations and at later timepoints post-dose, showing the competitive and reversible antagonistic effect of icotrokinra.

The drug substance of icotrokinra contains 5 peptide-related impurities which have shown pharmacological activity.

The *in vivo* PD of icotrokinra was evaluated in rats in which pharmacological activity is expected based on *in vitro* and *ex vivo* studies. In an IL-23-induced ear skin inflammation model, 1 up to 300 mg/kg icotrokinra was administered orally twice daily (BID) on four consecutive days, including one day prior

to the induction of inflammation (DD21039). icotrokinra dose-dependently inhibited IL-23-induced expression of IL-17A, IL-17F, TNF and IL-22 mRNA in ear tissue. From 10 mg/kg, icotrokinra also reduced IL-23R expression. icotrokinra reduced erythrema and ear thickening from the lowest dose onwards.

A once daily oral regimen at 20 mg/kg or twice daily subcutaneous regimen at 2 mg/kg inhibited cytokine expression but had no or less effect on erythema and ear thickening. From 1 mg/kg BID, the potency of icotrokinra was similar or stronger as compared to that of an anti-IL-23 antibody (anti-IL-23p19, 10 mg/kg IP QD).

In plasma, icotrokinra was only detected at the highest dose of 300 mg/kg BID (22 ng/mL). In ear tissue, exposure was measured from 10 mg/kg BID onwards (26.9 up to 1890 ng/g at the high dose), indicating that icotrokinra distributes to tissues. In the contralateral ear in which no inflammation was induced, the concentration of icotrokinra was about 2-fold higher (only measured in 10 and 30 mg/kg groups).

4.3.1.2. Secondary pharmacodynamics

Off-target binding or enzyme inhibition was evaluated against a panel of 44 targets including receptors, ion channels, transporters and enzymes (DD20022). At a concentration of 10 µM, no inhibition or activation >50% was observed for any of the targets. For two intracellular enzymes, COX1 and PDE3A, only a slight increase in activity (28.2% and 37.6%, respectively) was observed. The *in vivo* relevance of this effect at 10 µM (19 µg/mL) is very low given the much lower clinical exposure level (plasma-protein unbound $C_{max,ss}$ of 1.41 ng/mL at the recommended clinical regimen of 200 mg QD).

To investigate the potential risk of latent *M. tuberculosis* infection (LTBI) reactivation with icotrokinra, an *in vitro* model was developed to evaluate the impact of icotrokinra on TB antigen-specific immune responses by cells derived from LTBI donors (n=6). Icotrokinra (1 nM – 1 µM) did not inhibit intracellular IFNγ production by memory CD4+ T cells, memory $CD4^+$ T cell proliferation or IFNγ secretion by PBMCs. The positive control adalimumab (10 µg/mL), an anti-TNFα antibody, inhibited all three readouts.

4.3.1.3. Safety pharmacology

The safety pharmacology of icotrokinra was evaluated in a core battery of dedicated GLP-compliant studies. Chosen species for *in vivo* studies were rats and monkeys, given that binding data demonstrated similar affinity of icotrokinra for human, monkey and rat IL-23R, in the low pico-molar range.

To identify effects on the cardiovascular system, two *in vitro* hERG assays were performed. In the first study, which was performed at 34 ± 1 °C, icotrokinra at 0.78, 3.7, 14 and 927 µM reduced hERG K^+ channel current by 0%, 9.1%, 44.6%, and 24.6%, respectively (PTG-B2-017). In the second study, which was performed at near-physiological temperature (35-37°C), icotrokinra at 10 µM (19.0 µg/mL), 100 µM (190 µg/mL) and 300 µM (569 µg/mL) inhibited hERG K^+ channel current by 16.8%, 23.4% and 23.7% (TOX16822). In these studies, the IC_{50} values were not calculated but the IC_{50} for hERG inhibition can be considered to be higher than 14 µM (26.6 µg/mL free base), which corresponds to a >1000-fold safety margin versus the human modelled plasma protein-unbound $C_{max,ss}$ at 200 mg QD.

Cardiovascular safety was also evaluated *in vivo*. In a dedicated single oral dose study in conscious, telemetered monkeys, icotrokinra up to 300 mg/kg did not affect ECG parameters, heart rate or blood

pressure (PTG-B2-008), leading to an estimated safety margin of 57-fold at the NOEL. Furthermore, in the repeat-dose toxicity studies in monkeys, ECGs did not identify any adverse cardiovascular changes at exposures margins >300-fold.

Effects on the respiratory system were studied in rat via whole-body plethysmography following a single oral dose of icotrokinra up to 600 mg/kg (PTG-B2-015). No changes in respiratory function (tidal volume, respiration rate, minute volume) were observed, leading to an estimated safety margin of 48-fold at the NOEL.

CNS safety was evaluated in rat using the modified Irwin test following a single oral dose of icotrokinra up to 600 mg/kg (PTG-B2-016). There were no behavioural effects or CNS observations, leading to an estimated safety margin of 48-fold at the NOEL.

In addition, there were no adverse findings related to respiratory or CNS effects in the repeat-dose studies in rats and monkeys.

4.3.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed with icotrokinra. This is accepted given the high specificity for its target.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

Permeability studies

Permeability studies in Caco-2 cell monolayers showed very low icotrokinra permeability when incubated at 100 µM (P_{app} 0.134×10^{-6} cm/s after 30-minute incubations). Similarly, incubation of LLC-PK1 cells at 1-300 µM icotrokinra showed P_{app} values of $0.13\text{-}1.9\times10^{-6}$ cm/s. Icotrokinra was shown to be no substrate or inhibitor of P-gp using LLC-PK1 MDR1 knockout cells.

Single-dose studies

In mice dosed intravenously with 2 mg/kg, low clearance (9.24 ml/min/kg) and low volume of distribution (0.58 L/kg) were observed, resulting in a short half-life of 0.93 h. In orally dosed mice (20 mg/kg), t_{max} was 1-2 h and bioavailability was very low (<0.6%). In MDR1 (P-gp) knockout mice, no significant differences with regard to C_{max}, t_{max} and $AUC_{0\text{-}8h}$ were observed when compared to wild-type mice after a 40 mg/kg oral dose, indicating no involvement of P-gp.

In SD rats dosed intravenously with 2 mg/kg, low clearance (9.19 ml/min/kg ≈ 0.55 L/h/kg) and V_{ss} (0.57 L/kg) were observed, resulting in a short half-life of 0.91 h. A 2 mg/kg intravenous dose in bile-duct cannulated rats resulted in a similar half-life (0.88 h), with clearance of 5.02 ml/min/kg (≈ 0.30 L/h/kg) and V_{ss} of 0.29 L/kg. A third study compared icotrokinra disposition following intravenous (2 mg/kg), oral (20-300 mg/kg) and subcutaneous dosing (2 mg/kg). Half-life after intravenous dosing was 0.76 h. Oral dosing of 30-300 mg/kg showed fast absorption (t_{max} 0.5-1.0 h) and very low bioavailability (0.1-0.3%), with no and less than dose-proportional increases in C_{max} and AUC between 30-300 mg/kg, respectively. SC dosing of 2 mg/kg revealed 116% bioavailability. A food effect was observed, as fed rats hardly showed significantly lower exposure when compared to fasted rats receiving a 10 mg/kg oral dose. A comparison of 10 mg/kg oral dosing between bile-duct cannulated and intact rats showed slightly increased C_{max} and AUC_{last} values for bile-duct cannulated rats, with a concurrent increase of bioavailability from 0.13 to 0.22%, indicating a potential role for presence of bile in the intestine in icotrokinra absorption. Finally, a comparison between acetate and hydrochloride

salt forms of icotrokinra using 70 and 200 mg/kg oral dosing in fed rats revealed no significant differences with regard to AUC_{last}, C_{max} and bioavailability.

In dogs receiving a 0.5 mg/kg intravenous dose, clearance was low (1.37 ml/min/kg ≈ 0.08 L/h/kg), as well as volume of distribution (0.40 L/kg), resulting in a half-life of 3.4 h. Oral dosing of 10 mg/kg resulted in fast absorption (t_{max} 0.5-1 h) and low bioavailability of 0.67%. A food effect was observed in dogs receiving a 100 mg dose, with approximately 20% of exposure observed for fed state dogs when compared to fasted state dogs, with similar t_{max} values for both prandial states. A cross-over design, comparing different oral doses of 50 mg IR formulations (SMCC based or mannitol based) and the 50 mg tablet used in a phase 2B study, revealed similar C_{max} and AUC values for all three formulations. A cross-over design comparison of three formulations dosed at 200 mg (2 x 100 mg phase 2B tablets, 2 x 100 mg phase 3 tablets or 1 x 200 mg phase 3 tablets) revealed slightly higher exposure for the 2 x 100 mg phase 3 tablets although variation was high, with similar exposures for the 2 x 100 mg phase 2B tablets and the 1 x 200 mg phase 3 tablet.

In cynomolgus monkeys dosed intravenously with 1 mg/kg, clearance was low (1.84 ml/min/kg), as was volume of distribution (0.35 L/kg), resulting in a short half-life of 2.8 h. In a second monkey study, similar clearance and volume of distribution were observed after an intravenous dose of 1 mg/kg, resulting in half-life of 3.5 h. Oral dosing of 2.5, 7.5 and 22.5 mg/kg resulted in fast absorption (t_{max} 0.5-4 h for all three dose levels), while C_{max} and AUC increased dose-proportionally. Bioavailability was low, ranging from 0.25-0.30%. In a tolerability study, single-doses of 50, 300, 600 and 1000 mg/kg to males resulted in less than dose-proportional increase in C_{max} and AUC values, while absorption was fast (t_{max} 1-2 h). Females dosed with 300 mg/kg showed similar C_{max} and AUC when compared to the males dosed with 300 mg/kg.

Multiple-dose studies

After 28 days, mice dosed with 150, 500 or 1500 mg/kg/day showed less than dose-proportional increases in exposure for both males and females. There were no significant differences between males and females, except at the 150 mg/kg dose level, where exposure in females was more than 2-fold increased over males. In general, no or low accumulation upon multiple dosing was observed (accumulation ratios males ~1.2-1.6, females ~1.5-4.9). ADAs were observed in 5/12 animals receiving 150 mg/kg, in 4/12 animals receiving 500 mg/kg and in 2/12 animals receiving 1500 mg/kg. Exposure of icotrokinra unbound to ADAs was 82-98% of total icotrokinra, indicating only low impact of ADAs on exposure of either total or free icotrokinra.

After 26 weeks, mice dosed with 50, 150 or 500 mg/kg/day showed less than dose-proportional increases in exposure for both males and females. In general, exposure of total icotrokinra in females was higher than in males, with exposure ratios for female/male ranging from 0.38-2.4. For free icotrokinra (unbound to ADAs), female/male exposure ratios ranged from 0.73-1.2. Low to high accumulation was observed at all dose levels for both sexes, and was especially pronounced for total icotrokinra, with accumulation ratios (Ra) ~2.1-22 for males and ~5.3-10 for females. Using free icotrokinra (unbound to ADAs), accumulation ratios were lower: ~2.2-3.5 for males and ~2.8-4.5 for females. Therefore, ADAs are hypothesised to play a role in the observed accumulation of icotrokinra in mice. ADAs were observed in 51/59 animals receiving 50 mg/kg/day, in 51/56 animals receiving 150 mg/kg/day and in 30/44 animals receiving 500 mg/kg/day. Across dose levels, exposure of icotrokinra unbound to ADAs was 30-100% of total icotrokinra.

After 6 days of dosing rats with 50, 300 or 1000 mg/kg/day, exposure increased dose-proportionally, with no accumulation observed (accumulation ratios for males ~0.34-1.4, females ~1.2). Exposure in females (dosed only at 300 mg/kg) was comparable to males and showed similar accumulation. No analysis of ADA formation was performed but ADA levels are expected to be low given the short dosing period.

After 14 days of dosing rats with 70, 200 or 600 mg/kg/day, exposure increased less than dose-proportionally, with no or only small differences between males and females (male/female exposure ratios ranging from ~0.39-1.3). High levels of accumulation were observed for both sexes, with accumulation ratios ranging from ~4.5-47 for males and from 19-28 for females. No analysis of ADA formation was performed. After 1 month of dosing male rats with 70 or 200 mg/kg/day, exposure increased less than dose-proportionally. Accumulation was high, with accumulation ratios ranging from ~31-56. No analysis of ADA formation was performed. After 6 weeks of dosing male rats with 5, 20 or 70 mg/kg/day, exposure increased less than dose-proportionally. Accumulation ratios ranged from ~105-222, indicating high accumulation. No analysis of ADA formation was reported.

In another 6 weeks study using both male and female rats dosed with 5, 20 or 70 mg/kg/day, similar trends were observed: after 6 weeks, exposure increased less than dose-proportionally for both sexes. There were no relevant differences between females and males, with female/male exposure ratios ranging between ~0.43-1.14. When correcting for unbound icotrokinra (unbound to ADAs), the female/male exposure ratios were ~0.48-2.0. High accumulation was observed at all dose levels for both sexes, and was especially pronounced for total icotrokinra, with accumulation ratios ~85-289 for males and ~106-239 for females. ADAs were observed in 11/12 animals receiving 5 mg/kg/day, in 12/12 animals receiving 20 mg/kg/day and in 11/11 animals receiving 70 mg/kg/day. Across dose levels, exposure of icotrokinra unbound to ADAs was 7.60-13.4% of total icotrokinra for both sexes, resulting in significantly lower accumulation ratios for free (unbound to ADA) icotrokinra comparted to total icotrokinra, supportive of ADA-driven accumulation.

After 6 months of dosing rats with 1, 5 or 20 mg/kg/day, exposure increased less than dose-proportionally for both sexes. There were no relevant differences between females and males (female/male exposure ratios ranging between 0.5-2), except for the 20 mg/kg/day dose level (ratio female/male ~0.24). When correcting for unbound icotrokinra (unbound to ADAs), the female/male exposure ratios were all between 0.5-2. High accumulation was observed at all dose levels for both sexes, with accumulation ratios ~92-194 for males and ~16-194 for females. ADAs were observed in 23/24 animals receiving 1 mg/kg/day, in 24/25 animals receiving 5 mg/kg/day and in 21/23 animals receiving 20 mg/kg/day. After daily dosing at 20 mg/kg/day (no data collected at other dose levels or time points in the study) for 26 weeks, 15 out of 16 rats were classified as NAb-positive. Across dose levels, exposure of icotrokinra unbound to ADAs was 6.2-21% of total icotrokinra for both sexes.

After 1.5 years of dosing rats with 5, 10 or 20 mg/kg/day, exposure increased less than dose-proportionally for both males and females. There were differences between females and males (female/male exposure ratios ~1.5-4.7), although these differences were not observed at other time points. When correcting for unbound icotrokinra (unbound to ADAs), the female/male exposure ratios were ~0.5-3.1. High accumulation was observed at all dose levels for both sexes, and was especially pronounced for total icotrokinra, with accumulation ratios ~13-25 for males and ~33-41 for females. ADAs were observed in all rats after 7 weeks of dosing, and in all rats tested until the end of the study. Across dose levels, exposure of icotrokinra unbound to ADAs was 5.7-29% of total icotrokinra for both sexes.

In the FEED study, female rats receiving 5, 20 or 70 mg/kg/day from 21 days prior to mating until GD7, exposure increased less than dose-proportionally at GD7. When compared to study day 19, there was no or low accumulation of icotrokinra at GD7, with accumulation ratios ~1.1-3.8. When using unbound icotrokinra, accumulation ratios were ~1.6-6.9. The majority of the rats treated with icotrokinra were positive for ADAs at GD7 (18/20 receiving 5 mg/kg/day, 20/20 for both 20 and 70 mg/kg/day). Exposure of icotrokinra unbound to ADAs was 5% to 14% of the total exposure.

In the EFD study, female rats receiving 70, 200 or 1000 mg/kg/day from GD6 until GD17, exposure increased dose-proportionally at GD17. When compared to GD6, there was accumulation of icotrokinra

at GD17, with accumulation ratios ~4.6-9.0. The majority of the rats treated with icotrokinra were positive for ADAs at GD17 (5/6 receiving 70 mg/kg/day, 6/6 receiving 200 mg/kg/day and 5/6 receiving 1000 mg/kg/day). Exposure of icotrokinra unbound to ADAs was 17% to 43% of the total exposure.

In the PPND study, female rats receiving 20, 70, or 200 mg/kg/day from GD6 until LD20, exposure increased less than dose-proportionally at LD20. When compared to LD4, there was no accumulation of icotrokinra at LD20, with accumulation ratios 0.44-0.73. This low accumulation might be explained by potential ADA formation before LD4. Most rats treated with icotrokinra were positive for ADAs at LD12 and LD20 (17/19 receiving 20 mg/kg/day and 23/23 for both the 70 and 200 mg/kg/day receiving group). ADA formation was not studied before LD12. Exposure of icotrokinra unbound to ADAs was 6.4% to 18% of the total exposure.

In female rabbits receiving 50 or 200 mg/kg/day for 14 days, exposure increased dose-proportionally after 14 days. Accumulation was low, with accumulation ratios of 1.3 and 2.1, respectively, for the 50 and 200 mg/kg/day dose levels. No analysis of ADA formation was performed.

In the EFD study, female rabbits receiving 50, 200 or 500 mg/kg/day from GD7 to GD19, exposure increased more than dose-proportionally at GD19. No or minimal accumulation was observed, with accumulation ratios of ~0.62-2.4. As expected, there were no rabbits that were ADA positive at GD19 (0/27 for 50, 200 and 1000 mg/kg/day combined dose levels).

In cynomolgus monkeys receiving 2.5 mg/kg/day for 5 days, accumulation was absent, with accumulation ratios of 0.77-1.00 for either BID (1.25 mg/kg) or QD (2.5 mg/kg) dosing.

In cynomolgus monkeys receiving 10, 100 or 300 mg/kg/day for 14 days, exposure increased less than dose-proportionally for males, and dose-proportionally for females. In general, female exposure was slightly higher than male exposure, with male/female exposure ratios of 0.6-1.0. Accumulation was not observed, with accumulation ratios of ~0.9-1.7 for males and ~1.3-1.6 for females. No analysis of ADA formation was performed.

In cynomolgus monkeys receiving 30, 200 or 600 mg/kg/day for 17 weeks, exposure increased dose-proportionally for males, and less than dose-proportionally for females. In general, female exposure was slightly lower than male exposure, with female/male exposure ratios of 0.5-0.7. Accumulation was absent or low, with accumulation ratios of ~1.4-2.5 for males and ~0.9-1.8 for females. Approximately 45% of the monkeys treated with icotrokinra were positive for ADAs after 17 weeks (1/6 receiving 30 mg/kg/day, 5/6 receiving 200 mg/kg/day, and 2/6 receiving 600 mg/kg/day). Exposure for animals with ADAs were approximately 2 to 4-fold greater than values for animals with no ADAs. Exposure of icotrokinra unbound to ADAs was 26% to 112% of the total exposure. Analysis of neutralising antibodies was not performed.

In cynomolgus monkeys receiving 20, 75 or 200 mg/kg/day for 9 months, exposure appeared to increase more than dose-proportionally for males, and less than dose-proportionally for females, although variation was very high for some dose levels. In general, female exposure was slightly lower than male exposure, with female/male exposure ratios of 0.5-0.9 for the 75 and 200 mg/kg/day dose levels (female/male ratio 75 mg/kg/day was ~14). Accumulation was low to high, with accumulation ratios of ~1.8-7.4 for males and ~5.9-24 for females. Approximately 96% of the monkeys treated with icotrokinra were positive for ADAs after 9 months (7/8 receiving 20 mg/kg/day, 8/8 receiving 75 mg/kg/day, and 12/12 receiving 200 mg/kg/day). Neutralising antibodies were not observed for any of the samples tested at the end of recovery period (only 200 mg/kg/day tested). Exposure of icotrokinra unbound to ADAs was 15% to 81% of the total exposure.

4.3.2.2. Distribution

In vitro

Plasma protein binding (PPB) studies of icotrokinra were performed using classical equilibrium dialysis with plasma from pooled mixed gender mice (C57BL/6), rats (SD), monkey (Cynomolgus), human and pooled female rabbit (New Zealand White (NZW)). Plasma protein binding was moderate across all species and independent of the concentration. The fraction unbound (Fu) of icotrokinra was comparable in plasma from most preclinical species and human (Fu ~0.5) but about 20% lower in rabbit plasma (0.3). icotrokinra binding to human serum albumin (4% HSA, Fu 0.70) appeared to be higher than to human α1-acid glycoprotein (0.14% AAG, Fu 0.92).

In addition, the binding of icotrokinra to SD rat, cynomolgus monkey and human kidney tissue homogenates was evaluated *in vitro* using equilibrium dialysis. The percent unbound of icotrokinra ranged from 7.2% to 8.9% (rat), 7.3% to 10.7% (monkey) and 3.2% to 7.0% (human), respectively. On average the percentage unbound in kidney homogenate was comparable for both rat and monkey, while slightly lower in human kidney tissue, but at least more than 5-fold lower than in plasma.

The blood/plasma (B/P) ratio was studied *in vitro*, using pooled gender human, cynomolgus monkey, beagle dog, and Sprague Dawley rat whole blood spiked with icotrokinra and found to range from 0.49 to 0.85 (rat), 0.60 to 0.86 (dog), 0.43 to 0.80 (monkey) and 0.49 to 0.77 (human) suggesting a low distribution into blood cells.

In vivo

The *in vivo* tissue distribution of ^{14}C-icotrokinra was investigated after a single oral dose of 300 mg/kg (15 MBq/kg) using quantitative whole-body autoradiography (QWBA) in the male Lister Hooded rat (partially pigmented, n=1/time point) and, in addition, after 1, 4 and 24 hrs upon IV dosing (2 mg/kg, 3.8 MBq/kg). Following oral administration, radioactivity largely distributed to the GI tract and excretory tissues, where the highest ^{14}C-related radioactivity was found at 3-hour post-dose and for the other tissues at 3 - 24h post-dose. Tissue to Blood ratios (T/B), based on $AUC_{0\text{-last}}$, was 14-72x for intestine and 26x for stomach. Apart from the digestive tract, the highest T/B ratios were found in the excretory organs, including liver (2x), kidney (~4x), harderian gland (8x) and bone marrow (4x). In the other tissues, ^{14}C-label was mostly low (T/B <1x), too low to calculate or absent. The lowest ratios were seen in brain, spinal cord and eye lens. For most tissues at 168 hrs post-dosing, radiolabel was below the limit of detection. Upon IV dosing, a similar distribution profile was found, although now label was observed in all tissues studied with T_{max} mostly after 1 h. Apart from the kidney (T/B 84x), the highest T/B was seen in ear cartilage (5x), skin (2x) and stomach wall (1.6x). All other were lower than plasma level (1.6x). Preferential binding to melanin did not seem to be present given the uveal tract and (non)-pigmented skin values.

In a separate experiment, the above tissue distribution results were confirmed in Sprague Dawley rats, which were dosed IV with 2 mg/kg icotrokinra, after which tissue (brain, colon, epididymal fat, kidney, liver and skin) and plasma samples were collected at 0.167 up to 24 hours post-dose. AUC based T/Plasma ratios were 15x for kidney, 0.7x for skin, 0.2x for liver and 0.47x for colon. The tissue elimination half-live (T½) was found to be about 1 hour.

In two further studies tissue samples were collected and analysed for icotrokinra content. These include (1) skin tissues from SD rats dosed orally or subcutaneously for 7 days and (2) colon tissue from SD rats dosed orally for 7 days. icotrokinra content in skin followed the plasma profile with $AUC_{0\text{-last}}$ comparable to plasma and T_{max} at 1- 3 h after dosing. At 24 h, icotrokinra was not detectable in skin or plasma. The colon tissue was examined 24 h after last dosing and the tissue concentration found to be 1000 – 5500-fold higher than in plasma. However, although rinsed three times, contamination with non-absorbed icotrokinra cannot be excluded.

Maternal transfer of icotrokinra was studied in the PPND study following daily oral administration of icotrokinra (20, 70, or 200 mg/kg/day) to SD rats from GD6 to LD20. Maternal transfer of icotrokinra from the dam to pups was seen as in all pup plasma samples at 4 h post-dose on PND4 and PND12 icotrokinra was detected. Pup-to-dam concentration ratios ranged from 0.0048 to 0.29.

The *in vivo* tissue distribution of icotrokinra was also investigated in cynomolgus monkey by collecting tissues from other PK or toxicology studies. In a PK/mass balance study ^{14}C-icotrokinra (SD, PO, 300 mg/kg, 100 µC/kg) was administered to two male cynomolgus monkeys (see excretion); QWBA analysis of one residual animal carcass showed all tissues were BLQ at 96 hrs post-dosing.

In a PK study male cynomolgus monkeys were treated with icotrokinra (PO) for 5 days. Thereafter, at necropsy, the GI tract was recovered. The duodenum, jejunum, ileum, cecum, proximal colon, and distal colon were separately collected and rinsed. icotrokinra (C12h & C24h) was generally detected at higher levels in the large intestine (proximal and distal colon, cecum) than in the small intestine (duodenum, jejunum, and ileum).

In another PK study, tissue distribution of icotrokinra was measured in monkeys after IV dosing (1 mg/kg). On Day2 tissues (n=2) were collected at 1.5 and 6 h after dosing. icotrokinra was present in entheseal tissue and ligament/tendon tissue at concentrations similar to plasma and modestly lower than plasma in skin and intestinal tissues.

4.3.2.3. Metabolism

In vitro

In vitro metabolic profiling showed a high stability of icotrokinra in various matrices. High *in vitro* metabolic stability (90 – 126%) was found upon incubation of icotrokinra (0.01 - 1 µM) in plasma from C57BL/6 mice, Sprague Dawley rats, cynomolgus monkeys, and humans. icotrokinra (1 µM) also showed high metabolic stability (92 - 97%) upon 120 min incubation with hepatocytes from Sprague Dawley rats, cynomolgus monkeys and humans. When using kidney tissue homogenates, the metabolic stability of icotrokinra (0.02 - 2 µM) was slightly higher for rat (85% - 106%) and human (85% - 126%) as compared to monkey (57% - 62%). Similarly, high metabolic stability (75-112%) was seen with various GI matrices from Sprague Dawley rats, cynomolgus monkeys, and humans, such as faecal homogenates, intestinal mucosal scrapings, simulated gastric fluid and purified GI enzymes pepsin, trypsin, chymotrypsin, or pancreatin.

In vitro metabolic profiling using faecal homogenates from Sprague Dawley rats, cynomolgus monkeys and humans incubated with 200 µM icotrokinra under anaerobic conditions yielded five metabolites (M5, M14, M26, M25, M6). These appear to be formed via sequential removal of amino acids from the carboxyl terminus of the molecule. M5 and M14 were found in rat and monkey faecal homogenate and M14, M26, M25, M6 in human.

Following incubation of ^{14}C-icotrokinra (20 µM, 24h at 37°C, FK14612) with kidney tissue homogenates (n=1/species) from rats, monkeys, and humans, two metabolites, M6 (11 – 36%) and M12 (4 – 22%), in addition to icotrokinra (49 – 84%), were detected in kidney homogenates from all three species. Metabolites M6 and M12 were detected also in the urine and faeces from rats and monkeys, while human urine only M12 was found.

In vivo

In rat, metabolite profiling was conducted in plasma, urine, and faeces following a single oral dose of ^{14}C-icotrokinra (300 mg/kg, 1.15 MBq/kg) to male Sprague Dawley rats. In plasma at 7 and 24 hrs post-dose, unchanged parent (95.8%) was the major component. Also, the minor metabolites M6, M16

and M27 were detected, however at trace amounts in urine, apart from unchanged drug (0.06%), a total of 8 minor metabolites (each <0.06%) were detected, while in faeces, apart from the unchanged (unabsorbed) parent (73%) the metabolites M14 (1.7%) and M16 (1.1%) were found. Overall, in the rat, unchanged parent drug was by far the major ^{14}C-related component detected in plasma and excreta, with small amounts of minor metabolites formed mostly as a result of amide hydrolysis (whether or not combined with subsequent acetylation) or oxidation.

The *in vivo* metabolism of icotrokinra was also investigated in two male cynomolgus monkeys after a single oral dose of 300 mg/kg ^{14}C-icotrokinra. Plasma analysed by liquid scintillation counting (1, 2, 4, 7, 24 h post dose) indicated that unchanged icotrokinra was the only ^{14}C-label detected. When plasma aliquots were further analysed by LC-MS/MS, trace amounts of four minor circulating metabolites were detected, which were formed via amide bond hydrolysis (M5, M6 and M14) and via deamidation (M16).

In monkey urine, about 0.86% of the oral ^{14}C-dose accounted for unchanged icotrokinra, while four additional minor (0.01% - 0.06%) metabolites M5, M7, M9 and M11 were detected. Due to the low oral bioavailability, the recovery in urine was only 0.93%.

In faeces, unchanged icotrokinra accounted for the majority of the ^{14}C-label, mainly due to the large amount of unabsorbed drug. In addition, seven minor metabolites (M5, M6, M8, M10, M12, M13 and M14) were observed, each accounting for 0.01% to 0.90% of radioactivity. Additionally, faecal samples from a monkey PK study, dosed with unlabelled icotrokinra, were examined using LC-MS/MS, yielding similar results.

Assessment of plasma in healthy human volunteers revealed only the unchanged drug (92.2% - 99.2%), although in some of the samples low levels based on semi-quantitative analysis of a subset of the metabolites M16 (0.2% - 6.0%), M16a (0.2% - 3.7%) and M16b (0.4% - 4.6%) were found. In conclusion, parent drug was the main drug-related species with no major circulating metabolites detected in plasma following oral administration of 200 mg icotrokinra in healthy participants.

In urine samples from these clinical studies only trace amounts of icotrokinra (0.0002% - 0.0007%) were detected, although when, in another study, urine samples were concentrated M12 could be detected. In conclusion, parent drug was the main drug-related species with no major circulating metabolites detected in plasma following oral administration of 200 mg icotrokinra in healthy participants.

4.3.2.4. Excretion

The excretion of ^{14}C-icotrokinra-related radioactivity was investigated in male SD rats (n=3) after an oral dose (300 mg/kg, 1.15 MBq/kg) and followed for up to 4 days (96 hrs). Following oral administration, ^{14}C-icotrokinra-related radioactivity quickly declined in plasma and was excreted through renal elimination (0.2%) but mainly present in the faeces (96.8%). The total recovery of radioactivity was high, with 76% already recovered after 24 hours. The high recovery in faeces upon oral dosing, however, consists mainly of unabsorbed drug due to the very low oral bioavailability of icotrokinra.

When icotrokinra was given intravenously to SD rats, the faecal excretion was only 0.25% at 24 hrs after dosing and renal excretion amounted to 15% of the dose administered.

In addition, in a study using bile duct cannulated rats dosed intravenously with icotrokinra, excretion into the bile and urine was 0.5% and 49% of the icotrokinra dose, respectively, indicating that urinary clearance is the major elimination route for icotrokinra and biliary clearance at least 100-fold lower.

Furthermore, in another study, excretion of icotrokinra into faeces was evaluated after a single oral or subcutaneous administration of icotrokinra to SD rats. The majority of the orally administered dose was recovered as unchanged icotrokinra in faeces (94%, 87%, and 100% for the 30, 100, and 300 mg/kg dose, respectively), while following SC dosing only 2.9% was excreted in faeces as unchanged icotrokinra. This confirms that upon oral administration, the faecal icotrokinra content mainly consists of unabsorbed drug.

Mass-balance studies were also performed in male cynomolgus monkeys using ^{14}C-icotrokinra given orally, showing that icotrokinra was found mostly in faeces as unabsorbed dose (67% at 96 hrs post-dosing), while ≤1% was excreted in urine. Additionally, in studies using unlabelled icotrokinra upon single- and multiple-dosing to male cynomolgus, similar faecal recoveries were seen ranging from 25% – 31% (24 h) to 37% – 47% (48 h) upon single- and up to 63% for multiple-dosing on Day 5. These results are in line with the rat studies, showing a very low bioavailability (<1%) resulting in a high faecal recovery of unabsorbed icotrokinra.

4.3.2.5. Pharmacokinetic drug interactions

The results of the pharmacokinetic Drug-Drug Interactions (DDI) studies with icotrokinra will be evaluated in the clinical assessment report.

4.4. Toxicology

4.4.1. Single-dose toxicity

One non-GLP oral single dose toxicity study with icotrokinra was conducted in cynomolgus monkeys to determine the maximum tolerated dose and toxicokinetic characteristics There were no icotrokinra-related findings when dosed in females at 300 mg/kg and in males up to 1000 mg/kg.

4.4.2. Repeat-dose toxicity

Pivotal GLP-compliant repeated dose studies were conducted in Sprague Dawley (SD) rats and Cynomolgus monkeys and comprised studies of 2 weeks, 6 weeks and 6 months duration in rats and 2 weeks, 17 weeks and 9 months duration in monkeys. Recovery groups were included in the 2-week and 6-month rat studies and in the 2-week and 9-month monkey studies. SD rats and Cynomolgus monkeys were selected as species for the investigation of systemic toxicological effects based on IL-23R homology in monkeys and PD activity and binding affinity in both rats and monkeys. All animals received a daily oral dose of icotrokinra.

In the 2-week GLP rat study, there were no icotrokinra-related findings up to the highest tested dose of 600 mg/kg, except for non-adverse decreased uterus weights (15-19%) at the end of the dosing phase in females given ≥200 mg/kg. At the NOAEL was 600 mg/kg/day, the corresponding AUC_{last} values on Day 14 were 5490 ng.h/mL in males and 13900 ng.h/mL in females, providing 150-fold and 379-fold safety margins, respectively, over the human exposure at 200 mg QD dose.

In the 6-week GLP rat study, there were no icotrokinra-related findings up to the highest dose tested of 70 mg/kg. At the NOAEL of 70 mg/kg, the corresponding AUC_{last} values at the end of the study were 11300 hr*ng/mL in males and 12100 hr*ng/mL in females. While systemic exposure to total icotrokinra increased following repeated administration, free icotrokinra levels were reduced to 1060 hr*ng/mL in males and 1620 hr*ng/mL in females. These levels correspond to 308/330-fold (total exposure in males/females) and 29/44-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD.

In the 6-month GLP rat study, there were no icotrokinra-related effects up to the highest dose tested of 20 mg/kg, including effects on male fertility. At the NOAEL of 20 mg/kg, the corresponding AUC (0-24) values at the end of the study were 2250 hr*ng/mL in males and 547hr*ng/mL in females. While systemic exposure to total icotrokinra increased following repeated administration, free icotrokinra levels were reduced to 211 hr*ng/mL in males and 117 hr*ng/mL in females. These levels corresponded to 61/15-fold (total exposure in males/females) and 6/3-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD. There was sufficient inhibition of IL-23-induced of cytokine IL-17A production upon *ex vivo* blood stimulation with 4 ng/ml IL-23 when animals were dosed with 5 and 20 mg/kg. Animals given 20 mg/kg/day showed statistically significant inhibition of IL-23R binding-dependent bioluminescence reporter activity at the end of the dosing period. At the end of the recovery period, 15 out of 16 animals treated at 20 mg/kg were classified as positive for neutralizing antibodies (NAbs). None of the 16 samples from the control group were positive for anti-icotrokinra NAb at the end of the recovery period.

In the 2-week GLP monkey study, there were no icotrokinra-related findings up to the highest dose tested of 300 mg/kg/day. The corresponding AUC_{0-24} values on Day 14 were 1770 ng.h/mL in males and 3030 ng.h/mL in females, providing 48/83-fold safety margins over the human exposure at 200 mg QD dose.

In the 17-week GLP monkey study, there were no icotrokinra-related findings up to the highest dose tested of 600 mg/kg/day. The corresponding AUC_{0-24} values for total icotrokinra on Day 116 were 9440 ng.h/mL in males and 4610 ng.h/mL in females. With ADAs detected in 44% of the treated monkeys, free icotrokinra AUC_{0-24} values were 6370 ng.h/mL in males and 4720 ng.h/mL in females. These levels corresponded to 257/126-fold (total exposure in males/females) and 173/129-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD.

In the 9-month GLP monkey study, there were no icotrokinra-related toxicity findings up to the highest tested dose of 200 mg/kg/day. Age at initiation of dosing was 2.5-3.2 years old for males and 2.5-4.1 years old for females, which corresponds to the (pre-)pubertal developmental stage. Evaluation of immunophenotyping indicated no icotrokinra-related changes in the absolute counts or relative percentages of natural killer cells, total T-lymphocytes, T-helper lymphocytes, T-cytotoxic lymphocytes, B-lymphocytes, or monocytes. All animals produced anti-keyhole limpet hemocyanin (KLH) IgM and IgG responses after KLH immunisation (Day 162). icotrokinra-related decreases in anti-KLH IgM responses were observed in all dose groups on Days 169 through 190. icotrokinra-related decreases in anti-KLH IgG responses were observed mainly in females at ≥75 mg/kg/day on Days 169 through 190. At the end of dosing, there was statistically significant inhibition of IL-23 receptor (IL-23R) signaling-dependent bioluminescence reporter activity in animals treated at ≥20 mg/kg. In addition, icotrokinra at ≥20 mg/kg inhibited *ex vivo* IL-23-mediated production of IFN-γ up to 78%, 81%, and 96%. Overall, these data suggest that the ADAs had no neutralising potential given that pharmacodynamic activity of icotrokinra was maintained. In samples from recovery animals (control and 200 mg/kg animals), no NAbs were found. The absence of a correlative finding for the effects on TDAR, points to the NOAEL at 200 mg/kg. At this dose, AUC_{0-24} levels total icotrokinra at day 273 were 14400 ng.h/mL in males and 12900 ng.h/mL in females. Free (unbound to ADA) icotrokinra AUC_{0-24} levels were 2190 ng.h/mL in males and 6760 ng.h/mL in females. These levels correspond to 392/351-fold (total exposure in males/females) and 60/184-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD.

4.4.3. Genotoxicity

In the GLP-compliant evaluations of gene mutations in the Ames test and structural chromosomal aberrations in human peripheral blood lymphocytes, icotrokinra was negative for genotoxicity. In an *in vivo* micronucleus and comet assay, the potential of icotrokinra to induce clastogenic activity and/or

numerical changes of chromosomes in bone marrow and DNA damage in kidney and colon was evaluated in male Sprague Dawley rats. The kidney was chosen as it is considered the main elimination route of absorbed icotrokinra and the colon because icotrokinra is poorly absorbed and the majority of the oral dose is excreted as unchanged drug. icotrokinra dosed for three days up to 2000 mg/kg did not increase the incidence of micronucleated polychromatic erythrocytes (MnPCEs) in the bone marrow micronucleus evaluation nor increase DNA damage the colon and kidneys in the Comet assay. Systemic exposure was confirmed in the plasma, colon and kidneys.

4.4.4. Carcinogenicity

In the 1-month GLP CByB6F1 hybrid mice study, there were no icotrokinra-related findings up to the highest dose tested of 1500 mg/kg. At the NOAEL of 1500 mg/kg, the corresponding AUC_{0-24} values at the end of the study were 3680 hr*ng/mL in males and 2910 hr*ng/mL in females. Free icotrokinra (unbound to ADAs) levels at this dose were to 3160 hr*ng/mL in males and 2390 hr*ng/mL in females. These levels correspond to 100/79-fold (total exposure in males/females) and 86/65-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD. Despite the very low binding affinity for the mouse IL-23R, at the end of the study, *ex vivo* stimulated whole blood demonstrated reversible inhibition of IL-23-mediated stimulation of IL-17A and IL-17A/F by 75% at icotrokinra doses of 500 and 1500 mg/kg/day when measured two hours post-dose, suggesting pharmacological activity at these doses.

In the 26-week GLP TG rasH2 mice carcinogenicity study, there were no icotrokinra-related neoplastic findings up to the highest dose tested of 500 mg/kg. A non-proliferative microscopic finding included minimal to mild edema in the nasal cavity lumen in males dosed with 50 and 150 mg/kg. Although a dose-response relationship was not demonstrated, due the lack of edema in males in the concurrent control group and the ranges being outside of the testing facility historical control data, a relationship of nasal cavity edema with icotrokinra administration could not be ruled out. However, it was considered non-adverse due to the low severity and sufficient area of unaffected nasal airway to not interfere with respiration. At the highest dose of 500 mg/kg, the corresponding AUC_{tlast} at the end of the study were 2780 hr*ng/mL in males and 6700 hr*ng/mL in females for total icotrokinra and 2770 hr*ng/mL in males and 2040 hr*ng/mL in females for free icotrokinra (unbound to ADAs). These levels correspond to 76/183-fold (total exposure in males/females) and 75/56-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD.

In the 2-year GLP rat carcinogenicity study, there were no icotrokinra-related neoplastic or non-neoplastic findings up to the highest tested dose of 20 mg/kg. There was a dose-related incidence of fatal fibroadenomas in the mammary gland of female rats, but the total number of animals having fibroadenomas were within the range of historical control of the testing facility and were therefore not icotrokinra-related. At 20 mg/kg/day, for total icotrokinra, the mean AUC_{0-24} values on Day 546 were 580 hr*ng/mL for males and 2700 hr*ng/mL for females, respectively. For free (unbound to ADA) icotrokinra, the mean AUC_{0-24} values on Day 546 were 99.5 hr*ng/mL for males and 307 hr*ng/mL for females, respectively. These levels correspond to 16/74-fold (total exposure in males/females) and 3/8-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD.

4.4.5. Developmental and reproductive toxicity

No dedicated male fertility study was conducted. Instead, male reproductive organs were assessed in a repeated dose toxicity study. There were no icotrokinra-related effects on fertility up to the highest tested dose of 20 mg/kg/day in orally dosed rats.

Female fertility was evaluated in a dedicated FEED study in rats with oral icotrokinra doses up to 70 mg/kg. There were no icotrokinra-related effects on reproductive performance (mating, fertility, and pregnancy indices), estrous cyclicity, intrauterine survival, gross necropsy findings, effects on ovarian weights or systemic toxicity at any dose level. The pre-coital interval in the 70 mg/kg/day group was statistically significantly decreased compared to the control group. However, the value was within the historical control data range and the change occurred in a direction generally not considered toxicologically relevant and was therefore considered incidental. In addition, there was a significantly higher mean post-implantation loss and number of early resorptions in the 20 mg/kg/day group compared to the control group. However, the increased post-implantation loss was mainly attributed to one female with 75.0% post-implantation loss and there was no dose-response relationship. The NOAEL in this study was 70 mg/kg. At 70 mg/kg/day, total mean $AUC_{0\text{-}24hr}$ values were 11600 and 12300 hr*ng/mL on Study Day (SD) 19 and Gestation Day (GD) 7, respectively. Due to the presence of ADAs in the majority of the animals, free icotrokinra (unbound to ADA) mean $AUC_{0\text{-}24hr}$ values were 975 and 1740 hr*ng/mL on SD 19 and GD 7, respectively. The mean maternal $AUC_{0\text{-}24h}$ values correspond to 316/27-fold (total/free exposure at SD 19) and 335/47-fold (total/free exposure at GD7) the modelled human steady-state exposure at 200 mg QD.

In the rat EFD study, there were no embryo-fetal developmental effects that could be attributed to icotrokinra up to doses of 1000 mg/kg. In the dams, lower mean body weight gains were noted in the 200 and 1000 mg/kg/day groups. However, these changes were considered non-adverse because they were minimal and did not affect the mean absolute body weights in these groups. The NOAEL for maternal toxicity and embryo-fetal developmental toxicity was the highest tested dose of 1000 mg/kg. ADAs were present in most animals treated with icotrokinra for TK evaluation. At 1000 mg/kg/day, the mean maternal $AUC_{0\text{-}24h}$ value on GD 17 was 10900 ng*h/mL for total icotrokinra and 3920 ng*h/mL for free (unbound to ADA) icotrokinra, corresponding to 297/107-fold the modelled human steady-state exposure at 200 mg QD, suggesting a low risk for humans.

In the dose-range finding study in non-pregnant rabbits, there were no icotrokinra-related effects up to the highest dose of 1000 mg/kg.

In the pivotal rabbit EFD study, there was an icotrokinra-related increase in the number of females that aborted on GD26 in the high dose group (500 mg/kg/day) which was considered adverse, with concomitant slight decreases in body weight gain and food consumption at this dose level. There were no icotrokinra-related developmental effects on the embryo/foetus at any dose level. It can be agreed that 200 mg/kg is the NOAEL for maternal toxicity and that 500 mg/kg is the NOAEL for embryofetal development. At the NOAEL for EFD of 500 mg/kg/day, the maternal $AUC_{0\text{-}24h}$ value on GD19 in rabbits was 5,770 ng*h/mL (1,652 ng*h/mL when corrected for 28.64% fraction unbound in rabbits) corresponding to an AUC multiple of 95-fold over the modelled human $AUC_{0\text{-}24h,ss}$ at the 200 mg QD dose of 36.7 ng*h/mL (17.4 ng*h/mL when corrected for 47.51% fraction unbound in humans).

In a rat PPND study, at 200 mg/kg/day icotrokinra one female was euthanised in moribund conditions on LD 2 after clinical signs and body weight loss were noted after delivery. The totality of macroscopic observations in the trachea and microscopic changes in the lung and heart were suggestive of gavage error and/or aspiration related to gavage dosing. Therefore, the mortality seen in this one dam was not considered related to icotrokinra. The pups from this litter were euthanised along with the mother (with clinical signs of cold to touch and the absence of a milk band), were noted as normal at necropsy and caused slightly lower, but non-significant, mean viability index in the 200 mg/kg/day group. All other F0 females survived to the scheduled necropsy. Regarding F1 locomotor activity, a statistically significantly higher mean number of ambulatory counts for the combined intervals was noted for males at 200 mg/kg/day (99.53) when compared to control (76.08). The individual interval values were within historical control data ranges and considered not icotrokinra-related. The NOAEL for F0 maternal toxicity, F1 neonatal, parental systemic, and reproductive toxicity, and F2 developmental toxicity was

200 mg/kg. Toxicokinetic analysis showed that almost all mothers and all F1 animals developed ADAs and that icotrokinra reaches the pup plasma, most likely via milk. At 200 mg/kg/day, the mean maternal $AUC_{0\text{-}24h}$ value on LD12 was 4660 ng*h/mL for total icotrokinra and 848 ng*h/mL for free (unbound to ADA) icotrokinra, corresponding to 127/23-fold the clinical AUC for total/free levels. On post-natal day 12, the mean pup-to-maternal plasma ratio for icotrokinra was 0.042 to 0.29.

A weight-of-evidence (WoE) evaluation was conducted considering the factors detailed in ICH S11 (EMA 2020a) and the available non-clinical and clinical data for icotrokinra and other approved drugs targeting the IL-23 pathway. Rats used in the chronic toxicity studies were at an age which can be compared to an adolescent human, while the monkeys that were aged ≥2.1 years can be compared to humans aged >10 years. icotrokinra is a peptide that exhibits selectivity and subnanomolar inhibitory potency against the human IL-23R with low potential for off-target toxicity. There was no target organ toxicity in rats and monkeys dosed with icotrokinra for up to 6 months and 9 months, respectively, or any other clinically relevant adverse effects. The main potential concern associated with IL-23 inhibition in young children is impact to the developing immune system, potentially leading to an increased susceptibility to infections. No meaningful changes suggestive of immunotoxicity at high safety margins have been observed in lymphoid organs, clinical pathology parameters, immune cell populations or the T-cell mediated antigen response in adolescent monkeys aged 2 to 4 years treated with icotrokinra for up to 9 months. Data from approved monoclonal antibodies targeting the IL-23 pathway, including ustekinumab and guselkumab which are marketed for the treatment of moderate to severe psoriasis, also support a low risk for adverse effects on the developing immune system.

4.4.6. Toxicokinetics and exposure margins

Toxicokinetics of icotrokinra was studied in the 28 days and 26 weeks repeat-dose studies in mice, in the 7 days, 14 days, 28 days, 6 weeks, 26 weeks and 104 weeks repeat-dose, fertility- and early embryonic development, embryofetal development, and pre- and postnatal development studies in rats, in the 14 days and embryofetal development study in rabbits, and in the 5 days, 14 days, 17 weeks and 39 weeks repeat-dose studies in monkeys.

Interspecies comparison

PK studies in mice, rats, dogs and monkeys revealed low clearance across species, with clearance values of 9.24, 9.19, 1.37, and 1.84 mL/min/kg, respectively. Volume of distribution (V_{ss}) was low across species, with values reported at 0.58, 0.57, 0.40, and 0.35 L/kg in the mouse, rat, dog, and monkey, respectively. Short half-life values of 0.93, 0.91, 3.4, and 2.8 hours were observed for mouse, rat, dog, and monkey, respectively, which is well below the half-life in humans of ~12 hours. icotrokinra was rapidly absorbed, with t_{max} values reported between 0.5 and 4 hours for all four nonclinical species. The absolute bioavailabilities were very low: <0.7% for all four nonclinical species, whereas absolute bioavailability for humans was not reported (no IV study). Across nonclinical species, no relevant differences between males and females were observed. High levels of AUC accumulation were observed upon multiple dosing for mice, rat and monkey studies, which are hypothesised to be related to ADA formation and subsequently decreased clearance of ADA-bound icotrokinra. In humans, accumulation was not observed, correlating with low levels of ADA formation (~10%), and no neutralising ADAs.

Plasma protein binding of icotrokinra was not concentration dependent for any of the species tested, with mean percentages of free icotrokinra of 44.0% to 46.6% (mouse), 48.8% to 52.1% (rat), 28.1% to 29.7% (rabbit), 49.3% to 56.3% (monkey) and 44.8% to 50.3% (human) at 0.01, 0.1 and 1 µM. Based on these differences, exposure multiples should be corrected for plasma protein binding for rabbit only, which results in somewhat decreased exposure multiples for rabbit studies. Plasma

stability of icotrokinra was found to be high given the lack of degradation during the *in vitro* PPB studies (18 h at 37 °C). icotrokinra distribution to red blood cells was shown to be negligible across species: the blood/plasma (B/P) ratio ranged from 0.49 to 0.85 (rat), 0.60 to 0.86 (dog), 0.43 to 0.80 (monkey) and 0.49 to 0.77 (human) suggesting a low blood cell distribution. At the clinical $C_{max,}$ less than 5% is expected to be in the blood cells.

In clinical studies using healthy participants, assessment of human metabolites in plasma revealed that no major metabolites were identified: the unchanged drug accounted for the vast majority of icotrokinra exposure (92.2% - 99.2%), although in some of the samples low levels of the metabolites M16 (0.2% - 6.0%), M16a (0.2% - 3.7%) and M16b (0.4% - 4.6%) were found based on semi-quantitative analysis of a subset of animals. In rat plasma, unchanged parent (95.8%) was the major component and, by LC-MS/MS, the minor metabolites M6, M16 and M27 were found. Overall, in the rat, unchanged parent drug was by far the major ^{14}C-related component detected in plasma. In monkey, plasma analysis indicated that unchanged icotrokinra was the only ^{14}C-label detected, similar to rat and human *in vivo* metabolism studies.

Excretion studies in IV-dosed bile duct-cannulated and intact rats showed that icotrokinra was primarily excreted in the urine, with a minor role for faecal excretion: ~49% of radioactivity was recovered in urine, and ~0.5% in bile. However, due to the very low bioavailability (<0.7%), upon oral dosing the majority of icotrokinra was observed in the faeces. This was also observed for the monkey. Together, these results indicate that excretion in rats occurs primarily via urine and subsequently faeces, however due to the very low bioavailability, the majority of orally dosed icotrokinra was observed unabsorbed in faeces for both nonclinical species.

Exposure multiples

The AUC based exposure multiples of 15-61 and 351-392 were observed in repeat-dose studies up to 6 months in rats and 9 months in monkeys, respectively, and >16 for carcinogenicity studies. For reproductive toxicity studies in rats, exposure margins were >100. For the rabbit, a correction for plasma protein binding has been applied in the interspecies comparison table, since the fraction unbound (Fu) of icotrokinra was about 40% lower in rabbit plasma (Fu 0.3) compared to human plasma (Fu ~0.5). Taking this into account, there is a safety margin of ~95-fold the clinical exposure. For the other species, exposure multiples were not corrected for plasma protein binding as they were minor differences compared to humans. Exposure margins were not corrected for ADA binding, while neutralising antibodies were observed for almost all rats of the 6 months rat study. No neutralising antibodies were observed in the 9 months monkey study. It should be noted that for patients with renal impairment, exposure margins may decrease since their exposures (based on AUC) were up to 2.78-fold higher and no dose adjustments are proposed.

4.4.7. Local tolerance

No dedicated local tolerance studies were conducted with icotrokinra. As icotrokinra is administered orally, this is agreed.

4.4.8. Other toxicity studies

Regarding antigenicity, icotrokinra induced ADAs in rats, and to a slightly lesser extent in monkeys and mice, with no formation of ADAs in rabbits. In rats, these ADAs had neutralising potential.

No dedicated immunotoxicity studies were conducted. No meaningful changes suggestive of immunotoxicity at high safety margins have been observed in lymphoid organs, clinical pathology

parameters, immune cell populations or the T-cell mediated antigen response in monkeys treated with icotrokinra for up to 9 months. In monkeys, evaluation of immunophenotyping indicated no icotrokinra-related changes in the absolute counts or relative percentages of natural killer cells total T-lymphocytes, T-helper lymphocytes, T-cytotoxic lymphocytes, B-lymphocytes, or monocytes. All animals produced anti-keyhole limpet hemocyanin (KLH) IgM and IgG responses after KLH immunisation. icotrokinra-related decreases in anti-KLH IgM and in anti-KLH IgG responses were observed.

No drug dependence studies were conducted. As it is not a CNS acting drug, this is agreed.

There are no major human metabolites insufficiently present in animals that require non-clinical testing.

Since the peptide-related impurities are specified at a limit of NMT 1.0%, toxicological qualification is not needed (qualification threshold of 1.0% for peptide-related impurities (European Pharmacopoeia 11.8, substances for pharmaceutical use)). However, for certain impurities, the limits for drug product shelf-life specifications are above 1.0%. A GLP 1-month repeat-dose toxicity study was conducted with one batch of icotrokinra that included all relevant impurities and a potential impurity in support of the process modification. Rats were dosed at 0, 70 or 200 mg/kg/day. There were no toxicological findings in this study that could be attributed to administration with icotrokinra and impurities. Therefore, the NOAEL in this study is 200 mg/kg.

The potential of phototoxicity by icotrokinra was evaluated in 3T3 mouse fibroblasts stimulated with icotrokinra concentrations up to 100 µg/mL (solubility limit). In the assay, both the IC50(-UVR) and the IC50(+UVR) could not be calculated (icotrokinra does not show cytotoxicity without or with UVR exposure), therefore the photoirritancy factor could not be calculated. The mean photo effect value was <0.100, indicating that the test article has no phototoxic potential. It can therefore be concluded that icotrokinra has no phototoxic potential in 3T3 mouse fibroblasts.

4.4.9. Ecotoxicity/environmental risk assessment

Table 3. Summary of main study results: Phase I

Substance (INN/Invented Name):	icotrokinra		
CAS-number (if available):	free base: 2763602-16-8 salt: 304949-48-4 / 2763602-17-9		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log K_{ow}	OECD 107	log D_{ow}: -2.2 at pH 5 -2.2 at pH 7 -2.2 at pH 9	Potential PBT: N
PBT/vPvB statement	icotrokinra is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
PEC_{sw}, *default*	1.0	µg/L	>0.01 threshold: Y

Phase I			
Other concerns (e.g. chemical class)			N

Table 4. Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	648 mg·L^{-1} at pH 5 and 19.8°C 43.1 mg·L^{-1} at pH 7 and 19.8°C 46.1 mg·L^{-1} at pH 9 and 19.8°C	shake flask
Dissociation in Water	OECD 112	pK_a = 6.0	
Adsorption-Desorption *Soil 1* = Speyer 2.1 (Loamy sand)	OECD 106	$K_{FOC, soil\ 1}$ = 4058 L/kg_{oc}	
Soil 2 = Speyer 2.3 (Sandy loam)		$K_{FOC, soil\ 2}$ = 4767 L/kg_{oc}	
Soil 3 = Speyer 6S (Clay)		$K_{FOC, soil\ 3}$ = 38467 L/kg_{oc}	
Sludge 1 = Tilburg (Municipal)		$K_{FOC, sludge\ 1}$ = 278 L/kg_{oc}	
Sludge 2 = AA & Maas (Municipal)		$K_{FOC, sludge\ 2}$ = 274 L/kg_{oc}	
Ready Biodegradability Test	OECD 301F	7-8 % (28 d) not readily biodegradable	

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	EC_{10}	>100,000	µg/L	growth rate
Daphnia sp. Reproduction Test/*D. magna*	OECD 211	EC_{10}	6800	µg/L	reproduction
Fish, ELS/FSDT/FFLC/*P. promelas*	OECD 210	NOEC	90	µg/L	weight
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10}	>1,000,000	µg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/	OECD 218	EC_{10}	>1912	mg/kg_{dw}	emergence ratio/ development rate, normalised to 10% o.c.

*Risk characterisation**				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
STP	10 µg/L	10,000 µg/L	0.0001	No risk
Surface water	1.0 µg/L	9.0 µg/L	0.11	No risk
Groundwater	0.25 µg/L	0.90 µg/L	0.28	No risk
Sediment	3.9 mg/kg_{dw}	>19 mg/kg_{dw}	<0.20	No risk

* Based on the log D_{ow} no risk is expected for secondary poisoning. Based on the $K_{FOC, sludge}$, no risk for the soil compartment is expected.

Considering the above data from Phase I and Phase II, icotrokinra is not expected to pose a risk to the environment.

A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

The pharmacology of icotrokinra has been sufficiently evaluated using *in vitro* assays as well as *in vivo* studies. icotrokinra was shown to specifically and potently target IL-23R, leading to inhibition of IL-23-induced inflammatory responses. The effect of icotrokinra seems specific to IL-23 signalling as it did not inhibit IL-12-induced STAT4 phosphorylation, though an effect on IL-12-induced IFN-γ secretion or other downstream pathways was not determined.

Sprague Dawley rat and Cynomolgus monkey were both shown to be pharmacologically relevant species based on sequence homology and *in vitro* activity studies.

In a rat model of skin inflammation, the concentration of icotrokinra was found to be about 2-fold higher in the contralateral ear in which no inflammation was induced, suggesting slightly reduced exposure in inflamed tissue. Another rat study was performed using a colitis model. While icotrokinra was shown to have anti-inflammatory activity in the colon, the relevance of this finding for the current indication is low. Limitations of the *in vivo* PD studies include the partly prophylactic treatment and twice daily dosing scheme, which are not comparable to the clinical situation. Nevertheless, the PD of icotrokinra is supported by clear efficacy in clinical trials.

Using a panel of 44 targets, no off-target activity by icotrokinra was observed up to 10 uM, which corresponds to a large safety margin to the clinical exposure level. Local tissue icotrokinra concentrations may be substantially higher than in plasma, as demonstrated in the *in vivo* PD study, though icotrokinra is not expected to enter the cell. The underrepresentation of intracellular off-targets is therefore acceptable. The applicant did not investigate potential off-target interactions with additional interleukin receptors, since no other cytokine receptors are known to share the IL-23R subunit.

The potential risk of latent *M. tuberculosis* infection (LTBI) reactivation with icotrokinra, was evaluated in an *in vitro* model using immune cells derived from LTBI donors. It was not explained if IL-23 was present (endogenous or supplemented). Without a control for active IL-23/IL-23R signaling, it cannot be concluded that inhibition of the IL-23 pathway, either by icotrokinra or an IL-23 antibody, does not modify the immune response to TB antigen. Furthermore, it should be noted that *in vivo* immune

complexity, drug pharmacokinetics and patient heterogeneity cannot be fully replicated *in vitro* (for more information see safety discussion). The SmPC section 4.3 contraindicates icotrokinra in clinically important active infections (e.g. active tuberculosis), while section 4.4 contains relevant warning that treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

The safety pharmacology of icotrokinra was evaluated in a core battery of dedicated GLP-compliant studies. No issues were identified.

Pharmacokinetics (PK)

The bioanalytical methods were developed and validated to support the PK/TK analyses of icotrokinra in rat, mouse, dog, rabbit and monkey plasma. Liquid chromatography with tandem mass spectrometry (LC MS/MS) methods were employed to analyse plasma samples from both GLP and non GLP nonclinical toxicology studies in rat, rabbit and monkey. A non-qualified LC-MS/MS method was used in different ADME-studies (e.g. FK13750, FK14275, FK13969), though the applicant clarified that quality control samples were analysed alongside study samples to ensure the reliability of the results.

PK studies in mice, rats, dogs and monkeys revealed low clearance across species, with clearance values of 9.2, 9.2, 1.4, and 1.8 mL/min/kg, respectively. Volume of distribution (Vss) was low across species, with values reported at 0.58, 0.57, 0.40, and 0.35 L/kg in the mouse, rat, dog, and monkey, respectively. Short half-life values of 0.9, 0.9, 3.4, and 2.8 hours were observed for mouse, rat, dog, and monkey, respectively, which is well below the half-life in humans of ~12 hours. icotrokinra was rapidly absorbed, with t_{max} values reported between 0.5 and 4 hours for all four nonclinical species. The absolute bioavailabilities were very low: <0.7% for all four nonclinical species, whereas absolute bioavailability for humans was not reported but anticipated to be <5%. Across nonclinical species, no relevant differences between males and females were observed. High levels of exposure (AUC) accumulation were observed upon multiple dosing for mice, rat and monkey studies, which are hypothesised to be related to ADA formation and subsequently decreased clearance of ADA-bound icotrokinra. In humans, accumulation was not observed, correlating with low levels of ADA formation (~10%), and no neutralising ADAs.

Plasma protein binding of icotrokinra was not concentration dependent for any of the species tested, with mean percentages of free icotrokinra of 45% (mouse), 50% (rat), 29% (rabbit), 53% (monkey) and 48% (human) at 0.01 to 1 µM. Based on these differences, exposure multiples were corrected for plasma protein binding for rabbit only, which resulted in somewhat decreased exposure multiples for rabbit studies.

Plasma stability of icotrokinra was found to be high given the lack of degradation during the in vitro PPB studies (18h at 37C). icotrokinra was also found to be stable in hepatocytes (1 µM) and kidney tissue homogenates (0.02 - 2 µM) from humans, monkey and rat. In addition, a high stability was seen with icotrokinra (50 µM) in various GI matrices from Sprague Dawley rats, cynomolgus monkeys, and humans, such as faecal homogenates, intestinal mucosal scrapings, simulated gastric fluid and purified GI enzymes.

icotrokinra distribution to red blood cells was shown to be negligible across species: the blood/plasma (B/P) ratio ranged from 0.49 to 0.85 (rat), 0.60 to 0.86 (dog), 0.43 to 0.80 (monkey) and 0.49 to 0.77 (human) suggesting a low blood cell distribution. At the clinical Cmax less than 5% is expected to be in the blood cells. Tissue distribution studies in rat and monkey showed that icotrokinra was rapidly and widely dispersed into most tissues including the absorption and excretory organs, skin, bone marrow and ear cartilage with lowest levels in brain, spinal cord and eye lens. Tissue levels generally followed the icotrokinra PK profile in plasma. There was no sign of a specific melanin retention in pigmented tissues (skin, uveal tract).

In clinical studies using healthy participants, the assessment of human metabolites in plasma revealed that no major metabolites were identified: the unchanged drug accounted for the vast majority of icotrokinra exposure (92% - 99%), although in some of the samples low levels of the metabolites M16 (0.2% - 6.0%), M16a (0.2% - 3.7%) and M16b (0.4% - 4.6%) were found based on semi-quantitate analysis of a subset of samples. In rat plasma, unchanged parent (96%) was the major component and, by LC-MS/MS, the minor metabolites M6, M16 and M27 were found. Overall, in the rat, unchanged parent drug was by far the major 14C-related component detected in plasma. In monkey, plasma analysis indicated that unchanged icotrokinra was the only 14C-label detected, similar as seen in rat and human *in vivo* metabolism studies.

Excretion studies in IV-dosed bile duct-cannulated and intact rats, showed icotrokinra was primarily excreted in the urine, with a minor role for faecal excretion: ~49% of radioactivity was recovered in urine, and ~0.5% in bile. However, due to the very low bioavailability (<0.7%), upon oral dosing the majority of icotrokinra was observed in the faeces. This was also observed for the monkey. Together, these results indicate that excretion in rats occurs primarily via urine and subsequently faeces, however due to the very low bioavailability, the majority of orally dosed icotrokinra was observed unabsorbed in faeces for both nonclinical species.

Toxicology

The submitted validation reports are adequate and compliant with ICH M10. Upon request, the applicant clarified which ADA methods used in the toxicity studies were qualified and which were validated. Validation reports for the determination of total JNJ-77242113 in rat, mouse, rabbit and monkey plasma are adequate and conform with ICH M10. Free (unbound to ADA) fraction of test substance was measured using qualified methods.

In rats dosed up to 6 months, there were no icotrokinra-related effects up to the highest dose tested of 20 mg/kg, including effects on male fertility, except for hypersensitive behaviour in male animals that increased in a dose-dependent manner. Most clinical observations resolved during the recovery phase. At the NOAEL of 20 mg/kg, there was an AUC based safety margin of 61/15-fold (total exposure) and 6/3-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD. High levels of AUC accumulation were observed which were hypothesised to be related to ADA binding, subsequently decreased clearance of ADA-bound icotrokinra and reduced unbound icotrokinra levels. icotrokinra blood levels of rats dosed ≥ 5 mg/kg remained sufficient to exert pharmacodynamic activity despite the presence of ADAs, although it is not known if the presence of ADAs hampers pharmacodynamic activity.

In monkeys dosed up to 9 months, there were no icotrokinra-related effects up to the highest dose tested of 200 mg/kg. According to immunophenotyping analyses, there were increases (e.g. increase in absolute NK cells, Tc, Th counts) observed for Animal Nos. 2501 (20 mg/kg/day) and 4003 (200 mg/kg/day) that fell outside the level of the time matched control group and pre-study values, with some values reaching statistical significance. As these changes were sporadic and lacked dose dependence, they were not considered related to the administration of JNJ-77242113-AAC by the applicant. However, there were sporadic increases observed in absolute counts of NK, T, Th, and Tc at the recovery timepoint (Day 302) in group 4 (200 mg/kg/day). These can be attributed to high inter-day variability in measurements and not biologically or clinically relevant. During the dosing phase, no differences were found between treated and control animals, and total lymphocyte counts as well as clinical laboratory parameters remained unchanged. icotrokinra-related decreases in anti-KLH IgM responses were observed in all dose groups on Days 169 through 190. icotrokinra-related decreases in anti-KLH IgG responses were observed mainly in females at ≥75 mg/kg/day on Days 169 through 190. There was a limited number of animals in each group and a high intragroup variability, especially in control animals, which may have precluded the results from being statistically significant. Hence,

although not completely suppressed, icotrokinra-related decreases in T cell-dependent antibody response (TDAR) cannot be completely excluded. Nevertheless, together with the absence of effects on immunophenotyping and the presence of ADAs, the overall data suggest that icotrokinra-treated monkeys were still able to induce a primary antibody response to a foreign antigen. At the end of dosing, the pharmacodynamic activity of icotrokinra was maintained. These data suggest that the ADAs had no neutralising potential given that pharmacodynamic activity of icotrokinra was maintained and that no NAbs were found. Due to the absence of a correlative finding for the effects on TDAR, the NOAEL of 200 mg/kg is agreed. The AUC based safety margin at 200 mg/kg was 392/351-fold (total exposure in males/females) and 60/184-fold (free exposure in males/females) the modelled human steady-state exposure at 200 mg QD.

Despite the presence of ADAs in both rats and monkeys, the overall exposure across the studies is sufficient to conclude that the toxicological profile of icotrokinra was adequately evaluated

icotrokinra was neither genotoxic in vitro nor *in vivo*.

In the 26-week GLP TG rasH2 mice carcinogenicity study, there were no icotrokinra-related neoplastic findings up to the highest dose tested of 500 mg/kg. The only non-proliferative microscopic finding related to icotrokinra was a non-adverse effect on oedema in the nasal cavity lumen. In the 2-year GLP rat carcinogenicity study, there were no icotrokinra-related neoplastic or non-neoplastic findings up to the highest tested dose of 20 mg/kg. Due to the limited binding affinity of icotrokinra for mouse IL-23R, the studies were supplemented with a weight-of-evidence (WoE) approach. This was based on the absence of genotoxic potential of icotrokinra, the absence of findings in the chronic studies in rats or monkeys indicative of pre-neoplastic potential or endocrine disruption and the absence of carcinogenic findings in the 2-year rat and the 6-month transgenic mouse study. The exposure to icotrokinra in the chronic rat studies first increased due to accumulation and then declined, which was likely related to changes in ADA levels. Nevertheless, rats remained exposed above the modelled human steady-state exposure to icotrokinra throughout the study durations. Furthermore, no carcinogenic risks have been associated with approved IL-23 monoclonal antibody inhibitors nor with other IL-23 inhibitor drugs. It was also stated that no secondary pharmacology or off-target activity was detected that was suggestive of a carcinogenic risk, but it should be noted that the secondary pharmacology screen was limited. Nevertheless, taking into account the size of icotrokinra, cell entrance and thus DNA interaction is unlikely. Together, it can be concluded that there is no indication of carcinogenic potential for icotrokinra.

No risks for pre-and post-natal development, as well as for fertility and early embryonic development, are expected at the anticipated human exposure.

In the pivotal rabbit EFD study, there was an icotrokinra-related increase in the number of females that aborted on GD26 in the high dose group (500 mg/kg/day) which was considered adverse, with concomitant slight decreases in body weight gain and food consumption. There was no embryofoetal developmental toxicity related to the oral administration of icotrokinra up to the highest tested dose level. The NOAEL is agreed to be 200 mg/kg for maternal toxicity and 500 mg/kg for embryofoetal development. At the NOAEL for EFD of 500 mg/kg/day, the maternal AUC0-24h value on GD19 in rabbits was 5,770 ng*h/mL (1,652 ng*h/mL when corrected for 28.64% fraction unbound in rabbits) corresponding to an AUC multiple of 95-fold over the modelled human $AUC0\ 24h_{,ss}$ at the 200 mg QD dose of 36.7 ng*h/mL (17.4 ng*h/mL when corrected for 47.51% fraction unbound in humans).

Given the provided WoE, it is agreed that a juvenile animal study is not of added value for human risk assessment to support dosing with icotrokinra in paediatric subjects aged 12 years and older, as was also concluded in the PIP (EMA/PE/0000183329).

Regarding interspecies comparison, determining the suitability and the relevance to human for the calculation of the safety margin to human exposure (modelled human exposure and fluctuation of icotrokinra exposures in animals after repeated dosing) is challenging and safety margins should be viewed with caution and estimated highly conservative. Therefore, it is considered appropriate to calculate the safety margin for male fertility on D177 timepoint when the exposure was at its lowest. As the resulting safety margin of 61x is still of no concern for clinical use, there is no impact on risk assessment.

A GLP 1-month repeat-dose toxicity study was conducted with a batch of icotrokinra that included all impurities and a potential impurity in support of the DS process modification The toxicologically qualified impurity limits are agreed.

ERA

The dossier is complete.

4.5.2. Conclusions

icotrokinra is a high affinity antagonist of IL-23R. Its mode of action and specificity were sufficiently demonstrated *in vitro*. Monkey and rat are the most pharmacologically relevant species, while only low activity of icotrokinra is expected in mouse and rabbit. Proof-of-concept was demonstrated in rats with IL-23-induced skin inflammation. Twice daily dosing was needed for full efficacy. The potential for off-target activity or PD drug interactions of icotrokinra is low. No issues regarding safety pharmacology were identified.

The absorption, distribution, metabolism, and excretion (ADME) of icotrokinra was adequately evaluated in several *in vitro* systems (Permeability**,** PPB, metabolism/stability) and in *in vivo* single dose PK studies (PO, IV and/or SC) using the mouse, rat, Beagle dog and Cynomolgus monkey. Tissue distribution and mass balance *in vivo* studies were performed in both the rat and cynomolgus monkey. In addition, the *in vivo* multiple-dose TK of icotrokinra was conducted via oral administration to Sprague-Dawley rats, New Zealand White rabbits, and cynomolgus monkeys, which were used as part of the non-clinical safety program.

The repeat dose toxicity studies showed no target organs of toxicity of icotrokinra. There were no icotrokinra-related neoplasms in the 6-month transgenic mouse carcinogenicity study nor in the 2-year rat carcinogenicity study. There were no icotrokinra-related effects on fertility, early embryonic development, embryofoetal development, and on pre-and postnatal development, as reflected in the SmPC sections 4.6 and 5.3. icotrokinra appeared to be not genotoxic *in vitro* and *in vivo*.

The non-clinical information is reflected in the Product Information. The application is approvable from the non-clinical perspective.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

According to the applicant, all studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki.

A routine GCP inspection of the 77242113PSO3004 (ICONIC ADVANCE 2) trial was adopted at the October 2025 CHMP meeting.

5.1.2. Tabular overview of clinical trials

Table 5. Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 2b – dose-ranging studies					
77242113**PSO2001**	RD/DB/PC dose-ranging study 16- week treatment period	icotrokinra 100 mg BID; 100 mg QD; 50 mg QD; 25 mg BID; 25 mg QD; Placebo QD	Adults with moderate to severe plaque psoriasis (defined by BSA BSA ≥10%, PASI ≥12, IGA ≥3) who were candidates for phototherapy or systemic therapy	To evaluate the dose response, efficacy, safety and tolerability of icotrokinra vs placebo Primary endpoint: PASI75 at week 16	255 subjects randomised 100 mg BID: 42(42)/38 100 mg QD: 43(43)/41 50 mg QD: 43(43)/40 25 mg BID: 41(41)/40 25 mg QD: 43(43)/36 Placebo: 43(43)/36
77242113**PSO2002**	DB dose-ranging LTE study 36-week treatment period	icotrokinra: 100 mg BID; 100 mg QD; 50 mg QD; 25 mg BID; 25 mg QD Patients treated with placebo in PSO2001 switch to icotrokinra 100 mg QD	Eligible adults with moderate to severe plaque psoriasis who completed PSO2001 through week 16	Maintenance of efficacy of icotrokinra up to week 36 Primary endpoint: PASI75 at week 36	227 treated: 100 mg BID: 38(38)/35 100 mg QD: 40(40)/33 50 mg QD: 39(39)/33 25 mg BID: 40(40)/30 25 mg QD: 35(35)/27 PBO-->100 mg QD: 35(35)/29
Phase 3 – confirmatory studies					
77242113**PSO3001 (ICONIC-LEAD)**	RD, DB, PC 156-week treatment period	icotrokinra 200 mg QD or placebo (2:1)	Adults (n=618) and adolescents (n=66) with moderate to severe plaque	To evaluate efficacy, safety, PK, PD, immunogenicity of icotrokinra vs placebo.	684 subjects randomised icotrokinra: 456 (456)/407 Placebo: 228 (228)/200

	+ 4 week safety follow-up 16 weeks placebo control randomised withdrawal (adults) from week 24 to 52 Week 52 DBL		psoriasis (BSA ≥10%, PASI ≥12, IGA ≥3) who were candidates for phototherapy or systemic therapy for psoriasis.	Co-primary endpoint at W16: IGA score of 0 or 1 and a ≥2 grade improvement from baseline PASI90	
77242113**PSO3002 (ICONIC-ADVANCE 1)**	RD, DB, PC 156-week treatment period + 4 week safety follow-up Week 44 DBL	icotrokinra 200 mg QD or deucravacitinib 6 mg once daily, or placebo (2:2:1) Participants randomised to placebo crossed over to icotrokinra 200 mg QD at W16. Participants randomised to deucravacitinib switched to icotrokinra 200 mg QD at W24.	Adults (n=774) with moderate to severe plaque psoriasis (BSA ≥10%, PASI ≥12, IGA ≥3) who were candidates for phototherapy or systemic therapy for psoriasis.	To evaluate efficacy, safety, PK, PD, immunogenicity of icotrokinra vs placebo and vs deucravacitinib. Co-primary endpoint at W16 (vs placebo): IGA score of 0 or 1 and a ≥2 grade improvement from baseline PASI90	774 subjects randomised icotrokinra: 311 (311)/279 Placebo: 156 (156)/130 deucravacitinib: 307 (307)/271
77242113**PSO3003 (ICONIC TOTAL)**	RD, DB, PC 156-week treatment period + 4 week safety follow-up Week 52 DBL	icotrokinra 200 mg QD or placebo (2:1)	Adults (n=305) and adolescents (n=6) with plaque psoriasis who were candidates for phototherapy or systemic therapy for psoriasis with:	Primary: IGA score of 0 or 1 and a ≥2 grade improvement from baseline	311 subjects randomised icotrokinra: 208 (208)/184 Placebo: 103(103)/91

			BSA ≥1%, IGA ≥2, and at least 1 of the following: ss IGA score ≥3, sPGA G ≥3, hf PGA score ≥3		
77242113**PSO3004 (ICONIC-ADVANCE 2)**	RD, DB, PC 156-week treatment period + 4 week safety follow-up. Week 24 DBL	icotrokinra 200 mg QD or deucravacitinib 6 mg once daily, or placebo (4:4:1) Participants randomised to placebo crossed over to icotrokinra 200 mg QD at W16. Participants randomised to deucravacitinib switched to icotrokinra 200 mg QD at W24.	Adults (n=774) with moderate to severe plaque psoriasis (BSA ≥10%, PASI ≥12, IGA ≥3) who were candidates for phototherapy or systemic therapy for psoriasis.	To evaluate efficacy, safety, PK, PD, immunogenicity of icotrokinra vs placebo and vs deucravacitinib. Co-primary endpoint at W16 (vs placebo): IGA score of 0 or 1 and a ≥2 grade improvement from baseline PASI90	731 subjects randomised icotrokinra: 322 (322)/299 Placebo: 82 (82)/74 deucravacitinib: 327 (327)/303

RD = randomised; DB = double blind; DBL = database lock; PC = placebo controlled; LTE = long-term extension; QD = once daily; BID = twice daily; PBO = placebo

5.2. Clinical pharmacology

5.2.1. Methods

LC-MS/MS assays for the quantification of icotrokinra in human EDTA plasma were developed and validated. The assay was subsequently modified to improve chromatographic separation. A partial validation was carried out. These assays were used for phase I and II studies: PN-235-01, PSO1002, PSO1003, PSO2001, and PSO2002, phase I and III studies: PSO1006, PSO1007, PSO1009, PSO3001, PSO3002, PSO3003, and PSO3004 and phase I and III studies: PSO1004 and PSO3001.

To support Phase 3 studies, the Janssen Research & Development ADA method was used in studies PN-235-01, PSO1002, PSO2001, PSO2002 and in studies PSO3001, PSO3002, PSO3003, and PSO3004. The Janssen Research & Development ADA method was also used in study PSO3001. Validation was performed for all methods.

Confirmed positive samples for ADA to icotrokinra were further characterised for neutralising activity using a validated NAb assay. A competitive ligand binding assay method for detection and characterisation of NAb to icotrokinra was developed by Janssen Research & Development. To support Phase 3 studies, the Janssen Research & Development NAb method was validated and performed for studies PSO3001, PSO3002, PSO3003, and PSO3004.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The pharmacokinetics of icotrokinra were investigated in 7 Phase 1 studies, 2 Phase 2 studies and 4 Phase 3 studies. In addition, the applicant has undertaken a population PK analysis and exposure-response analyses regarding efficacy and safety.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

The popPK model was used to characterise the PK of icotrokinra, to identify covariates and to identify the potential effect of ADAs on the PK of icotrokinra. Further, the model was used to conduct simulations to support the dose selection for the Phase 3 studies and to provide exposure metrics for the exposure-response analyses. The model was also used to compare the pharmacokinetics in adolescents to adults.

The population PK (pop PK) analysis was based on studies PSO1002, PSO1003, PSO1004, PSO1006, PSO2001, PSO2002, PSO3001, PSO3002, PSO3003, and PSO3004 conducted in healthy participants and participants with psoriasis. These comprised 2551 participants (2411 participants with psoriasis and 140 healthy participants; 1726 males and 825 females; 2479 adults and 72 adolescents; aged 12 – 87 years; body weight 39 – 211 kg), and a total of 12,299 plasma icotrokinra concentration records. Subjects from Phase 3 studies (n=2201) received a dose of 200 mg QD. Other subjects in the dataset were treated with a single dose ranging 100 – 1000 mg or multiple doses ranging from 25 mg QD up to 100 mg BID.

The starting point for the population PK model was a model based on pooled data from studies PSO1003, PSO2001, and PSO2002. This is a one-compartment model with linear elimination and first-order absorption that included a lag time (TLAG). The population PK model was parameterised in terms of apparent central volume of distribution (Vc/F), apparent clearance (CL/F), and absorption rate constant (K_a). Inter-individual variability (IIV) was quantified on CL/F and Vc/F with a correlation between IIV on CL/F and Vc/F. Residual unexplained variability was modeled using a proportional error

model. Later, the model was updated with data from additional studies. The effects of body weight on CL/F and V/F and food effects on bioavailability and K_a were included in the structural PK model *a priori*. Fixed standard allometric exponents of 0.75 and 1 were used for the effect of body weight on CL/F and V/F. Other covariates were included in a stepwise approach, with as criteria a 6.64-point reduction of the objective function value for entry (p=0.01) and 10.83 points for removal (p=0.001).

5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable.

5.2.2.3. Absorption

Following oral administration of a 200 mg tablet of icotrokinra in healthy participants, the median (range) t_{max} of icotrokinra was 2.00 (0.25-8.00) hours under fasting conditions. The median C_{max} (%CV) and median AUC_{inf} (%CV) were 3.62 (41%) ng/mL and 44.8 (26%) ng*h/mL, respectively (Study PSO1006).

Based on nonclinical data, icotrokinra shows low oral bioavailability (<1%).

Post hoc PK parameters were calculated based on popPK (see Table 6). Estimated exposure at a dose of 200 mg QD was slightly higher in adolescents compared to adults, but age group (adolescents versus adults) was not a significant covariate in the popPK model.

Table 6. Post hoc estimates of PK parameters for adults and adolescents, based on the Phase 3 studies (dose 200 mg QD)

	Adolescents (N=69)	Adults (N=2043)	Overall (N=2112)
$C_{max,ss}$ (ng/mL)			
Mean (SD)	3.37 (2.95)	2.92 (1.77)	2.93 (1.82)
GeoMean (CV%)	2.84 (54.9)	2.60 (48.0)	2.60 (48.2)
Median (5th - 95th)	2.69 (1.50 - 6.41)	2.52 (1.32 - 6.00)	2.53 (1.32 - 6.02)
Range	1.06 - 20.4	0.596 - 31.1	0.596 - 31.1
$C_{avg,ss}$ (ng/mL)			
Mean (SD)	1.90 (2.34)	1.52 (0.977)	1.53 (1.05)
GeoMean (CV%)	1.48 (64.2)	1.34 (48.7)	1.34 (49.3)
Median (5th - 95th)	1.44 (0.786 - 3.51)	1.29 (0.690 - 3.20)	1.29 (0.690 - 3.21)
Range	0.522 - 17.0	0.325 - 11.3	0.325 - 17.0
$C_{trough,ss}$ (ng/mL)			
Mean (SD)	0.913 (1.84)	0.619 (0.651)	0.628 (0.722)
GeoMean (CV%)	0.525 (105.8)	0.482 (71.1)	0.483 (72.3)
Median (5th - 95th)	0.477 (0.174 - 2.60)	0.478 (0.189 - 1.66)	0.478 (0.187 - 1.67)
Range	0.0761 - 13.7	0.0340 - 8.63	0.0340 - 13.7
$AUC_{0\text{-}24,ss}$ (h*ng/mL)			
Mean (SD)	45.6 (56.2)	36.4 (23.5)	36.7 (25.2)
GeoMean (CV%)	35.4 (64.2)	32.2 (48.7)	32.3 (49.3)
Median (5th - 95th)	34.6 (18.9 - 84.3)	30.9 (16.6 - 76.8)	31.0 (16.6 - 77.2)
Range	12.5 - 408	7.80 - 272	7.80 - 408

$AUC_{0\text{-}24,ss}$=steady-state area under the concentration-time curve from 0 to 24 hours; $C_{avg,ss}$=average drug concentration at steady state; $C_{max,ss}$=steady-state maximum plasma icotrokinra concentration; $C_{trough,ss}$=steady-state trough concentration; CV=coefficient of variation; Geo=geometric; N=number of participants; PK=pharmacokinetics.
Based on final model (run292).

5.2.2.4. Bioequivalence

Bioequivalence studies were performed (i.e. PSO1003 and PSO1006) to compare the phase II immediate release tablet with a phase I oral solution, and to compare the phase III immediate release tablet with the phase II immediate release tablet (Table 7 and Table 8).

Table 7. Table Statistical comparison exposure parameters for 100 mg phase II oral IR tablet compared with 100 mg phase I oral solution in healthy adult participant under fasting conditions (study PSO1003)

	N		Geometric Means				
PK Parameter	Solution formulation fasted (Reference)	Film coated tablet fasted (Test)	Solution formulation fasted (Reference)	Film coated tablet fasted (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra-participant CV (%)
C_{max} (ng/mL)	14	14	1.83	1.95	106.39	83.95-134.83	37.8
AUC_{last} (h*ng/mL)	14	14	19.9	21.0	105.59	90.57-123.10	24.0
AUC_{∞} (h*ng/mL)	13	13	19.9	21.8	109.68	94.40-127.43	22.5

Note: Log transformed PK parameters were analyzed by mixed model analysis of variance with treatment, sequence, and period as fixed effects, and participant in sequence as a random effect and the results were back-transformed using anti-logarithm.
Participants who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods are included in the analysis.
N: number of participants who completed the study and for which an evaluable PK parameter could be obtained.
Intra Participant CV(%) = 100* (sqrt(exp(MSE)-1).

Table 8. Statistical comparison exposure parameters for 200 mg phase III oral IR tablet compared with 2x100 mg phase II IR tablet in healthy adult participant under fasting conditions (study PSO1006)

PK Parameter	Intervention	n	Geometric Mean	Comparison	GMR (%)	90% CI (%)	Inter-participant CV (%)	Intra-participant CV (%)
C_{max} (ng/mL)	A	24	3.40	A vs. C	88.08	74.28-104.45	26.7	35.6
	C	23	3.86					
AUC_{last} (ng.h/mL)	A	23	41.1	A vs. C	94.20	85.06-104.33	21.0	20.5
	C	23	43.7					
AUC_{∞} (ng.h/mL)	A	23	43.8	A vs. C	94.90	85.59-105.21	19.6	20.7
	C	23	46.2					

PK parameters were log transformed and submitted to a linear mixed effects model controlling for intervention, sequence, and period as fixed effects, and participant within sequence as a random effect
The results are presented on original scale after anti-logarithm transformation.
n: number of data included in the model; GMR: geometric mean ratio; CI: confidence interval; CV: coefficient of variation
A: a single oral dose of 200 mg JNJ-77242113 formulated as 1x200-mg Phase 3 IR tablet, fasted
C: a single oral dose of 200 mg JNJ-77242113 formulated as 2x100-mg Phase 2 IR tablets, fasted

5.2.2.5. Influence of food and drinks

In healthy participants (Study PSO1006), coadministration of a single icotrokinra 200 mg tablet with a high-fat, high-calorie meal decreased icotrokinra C_{max} and AUC_{inf} by 59% and 43%, respectively, relative to the fasted state (phase III formulation). Similar reduction in systemic bioavailability for high-fat (~50%) and low-fat (~45%) breakfast was observed in Study PSO1003 (phase II formulation). With respect to timing of the meals, a reduction in systemic bioavailability was also observed when taking icotrokinra 2 h (~40%) or 1 h (~50%) after food or when the tablet is taken 30 min (~40%) before food (phase II formulation).

Administration of a single icotrokinra 200 mg tablet with caffeine did not result in a pronounced difference in exposure. Administration of a single icotrokinra 200 mg tablet with whole milk or a sugar solution decreased the bioavailability (AUCinf) by 24% and 18%, respectively (phase III formulation).

5.2.2.6. Distribution

Based on clinical data, icotrokinra is 52% bound to plasma proteins. icotrokinra appeared to preferentially bind to human serum albumin compared to human α1-acid glycoprotein. Mean blood-to-plasma and blood cell-to-plasma ratios were <1 (0.53 for human at the clinically relevant concentration). The typical V/F is 92,800 L (IIV: 61.6%) based on population PK modelling. Based on *in vitro* studies, icotrokinra is not a substrate of drug transporters.

Detectable concentrations of icotrokinra were noted in sigmoid colon and rectal biopsy samples collected in the subjects following 25 mg icotrokinra and 100 mg icotrokinra.

5.2.2.7. Metabolism

icotrokinra is a peptide and is likely metabolised by peptide catabolism into smaller peptides. icotrokinra is not metabolised by CYP enzymes. Stability was assessed *in vitro* in plasma, hepatocytes, faecal homogenates, and intestinal mucosal scrapings from several species, and in simulated gastric fluid and solutions containing the purified GI enzymes pepsin, trypsin, chymotrypsin, or pancreatin. icotrokinra appeared to be metabolically stable in all matrices tested, with half-lives >24 hours.

5.2.2.8. Elimination

The majority of the drug is not absorbed. In the FIH study, 37% to 81% of the administered dose was recovered in faeces up to 24 hours. According to the applicant nonclinical and clinical data indicate renal clearance to be the main route of elimination of drug from plasma. Based on the relationship between exposure and renal function in the renal impairment study, the majority of the absorbed drug would be renally cleared. In rat and monkey mass-balance studies, 0.20% and 0.97% of the radioactive dose was recovered in urine, respectively. These values are close to the oral bioavailability for each species. The median $t_{1/2}$ of icotrokinra in human is 12 hours. For the human FIH and RI studies, very low amounts (<0.001% of the administered dose) of intact drug are excreted in urine and the median renal clearance of icotrokinra was low (0.008 L/h, overall CL/F is 6550 L/h). No metabolites were observed in plasma or urine from healthy volunteers dosed up to 1000 mg in Phase 1, except for metabolite M12 which was detected in urine samples from study PSO1007.

5.2.2.9. Dose proportionality and time dependency

Following single oral administration, icotrokinra C_{max} and AUC increased roughly in a dose-proportional manner over a dose range of 10 to 1000 mg (approximately 0.05-5 times the recommended dose) in healthy participants (study PN235-01).

After repeated once-daily dosing of icotrokinra, steady state is expected within 3 days with minimum drug accumulation based on a half-life of 12 hours. The accumulation index was 0.7 to 1.6-fold for C_{max} and 0.9 to 1.5-fold for AUC, at day 10 versus day 1 with once daily dosing (study PN235-01).

5.2.2.10. Pharmacokinetics in the target population

Pop PK analysis showed no relevant differences in PK between subjects with and without psoriasis.

5.2.2.11. Special populations

Renal impairment

A dedicated renal impairment study was performed in adult subjects. In Part A, subjects with severe renal impairment (not on dialysis) or end-stage renal disease (not on dialysis) were compared with matched controls with normal renal function and in Part B, subjects with moderate renal impairment were compared with matched controls with normal renal function. In subjects with moderate renal impairment, C_{max} increased 1.79-fold and AUC_{inf} increased 2.47-fold compared to subjects with normal renal function. In subjects with severe renal impairment, C_{max} increased 1.27-fold and AUC_{inf} increased 2.78-fold compared to subjects with normal renal function. See the results in the Table 9 and Table 10 below.

Table 9. PK of icotrokinra in Plasma After Single-dose Oral Administration of 200 mg in Participants With Moderate RI and Normal Renal Function, Part B (Study PSO1007)

	Moderate RI		Normal Renal Function		Ratio of Geometric Means (%)	90% CI	Between Participants CV (%)
PK Parameters	N	Geometric Means	N	Geometric Means			
C_{max} (ng/mL)	5	4.80	5	2.68	179.01	(106.92, 299.71)	46.0
AUC_{last} (ng*h/mL)	5	85.98	5	35.69	240.93	(154.67, 375.32)	39.1
AUC_{inf} (ng*h/mL)	5	89.64	5	36.32	246.83	(158.85, 383.53)	38.8

AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; RI=renal impairment.

Results are based on ANCOVA model without adjusting baseline covariates.

Source: Mod5.3.1.1/77242113PSO1007/Tab10

Table 10. PK of icotrokinra in Plasma After Single-dose Oral Administration of 200 mg in Participants With Severe RI and Normal Renal Function, Part A (Study PSO1007)

PK Parameters	Severe RI		Normal Renal Function		Ratio of Geometric Means (%)	90% CI	Between Participants CV (%)
	N	Geometric Means	N	Geometric Means			
C_{max} (ng/mL)	8	3.85	8	3.03	126.84	(73.58, 218.65)	68.2
AUC_{last} (ng*h/mL)	8	96.15	8	36.85	260.95	(166.65, 408.62)	54.4
AUC_{inf} (ng*h/mL)	7	104.83	8	37.66	278.33	(168.38, 460.07)	59.2

AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; RI=renal impairment.

Results are based on ANCOVA model without adjusting baseline covariates.

Source: Mod5.3.1.1/77242113PSO1007/Tab9

In popPK analyses, mild renal impairment did not have a meaningful impact on C_{max} or AUC (1.1 and 1.2-fold increases were observed for C_{max} and AUC, respectively). Subjects with moderate renal impairment had a 1.4-fold higher C_{max} and a 1.5-fold higher AUC than subjects with normal renal function. The number of subjects with moderate renal impairment in the dataset was however low (21 subjects, among whom only one with eGFR <45 mL/min/1.73m^2).

Hepatic impairment

No dedicated hepatic impairment study was performed and patients with hepatic impairment were not present in the popPK dataset. In the popPK analysis there was however no significant impact of AST, ALT, ALP, total bilirubin, albumin, and GGT on the PK of icotrokinra. No significant effect of hepatic impairment on the PK of icotrokinra is expected, since it is a peptide and not metabolised by hepatic enzymes.

Gender

The popPK database contained data of 1726 males and 825 females. Gender was not a significant covariate in the popPK model.

Ethnic factors

The popPK database contained data of 2551 subjects, among whom 1940 white (including 311 Hispanic or Latino), 44 black, 514 Asian (including 75 Japanese and 135 Chinese), 25 other and 28 with race unknown/not reported. In the pop

PK model, race, ethnicity, Japanese versus non-Japanese, Chinese versus non-Chinese and East Asian region versus non-East Asian region were not significant covariates.

Weight

In the popPK model, the effect of body weight on CL/F and V/F was included in the model *a priori*. CL/F and V/F of icotrokinra increased with increasing body weight. Patients weighing ≥ 90 kg had a 17% lower estimated AUC and 20% lower estimated C_{max} compared with participants weighing <90 kg

(among patients weighing 39 – 211 kg).

Elderly

In the popPK model, age was not a significant covariate. The dataset contained data from subjects ranging from 12 to 87 years of age. Information was provided regarding the numbers of subjects in the age groups 65-74 years (n=211), 75-84 years (n=34) and 85+ years (n=3) in the phase III studies.

Paediatric population

The popPK database contained data from 2479 adults and 72 adolescents (at least 12 years old and weighing at least 40 kg). Age group (adults versus adolescents) was not a significant covariate in the popPK model.

Effect of ADAs

Among icotrokinra-treated participants who developed ADAs, population PK analysis using pooled data up to Week 52 showed that C_{max} and AUC increased by 1.2- and 1.3-fold, respectively, compared with participants who did not develop ADA. Participants with ADA titre of greater than or equal to 100 tended to have a 1.5-fold higher C_{max} and a 2-fold higher AUC compared with participants having ADA titre of less than 100 or who were ADA negative. The popPK dataset contained data from 2404 subjects who were ADA negative and 146 subjects who were ADA positive. Among the ADA positive subjects, there were 31 subjects with an ADA titre ≥ 100.

5.2.2.12. Pharmacokinetic interaction studies

In vitro

icotrokinra as substrate

icotrokinra was stable in plasma, hepatocytes, faecal homogenates, and intestinal mucosal scrapings from several species including humans, and also in simulated gastric fluid. icotrokinra was not further investigated as substrate of hepatic enzymes. icotrokinra is a peptide and peptides are generally known to be metabolised by proteases and not by classical hepatic drug-metabolising enzymes.

icotrokinra was not a substrate of P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K or BCRP *in vitro*.

Effect of icotrokinra on other medicinal products

No reversible inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 by icotrokinra was observed *in vitro*. Time-dependent inhibition was not investigated.

icotrokinra did not induce CYP1A2, CYP2B6 or CYP3A4 *in vitro*.

icotrokinra did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K and BSEP *in vitro*.

The concentrations of icotrokinra which were investigated exceeded the cut-off values for systemic, portal vein and intestinal concentrations.

In vivo

No *in vivo* DDI studies were performed because based on in vitro studies, icotrokinra is not a CYP enzyme substrate, inhibitor, or inducer and icotrokinra was not a substrate or inhibitor of transporters at clinically relevant concentrations.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

icotrokinra is a 13-amino acid cyclic peptide and first-in-class oral IL23R antagonist and selectively binds to the IL-23 receptor to competitively antagonise the binding of its ligand. Consequently, icotrokinra inhibits the IL-23/IL-23R dependent release of pro-inflammatory cytokines, most notably IL-17 (McKenzie 2006; Camard 2025). IL-23 pathway activation is upregulated in PsO (Krueger 2024), with increased IL23R transcript expression in lesional psoriatic skin. The increase in IL23R transcript expression in psoriasis skin is generally restricted to the T cell population, whereas IL23A ligand transcript (for the IL-23 p19 subunit) is expressed across a broader population of cells including myeloid, plasma, and T cell subsets (Reynolds 2021).

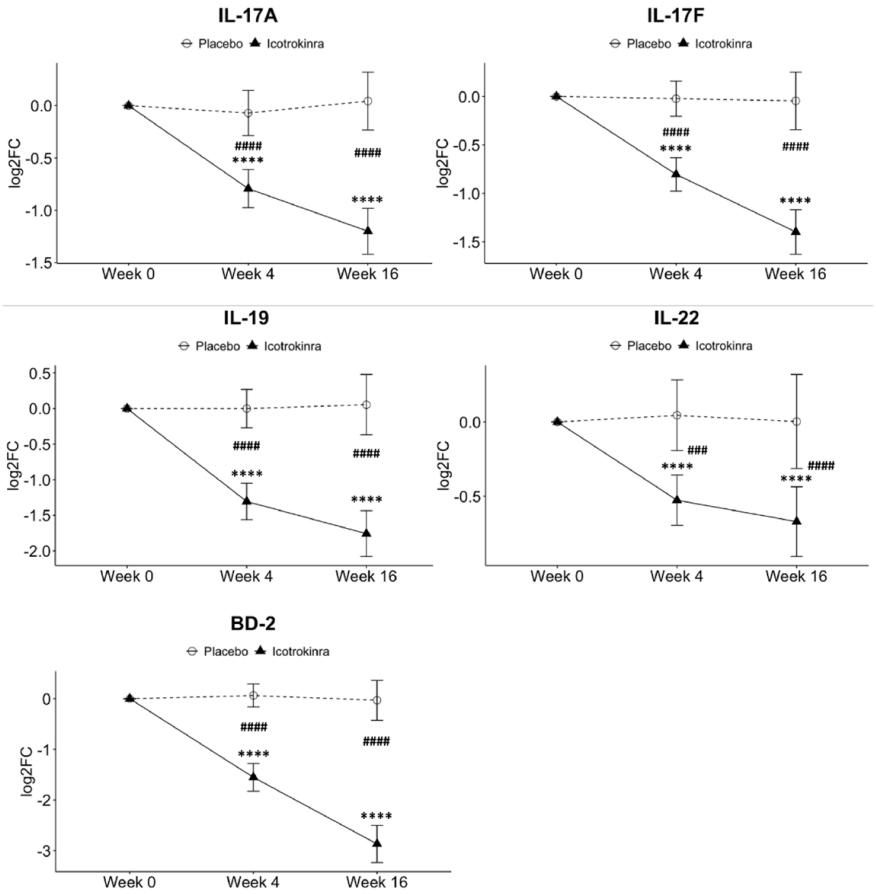
5.2.3.2. Primary and secondary pharmacology

To examine the biological and PD impact of icotrokinra in plaque psoriasis, biomarkers were assessed in serum and skin tissue, collected from a subset of participants in clinical studies PSO3001, PSO3002, PSO3003.

Serum biomarkers

Treatment with icotrokinra 200 mg once daily resulted in a reduction of serum biomarkers related to psoriasis disease activity and/or the mechanism of action of icotrokinra. Serum concentrations of IL-17A, IL-17F, IL-22, IL-19 and BD-2 were statistically significantly reduced at Week 4 and Week 16 compared to baseline.

Figure 2. Serum levels of IL-17A, IL-17F, IL-19, IL-22, BD-2 in placebo vs icotrokinra (PSO3001)

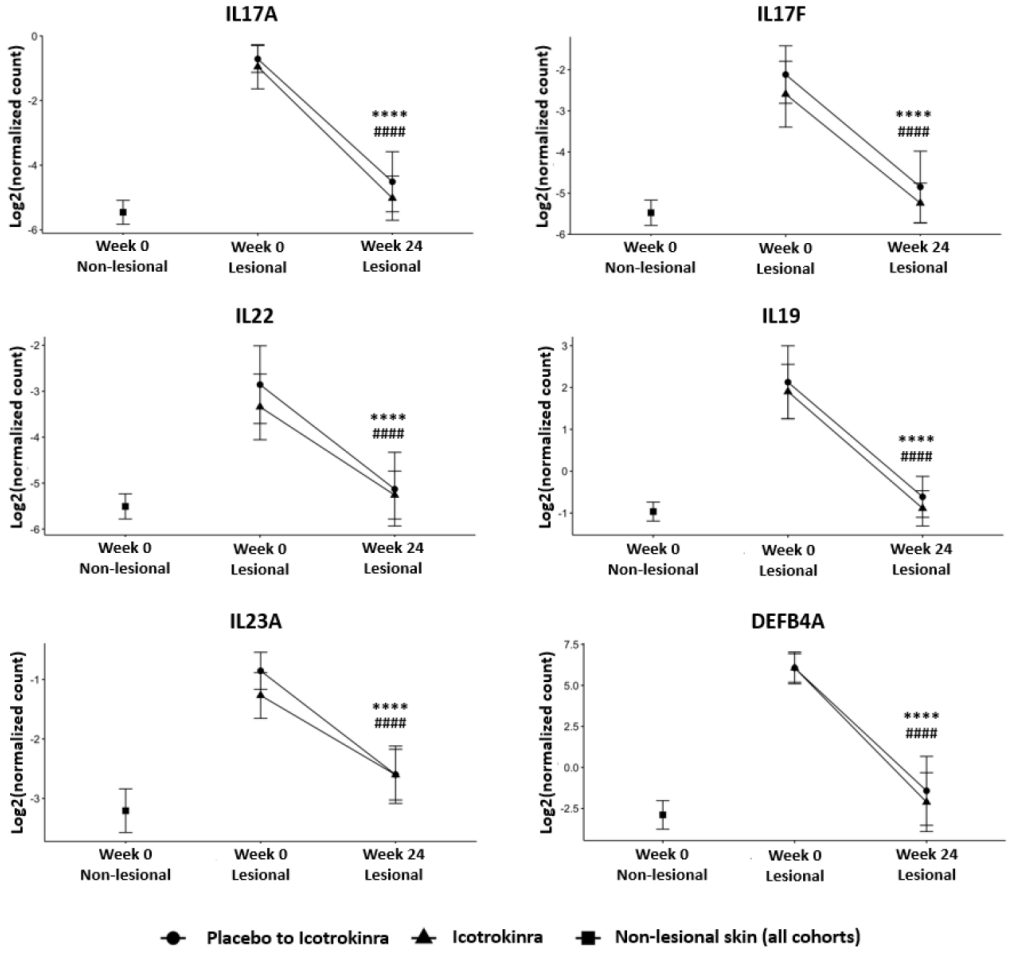


BD-2=beta-defensin 2; CI=confidence intervals; FC=fold change (post-treatment concentration divided by baseline concentration); IL=interleukin; log2=logarithm to the base 2.
Points show mean values; whiskers show 95% CIs. p-values for between arm comparisons (#, placebo versus icotrokinra) and pairwise estimation for within arm time effect (*, versus W0).
*/# p<0.05, **/## p <0.01, ***/### p<0.001, ****/#### p<0.0001.
n=113-114 for icotrokinra; n=52-53 for placebo.
Source: Mod5.3.4.2/BMR-Serum/Fig3

Gene expression in skin biopsies

Skin biopsies were collected from participants that consented to the optional sub-study and were analysed by bulk RNA-sequencing analysis to assess the PD effects of icotrokinra treatment on skin transcriptomics, especially on genes and pathways relevant to PsO and IL-23/Th17 pathway. Baseline non-lesional, baseline lesional, and week 24 lesional (collected from the same lesional area as baseline) skin biopsies from 46 participants were used for paired analysis. Based on skin biopsy analyses, treatment with icotrokinra 200 mg once daily resulted in a reduction in gene expression of the IL-23/Th17 pathway and psoriasis associated gene expression profiles at Week 16 and Week 24. Expression levels of IL17A, IL17F, IL19, IL22 and DEFB4A genes were normalised to non-lesional skin levels at Week 24.

Figure 3. Gene expression of PsO and IL-23/IL-17 related genes (PSO3001)



CI=confidence intervals; *DEFB4A*=gene that encodes beta-defensin 2; IL=interleukin; PsO=psoriasis; Th17=T helper 17 cell.
Points show mean values, whiskers show 95% CIs. p-values from lmer model with interaction term shown for pairwise estimation for within arm time effect (*, versus Week 0 lesional, icotrokinra cohort ; #, versus Week 0 lesional, placebo crossover to icotrokinra cohort). ****/#### p<0.0001.
n=28 (icotrokinra cohort), n=18 (placebo crossover to icotrokinra cohort).
Source: Mod5.3.4.2/BMR-Tissue3001/Fig5

Histology

Skin biopsies were also used to evaluate the impact of treatment on skin morphology and epidermal thickness, as well as T-cell expression. Treatment with icotrokinra 200 mg once daily resulted in improvement of histological features of psoriasis skin at Week 24 and Week 52, including reductions in epidermal thickness, T cell density and CD8 tissue resident memory T cell density (refer to module 2.7.2 section 2.3.1).

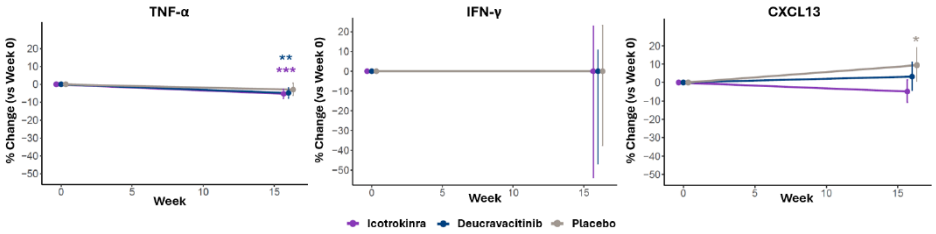
Cytokines important in protection against M. tuberculosis

Serum samples at screening, baseline and week 16 from studies PSO3001, PSO3002, PSO3003 were used to measure cytokines considered important in conferring protection against *M. tuberculosis* infection and/or granuloma formation (i.e., TNFα, IL-6, IL-12p70, IFNγ, and CXCL13). Samples from 320 study subjects and from 40 demographically matched healthy subjects were analysed.

Levels of IL-12p70 and IL-6 were below the limit of detection in all or the majority (65% across study groups) of the samples, respectively.

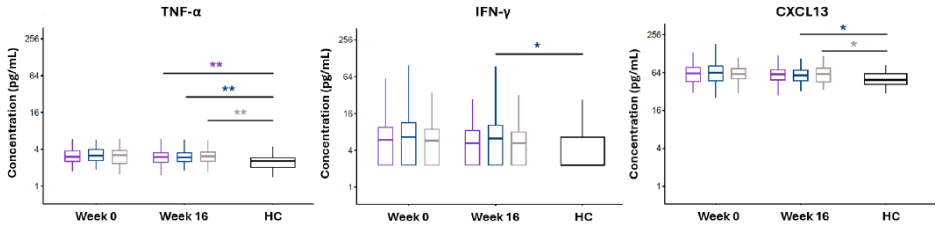
For PSO3001 and PSO3002 there was no statistically significant reduction in IFNγ and CXCL13 serum levels at Week 16 by icotrokinra or deucravacitinib. A small, yet statistically significant reduction in TNFα serum level was observed in icotrokinra and deucravacitinib (Figure 4). Week 16 TNFα serum level remained statistically significantly elevated compared to healthy controls (Figure 5).

Figure 4. Percent change of serum concentrations in PSO3001 and PSO3002



Data plotted as mean and 95% confidence interval (TNF-α and CXCL13) and median and interquartile range (IFN-γ) using % changes converted from the LMM models (TNF-α and CXCL13) or Wilcoxon test (IFN-γ) using log2ratios. Comparison vs Week 0, *p<0.05, **p <0.01, ***p<0.001.

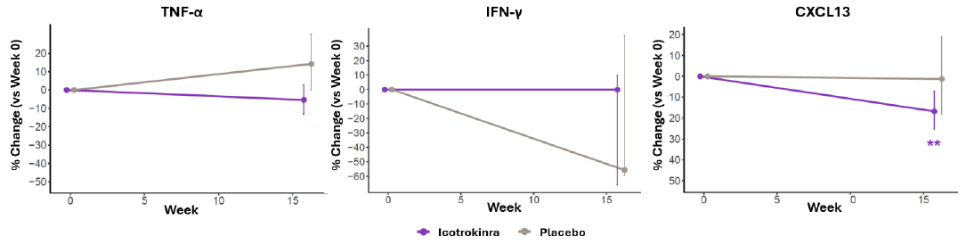
Figure 5. Serum concentrations at week 16 vs healthy controls in PSO3001 and PSO3002



HC: healthy controls. Data plotted as mean and 95% confidence interval (TNF-α and CXCL13) and median and interquartile range (IFN-γ). Comparison performed on log2 transformed concentration values and only comparison of Week 16 vs healthy controls shown in figure, *p<0.05, **p<0.01.

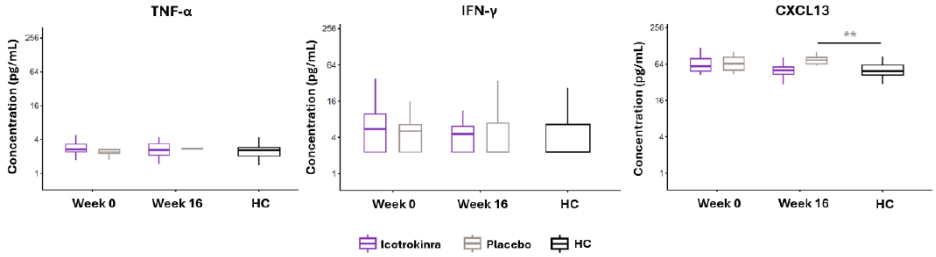
For PSO3003, analysis of icotrokinra and placebo showed no significant reduction in TNFα and IFNγ serum levels at Week 16. While a small reduction in CXCL13 serum level was observed in icotrokinra cohort (Figure 6), Week 16 serum level was similar to healthy controls (Figure 7).

Figure 6. Percent change of serum concentrations in PSO3003



Data plotted as mean and 95% confidence interval (TNF-α and CXCL13) and median and interquartile range (IFN-γ) using % changes converted from the LMM models (TNF-α and CXCL13) or Wilcoxon test (IFN-γ) using log2ratios. *Comparison vs Week 0, **p <0.01.

Figure 7. Serum concentrations at week 16 vs healthy controls in PSO3003



HC: healthy controls. Data plotted as mean and 95% confidence interval (TNF-α and CXCL13) and median and interquartile range (IFN-γ). Only comparison of Week 16 vs healthy controls shown in figure. **p <0.01.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Not applicable.

5.2.3.4. Genetic differences in PD response

Not applicable.

5.2.3.5. Immunological events

In the icotrokinra phase 3 studies, the overall incidence of antibodies to icotrokinra through week 52 was 9.6% (199/2083 participants). Of the participants who were ADA positive, 60% (119/199) of the participants had the lowest measurable titre of 1:50 and 3% (6/199) had a peak titre of ≥1,000. Among the participants who were positive for antibodies to icotrokinra, none were positive for NAb. As mentioned above, population PK analysis using pooled data up to week 52 showed that C_{max} and AUC increased by 1.2- and 1.3-fold, respectively, compared with participants who did not develop ADA. There was no clinically relevant effect of ADA on safety or efficacy of icotrokinra over the treatment duration of 52 weeks. Validity and usefulness of the assay are commented on in the discussion.

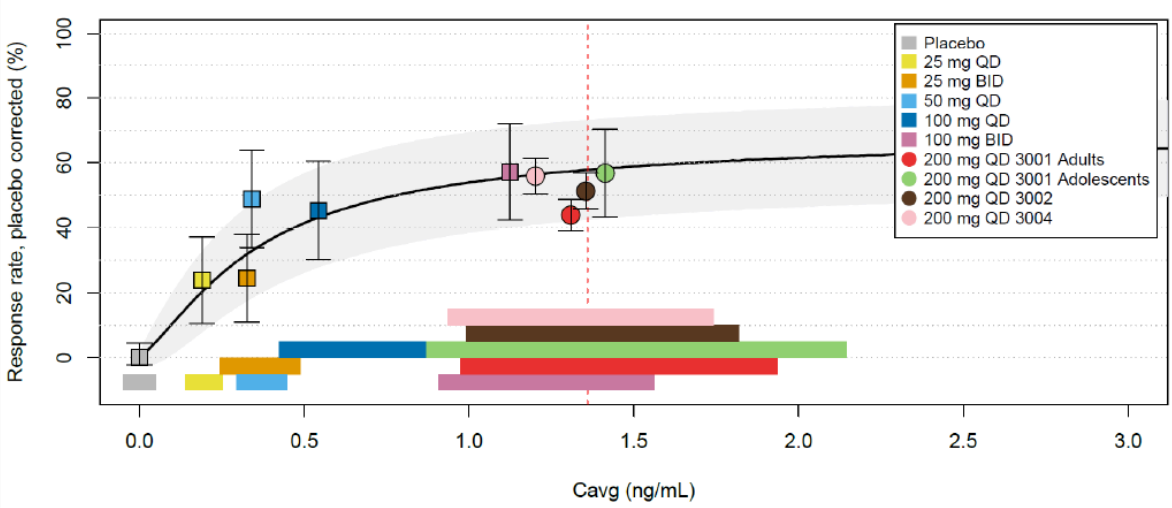
5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Efficacy

Initial exposure-response analyses were performed using logistic regression based on studies PSO2001 and PSO2002. Exposure metrics C_{trough} and C_{avg} were derived from the final popPK model. The relationship was described slightly better with C_{avg} than with C_{trough}. Later, placebo-corrected response rates from studies PSO3001, PSO3002, and PSO3004 were overlaid onto the previously fitted exposure-response curves. Investigated endpoints were PASI (psoriasis area and severity index) and IGA (investigator global assessment) at weeks 16 and 24. The dataset contained data from 231 subjects at week 16 and from 220 subjects at week 24, including the placebo group.

A plot of observed and predicted PASI90 response rate versus C_{avg} which was based on studies PSO2001 and PSO2002 and overlaid with the results from studies PSO3001, PSO3002 and PSO3004, is shown in Figure 8. A similar relationship was found between C_{avg} and IGA0/1.

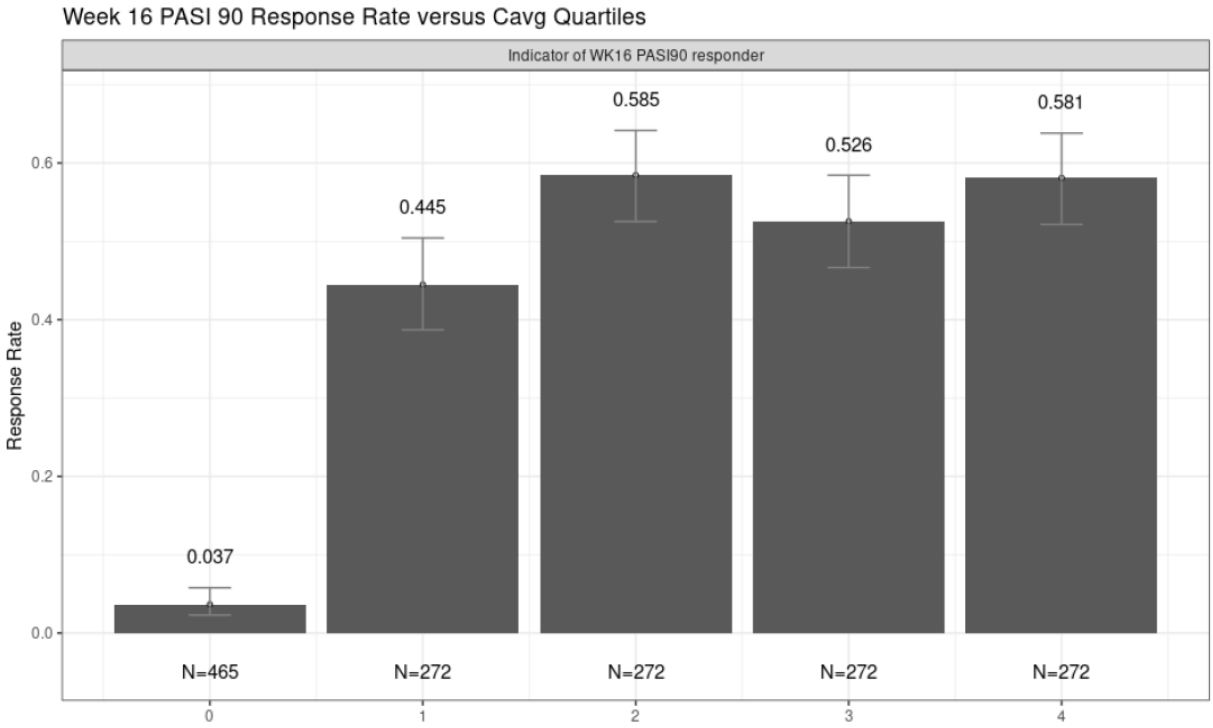
Figure 8. Placebo-corrected PASI90 response rate versus steady-state C_{avg} at week 16, by age group and study



BID=twice daily; C_{avg}=average drug concentration; QD=once daily.
Horizontal colored bars represent 25th-75th percentile of PK post hoc steady-state exposure metrics. Boxes or circles and whiskers represent the observed, placebo-corrected, response rates and corresponding 95% CIs. Vertical dashed line represents simulated C_{avg} of 1.36 ng/mL for the 200 mg QD regimen based on Phase 1 and Phase 2 population PK model.

Regarding the Phase 3 studies, a graphical approach was applied, as the Phase 3 studies included only a single dose (200 mg QD). Investigated endpoints were IGA0/1 (an IGA score of cleared [0] or minimal [1] and ≥ 2 grade improvement from baseline) at week 16 and PASI90 (≥ 90% improvement from baseline in PASI) at week 16. Exposure was based on C_{avg}. A plot representing the proportion of PASI90 responders in the PSO3001, PSO3002, and PSO3004 studies for the icotrokinra and the placebo group versus icotrokinra C_{avg} classified into quartiles is presented in Figure 9. Overall, the 200 mg once daily dose consistently provided high response rates across the quartiles of exposure. A comparable picture was found for the relationship between C_{avg} and IGA0/1 response rate.

Figure 9. Pooled PSO3001, PSO3002, and PSO3004 Week 16 PASI90 Response Rate Versus Steady-state C_{avg} Quartiles



C_{avg}=average drug concentration; N=number of participants; PK=pharmacokinetics; WK=Week.
Post hoc population PK metrics are based on PSO3001, PSO3002, PSO3003, and PSO3004+Phase 1+2 model (run292). Placebo was assigned a value of 0 (quartile=0). "1" denotes first quartile (range: 0.325 - 0.957 ng/mL), "2" denotes second quartile (range: 0.960 - <1.29 ng/mL), "3" denotes third quartile (range: 1.29 - <1.8727 ng/mL), "4" denotes fourth quartile (range: 1.8728 - 17.0 ng/mL). CIs are calculated based on the Wilson method.

Slightly higher response rates in adolescents compared to adults were found for PASI90 and IGA0/1 (see Figure 10). This is ascribed to a body weight effect, since there was also a slightly higher PASI90 response rate in adults weighing < 90 kg than in adults weighing ≥90 kg (Figure 11). A comparable picture was shown for IGA0/1 response rate.

Figure 10. Pooled PSO3001, PSO3002, and PSO3004 Week 16 PASI90 and IGA0/1 Response Rate Versus Steady-state C_{avg} Quartiles by Age Group

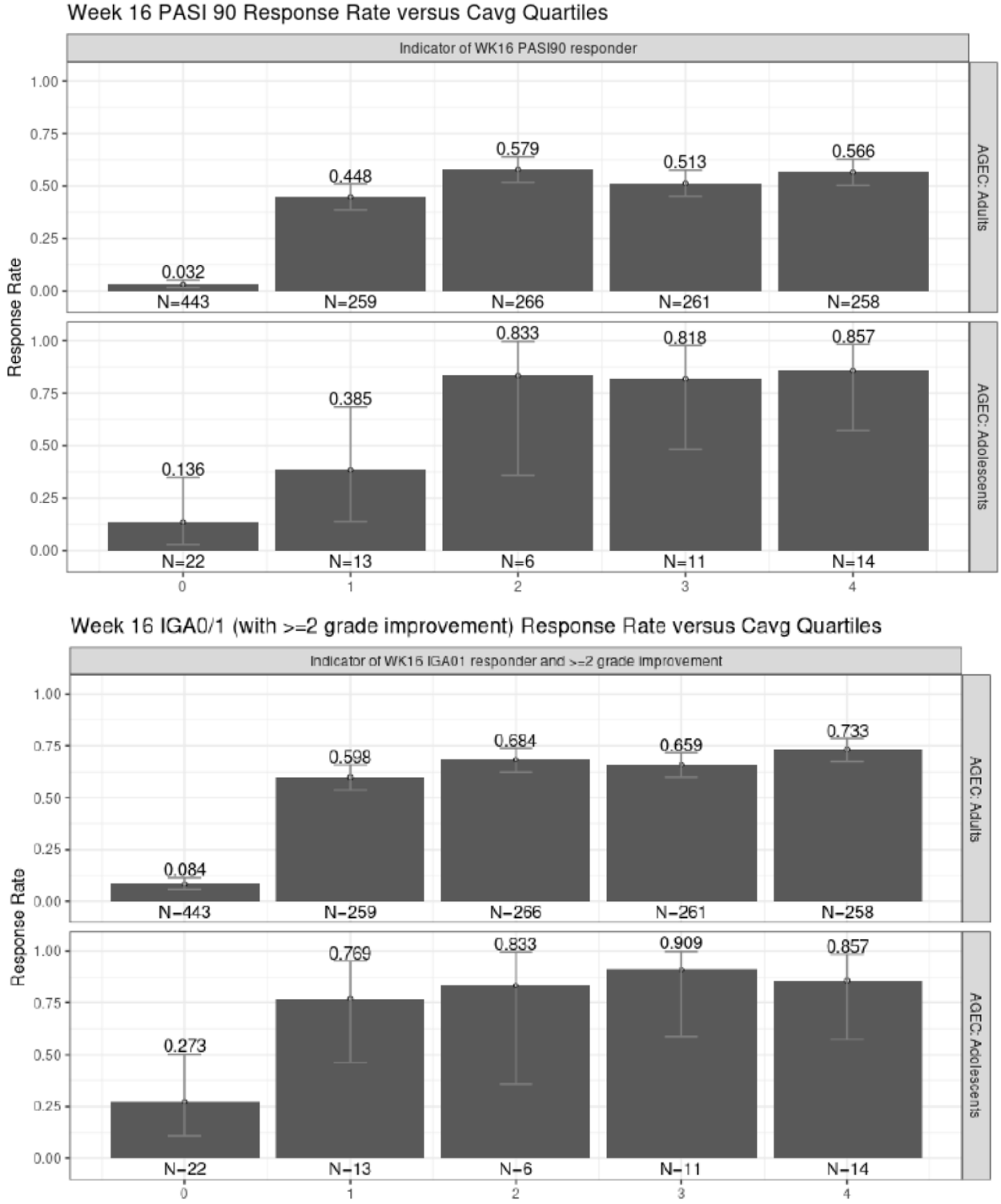
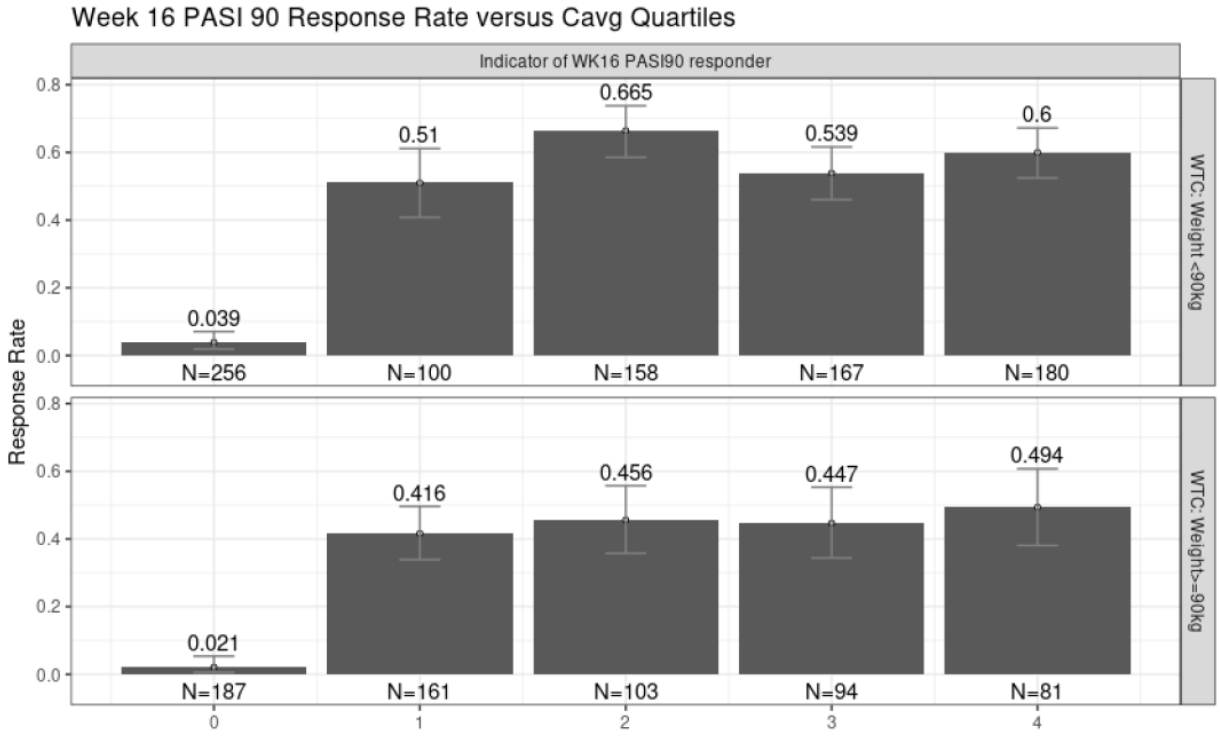


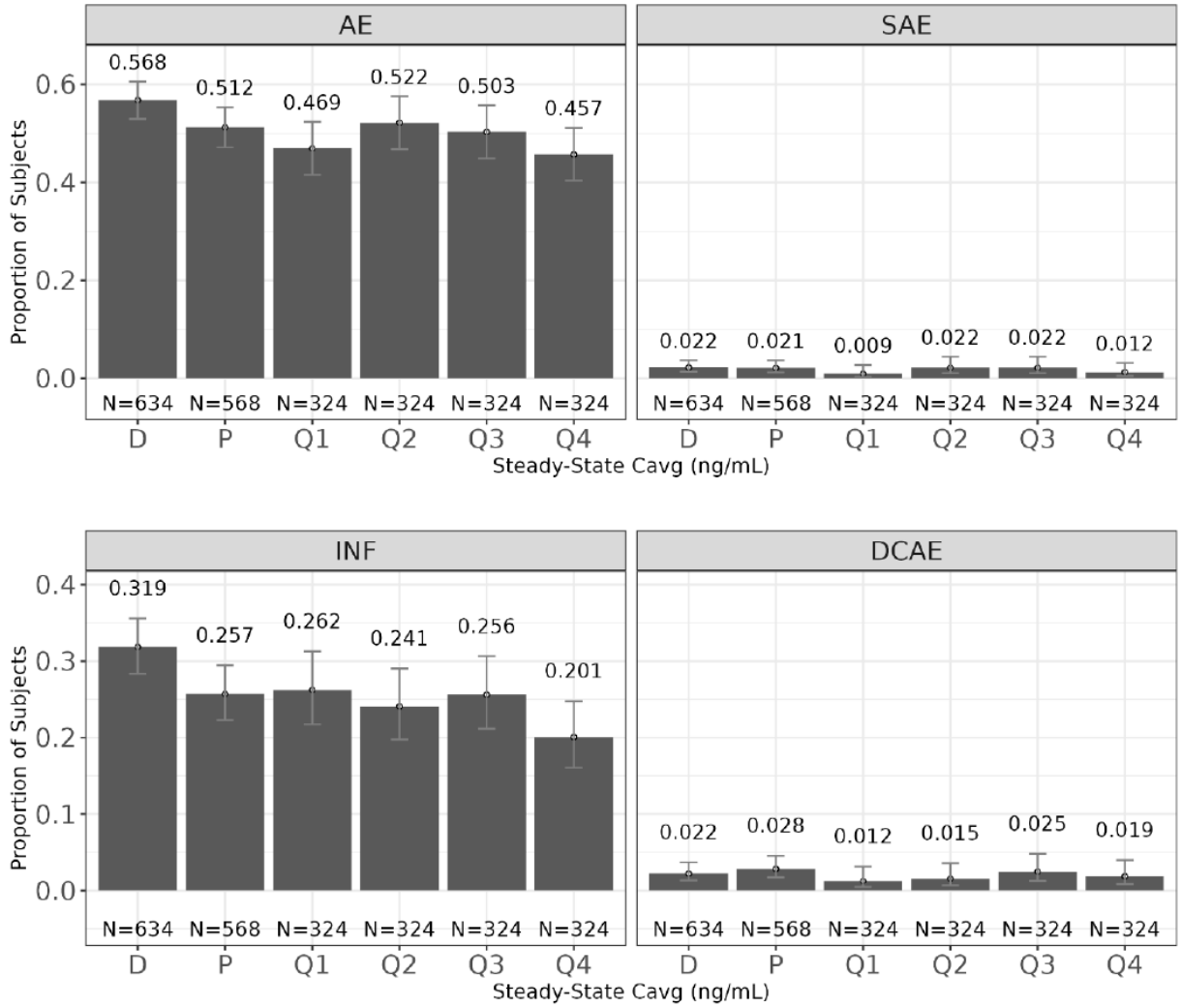
Figure 11. Pooled PSO3001, PSO3002, and PSO3004 Week 16 PASI90 Response Rate Versus Steady-state C_{avg} Quartiles by Adult Weight Group



Safety

A plot showing the proportion of patients with safety events (adverse events [AE], serious adverse events [SAEs], infections [INF] and AEs leading to discontinuation [DCAE]) versus C_{avg} quartiles in studies PSO3001, PSO3002, PSO3003 and PSO3004 is shown in Figure 12. The plot also shows the placebo and deucravacitinib-treated categories. There was no apparent exposure-safety relationship. A similar picture was shown for the relationship of the safety endpoints with C_{max}.

Figure 12. Proportion of Participants with Treatment-emergent AEs, SAEs, Infections, or AEs Leading to Study Agent Discontinuation Through Week 16 by Quartile of Steady-state Average Plasma icotrokinra Concentration in Studies PSO3001, PSO3002, PSO3003, and PSO30.



AE=adverse event; C_{avg}=average drug concentration; D=deucravacitinib; DCAE=discontinuations due to adverse events; INF=infections; P=placebo; SAE=serious adverse event.

First quartile (Q1) ≤0.96 ng/mL, second quartile (Q2) ≥0.96 to <1.29 ng/mL, third quartile (Q3) ≥1.29 to <1.86 ng/mL, fourth quartile (Q4) ≥1.86 ng/mL are based on participants who received at least 1 dose of icotrokinra.

5.2.5. Dose selection and therapeutic window

The 200 mg QD dose was selected for Phase 3 based on popPK and exposure-response analyses regarding efficacy and supported by human safety and tolerability data from the Phase 1 and Phase 2 studies. Data from study PSO2001 were used to develop popPK and exposure-response models. An exposure-related increase in efficacy response was observed from 25 mg QD up to 100 mg BID, which plateaued at a dose of 100 mg BID. The exposure-response model indicated that at a dose of 200 mg QD efficacy is expected to be comparable to 100 mg BID. Based on the model predictions and considerations of patient acceptability, the 200 mg QD dose was selected for the Phase 3 studies. The dose of 200 mg daily is mentioned to be safe. Higher doses than 200 mg daily were not investigated regarding safety. Adolescents 12 – 18 years old and weighing at least 40 kg received the same dose as adults. Estimated response rates in adolescents were at least comparable to those in adults.

According to the applicant the 200 mg QD regimen of icotrokinra demonstrated clinically meaningful efficacy (efficacy endpoints PASI90 and IGA 0/1) in the Phase 3 PsO studies (Studies PSO3001, PSO3002, PSO3003 and PSO3004). Based on the population PK analysis from these phase 3 studies, the median (5th-95th percentile) steady state C_{avg} at the 200 mg QD dose was estimated as 1.29 (0.690 – 3.21) ng/mL.

The 5th percentile exposure of 0.690 ng/mL achieved in ≥ 95% of Phase 3 participants using the to be approved 200 mg QD dose could be considered as the lowest exposure associated with clinically meaningful efficacy demonstrated in the pivotal studies. The highest observed concentration of icotrokinra in patients with moderate to severe plaque psoriasis was 119 ng/ml. No safety concerns were identified; therefore, the applicant proposed 119 ng/ml to be the highest exposure not leading to clinically relevant safety issues.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical method

Method validation was acceptable. Validation is in line with ICHM10 and assays showed acceptable results. Stability has been shown for at least 161 days, which covers the storage of drug samples. In study accuracy and precision was in line with values obtained during method validation. In addition, ISR was performed and complied with requirements in ICHM10. Cross-validation between methods showed very similar results indicating that methods can be used interchangeably. However, a medium QC around 30-50% of the calibration curve range during method validation and sample analysis by Agilex was missing, which is not in line with the current ICH M10 and former EMA GL on bioanalytical method validation. The applicant discussed absence of impact on clinical pharmacokinetics results. In addition, the applicant justified that the use of different salts of the drug substance, i.e. icotrokinra acetate and icotrokinra HCl has no significant effect on the quantification of the analyte. This is accepted.

ADA

Separate assay validation was performed in all laboratories, and cross validation was performed between laboratories. Method validation provided acceptable results. The assays provided indicate that ADAs could be detected with sufficient precision and that interference with icotrokinra does not influence ADA detection around clinically relevant drug concentrations. The ADA detection in clinical studies is therefore expected to give a reasonable impression on the presence/absence of anti-drug antibodies.

NAb assay

In general, the NAb assay development and validation is considered acceptable. Assays were executed in three laboratories. Separate assay validation was performed in all laboratories, and cross validation was performed between laboratories. Method validation provided acceptable results.

Population PK model

The popPK model was used to characterise the PK of icotrokinra, to identify covariates and to identify the potential effect of ADAs on the PK of icotrokinra. Further, the model was used to conduct simulations to support the dose selection for the Phase 3 studies and to provide exposure metrics for the exposure-response analyses. The model was also used to compare the pharmacokinetics in adolescents to adults. Data from adolescents were present in the dataset for the model to a sufficient extent (72 adolescents). The model was not used for extrapolation. Parameters were estimated with

acceptable precision (%RSE is 2 – 21%). Unexplained inter-individual variability in CL/F, V/F and K_a was moderate to high (52.6 – 84.7%). The residual error was also rather high (48.1%). Shrinkage was acceptable for the inter-individual variability regarding CL/F and V/F (21 – 26%) but high for the inter-individual variability on K_a (60%). The pcVPCs and goodness-of-fit plots showed an acceptable fit and estimated and measured values of C_{max}, AUC and CL/F were sufficiently comparable to those estimated by the model. Considering that the model is not used for extrapolation, it can be considered fit for purpose.

Bioequivalence

It is agreed with the applicant that oral solution, phase II tablet and the phase III tablet, although not formally bioequivalent in line with ICHM13A, result in very similar exposures. It is therefore in principle agreed that differences are not clinically relevant and PK results can be compared between studies. Some aspects, however, were further discussed by the applicant. For some participants, some PK parameters were excluded from descriptive statistics and inferential statistics due to a low correlation coefficient (R^2_{adj}). Indeed, for PSO1006, according to the study protocol, if $R^2_{adj} \geq 0.900$ is not met, $t_{1/2}$, λ_z, AUC_∞, and related parameters were to be reported as approximations. In addition, for four study participants in PSO1003 and for one participant in study PSO1006, some PK parameters were excluded from descriptive statistics and inferential statistics as $\%AUC_{\infty,ex}$ was >20.00%. The exclusion of PK parameters based on predefined criteria (R^2_{adj} <0.9 and AUC extrapolated >20%) is considered acceptable and in line with standard PK practice to ensure reliability of terminal phase estimates.

Influence of food

The applicant has performed an extensive program investigating the effect of different types of food and drinks on icotrokinra exposure. Food has a pronounced influence on AUC and C_{max}. AUC_{0-t} is reduced by 40-50% regardless of when icotrokinra is taken: together with a high-fat meal (-46%), together with a low-fat meal (-47%), 2 hours after a meal (-41%), 1 hour after a meal (-50%), or when a meal is taken 30 minutes after icotrokinra administration (-39%). In addition, AUC_{0-t} decreased 24% or 16% when taken with whole milk or sucrose solution, respectively. The applicant proposed in SmPC section 4.2: 'the tablets should be taken upon waking on an empty stomach with water at least 30 min before eating food (see section 5.2)'. This is also in line with SmPC section 5.2 and the Phase III posology recommendation. Caffeine and whole milk food effects are also referenced in the SmPC section 5.2 'Oral administration of a single icotrokinra 200 mg tablet with caffeine resulted in no difference in exposure. Co-administration of a single icotrokinra 200 mg tablet orally with whole milk decreased C_{max} by 33% and AUC_∞ by 24% compared with co-administration with water.'

It is agreed that this posology is relatively practical for the user and food effect in this case likely will not affect efficacy, as this is similar to the phase III food recommendations, and exposure appears in a relatively flat part of the exposure-response relationship (see section 5.2.4). In addition, it is reassuring that efficacy seems not dependent on exposure quartile range when 200 mg dosing is used (see section 5.2.4).

Dispersion

The formulation of icotrokinra IR tablet was developed to be dispersible for patients who have difficulty swallowing tablets whole. *In vitro* compatibility studies showed that 200 mg film-coated tablets dispersed in water can be dosed accurately when administered according to the instructions (see Quality part). Suspension of the 200 mg tablet in a glass of water (total amount 240 mL) as alternative method of administration was also allowed for adolescents who had difficulties with swallowing tablets in clinical phase 3 studies PSO3001 and PSO3003 and is included in the product

information (SmPC section 4.2). This method of administration was used by a very small number of patients. Nonetheless, no signal of PK deviation has been identified. In addition, the active substance appears to have a wide therapeutic window, hence even in case of moderate differences in exposure no significant clinical impact is expected.

Absorption, distribution, metabolism, excretion

Estimated exposure was slightly higher in adolescents compared to adults. Although the effect on the PK was limited, there was also a slightly higher response rate in the exposure-response analysis at the investigated efficacy endpoints in adolescents compared to adults (see further below).

Based on *in vitro* DDI studies, it was concluded that icotrokinra is not the substrate of several transporters (see below). A passive uptake mechanism is considered plausible.

Based on current information icotrokinra is considered a BCS class IV substance.

Data provided by the applicant shows that icotrokinra binding to plasma proteins is moderate. icotrokinra does not appear to distribute into red blood cells, as the blood-to-plasma ratio was 0.53. Distribution into tissues is likely to be present with the V/F of 92,800 L and an expected F of ~0.5% (as referenced in SmPC section 5.2). The applicant took biopsies of sigmoid colon and rectal tissue for exploratory PK determination in study PN-235-01. K_p ratios observed in rat and monkey studies, where levels were around 1 for most tissues, indicate that no significant accumulation after single dose (rat) or two doses (monkey), was observed.

The metabolism of icotrokinra has been sufficiently described. Involvement of CYP enzymes has been sufficiently excluded and catabolism into smaller peptide metabolites is likely given the nature of the product. The applicant indicated that renal clearance was the major elimination pathway, based on data from the renal impairment study. Although it is agreed that the reduced clearance in renally impaired subjects indeed indicates involvement of the kidney, only trace amounts of intact drug and/or metabolites were recovered in human urine. The hypothesis provided by the applicant was that peptide metabolites might be reabsorbed. The differences between non-clinical species and human regarding renal excretion of icotrokinra are not completely explained. From non-clinical studies there is, however, no specific tendency of icotrokinra tissue accumulation. The hypothesis that renal metabolism could play a more prominent role in the human situation (with reuptake of peptides) can be accepted.

A justification of the claimed 3-day interval for reaching steady-state plasma concentrations was provided by the applicant.

Dose proportionality and time dependency

It is agreed with the applicant that exposure increased roughly proportionally with the dose administered and that plasma accumulation is limited.

Therapeutic window

In the Phase 2b study PSO2001 and its LTE PSO2002 five dosing regimens were studied, including both once daily (25 mg QD, 50 mg QD, and 100 mg QD) and BID dosing regimens (25 mg BID and 100 mg BID). The 25 mg QD icotrokinra dose was expected to inhibit *ex vivo* PD activity but was not considered optimal for clinical efficacy, whilst the 100 mg BID dose was chosen to maximise the effect, with a model predicted >95% PD inhibition for >90% of participants. The exposure estimate at the highest dose (100 mg BID) is at least 45-fold lower than exposures at the NOAEL in rats and monkeys. A clear exposure–response relationship could be demonstrated when C_{avg} was plotted against PASI90 response rate at Week 16, with a plateau at or near the highest dose tested of 100 mg BID.

Data from Phase 1 and Phase 2 studies provided no evidence of a dose-dependent increase in the occurrence of AEs and lab abnormalities across the icotrokinra treatment groups, up to 200 mg per day for up to 52 Weeks. Exposure-safety analysis of Phase 3 data found similar AE rates across quartiles of icotrokinra exposure.

For the lower boundary of the therapeutic window, the 5th percentile of steady state C_{avg} at the 200 mg dose QD was used (0.690 ng/mL), since the 200 mg QD dose showed a relevant exposure associated with clinically meaningful efficacy at the PASI90 and IGA 0/1 endpoints.

Regarding safety, the upper limit of the therapeutic window cannot be established as no dose limiting toxicities have been observed. The upper limit of 119 ng/mL proposed by the applicant seems rather arbitrary, given that it was not observed at the highest dose of 1000 mg but at a dose of 50 mg and could possibly be due to an analytical error/outlier. The upper limit of the therapeutic window could not be established due to limited safety data at doses higher than 200 mg QD. Given that the safety profile of icotrokinra is well characterised, this is acceptable.

Special populations

In the dedicated renal impairment study, in subjects with moderate renal impairment, C_{max} increased 1.79-fold and AUC_{inf} increased 2.47-fold compared to subjects with normal renal function. In subjects with severe renal impairment, C_{max} increased 1.27-fold and AUC_{inf} increased 2.78-fold compared to subjects with normal renal function (as reflected in SmPC section 5.2). The applicant proposes no dose adjustment in patients with renal impairment because the observed concentrations are considered safe. Since there are no safety issues (see section 5.4) and no exposure-response safety findings were identified (see further below), this is agreed. Recommendations regarding treatment of ESRD patients were added to the product information section 4.2 ('No dose adjustment is recommended for patients with mild, moderate or severe renal impairment'). Icotyde has not been studied in patients with end-stage renal disease and should only be used in these patients if the benefit outweighs the possible risk (see section 5.2).

No dedicated hepatic impairment study was performed and patients with hepatic impairment were not present in the popPK dataset, as reflected in SmPC section 5.2. No significant effect of hepatic impairment on the PK of icotrokinra is expected, since it is a peptide and not metabolised by hepatic enzymes. In section 4.2 of the SmPC is stated: 'No dose adjustment is recommended in patients with mild, moderate or severe hepatic impairment (see section 5.2).'

In the popPK analysis, patients weighing ≥ 90 kg had a 17% lower estimated AUC and 20% lower estimated C_{max} compared with participants weighing <90 kg. Though this implies a low impact of body weight on the PK, PASI90 and IGA0/1 response rates were also slightly higher in adults weighing < 90 kg than in adults weighing ≥90 kg (see further below). It is however not necessary to make dose adjustments. Body weight is reflected in SmPC section 5.2 as appropriate.

In the popPK model, age was not a significant covariate. The popPK dataset contained data from subjects ranging from 12 to 87 years of age. Although age group (adults versus adolescents) was not a significant covariate in the popPK model, the exposure in adolescents was slightly higher than in adults and in the exposure-response analyses, response rate in the investigated efficacy endpoints was also somewhat higher in adolescents than in adults. It is likely that this is an effect of a lower body weight in adolescents compared to adults. However, since there was no significant exposure-response relation regarding efficacy or safety among subjects who were treated with 200 mg QD, no dose adjustment is necessary, as reflected in SmPC sections 5.2.

Pharmacokinetic drug-drug interactions

No *in vivo* DDI studies were performed. icotrokinra was not considered an enzyme substrate, because icotrokinra is a peptide and peptides are generally known to be metabolised by proteases and not by classical hepatic drug-metabolizing enzymes. *In vitro*, icotrokinra was not a reversible inhibitor nor an inducer of CYP enzymes and not a substrate or inhibitor of transporters at clinically relevant concentrations. Time-dependent inhibition of CYP enzymes is not expected considering that icotrokinra was not taken up by hepatocytes and that peptides are not metabolised by CYP enzymes. This is appropriately reflected in SmPC section 4.5.

The solubility of the 200 mg IR tablet formulation (G078) was found to be highly pH-dependent, with lower solubility at higher pH-values. According to the *Guideline on the investigation of drug interactions* (CPMP/EWP/560/95/Rev. 1 Corr. 2) 'if the solubility of the drug or the dissolution of the formulation is markedly pH dependent in the physiological pH range, the potential effect of drugs which increase gastric pH, such as proton pump inhibitors, H_2-receptor antagonists or antacids, should be investigated *in vivo*'. With regard to the *in vitro* data, the overall evidence suggests that although dissolution in simulated gastric media is slower at elevated pH, complete dissolution is achieved upon transition to intestinal conditions. Furthermore, the reported solubility in intestinal media (FaSSIF) is high and does not indicate a risk of solubility-limited absorption at the proposed dose. These findings support the view that any pH-related effect is likely limited to a delay in gastric dissolution rather than a reduction in the extent of absorption. The clinical data provided are based on a post hoc population PK analysis from Phase 3 studies comparing subjects with and without concomitant use of acid-reducing agents (ARAs). No relevant effect on AUC or C_{max} was observed. While these results are reassuring and consistent with the *in vitro* findings, the analysis has some limitations, including the non-randomised design, the heterogeneous definition of ARAs (including PPIs, H_2 antagonists and antacids), and the absence of detailed information on dose, timing and duration of ARA use. Evidence from biopharmaceutic and clinical data, however, consistently indicate that a clinically relevant impact of PPIs on icotrokinra exposure is unlikely.

Pharmacodynamics

Mechanism of action

The mechanism of action for icotrokinra has been sufficiently characterised. IL-23R expression is upregulated in psoriatic skin. icotrokinra reversibly binds to the IL-23R to competitively antagonise the binding of ligand IL-23, thus inhibiting proinflammatory processes. The impact on biomarkers related to the IL-23/IL-17 axis is consistent with the described mechanism, and histological analysis of skin samples support the anti-inflammatory effects.

Primary and secondary pharmacology

Serum levels and gene expression of cytokines related to the IL-23/IL-17 axis, in serum and skin, support the mechanism of action of icotrokinra. IL-23-induced IFN-g secretion by human whole blood cells from icotrokinra-treated subjects from phase 1 study PN-235-01 was decreased in a dose-dependent manner.

Similarly, plasma levels of Th17-axis cytokines IL-17A, IL-17B and IL-22 as well as the defensin BD-2 were decreased in a dose-dependent manner in icotrokinra-treated patients from phase 2 study PSO2001/PSO2002. Best inhibition was achieved with the highest dose of 200 mg per day, which corresponds to the proposed dose.

Plasma levels of Th17-axis cytokines IL-17A, IL-17F, IL-19 and IL-22 as well as the defensin BD-2 at baseline were increased in psoriasis patients in phase 3 study PSO3001 as compared to those in healthy subjects. After 16 weeks of icotrokinra treatment, plasma levels decreased to levels similar to

those in healthy subjects. Placebo did not have any effect.

Skin expression levels of Th17-axis genes, such as *IL-17A, IL-17B, IL-19, IL-22 and IL-23a* as well as *DEFB4A* (encoding for the defensin BD-2), were increased in lesional vs non-lesional skin of psoriasis patients in phase 3 studies PSO3001 and PSO3002 at baseline. After 24 weeks of icotrokinra treatment in study PSO3001, expression levels in lesional skin decreased to levels similar to those in non-lesional skin. After 16 weeks of icotrokinra treatment in study PSO3002, similar results were obtained, although non-lesional skin expression levels were not (yet) reached. Placebo did not have any effect.

Histological results further supported the anti-inflammatory mechanism and clinical improvement, with reduced epidermal thickness and reduced T cell density in skin biopsies.

Overall, icotrokinra treatment resulted in substantial amelioration of PD indicators of IL-23 / Th17 axis overactivation in psoriasis patients, often reaching levels similar to those in healthy individuals or non-lesional skin.

In humans, IL-23 is especially important in driving an early response to pathogens by directly influencing IL-17 production (McKenzie 2006), mainly in protection against bacterial and fungal infections (Schinocca 2021). In line with that, IL23R expressing cells are mainly located in lung, skin and the gastrointestinal tract (McKenzie 2006; Camard 2025). It has been reported that IL23R-deficient patients are susceptible to mycobacterial infections (Philippot 2023). However, it also is hypothesised that the rapid IL-23-IL-17 pathway is less important for IL-12 mediated long term protective responses (McKenzie 2006), including against mycobacteria (Chakerian 2006).

No major impact on selected cytokines important for an immune response against *M. tuberculosis* was seen. Concentrations of IL-6 and IL-12p70 were not detectable for the majority of samples, while IFNγ, and CXCL13 concentrations after 16 weeks of treatment with icotrokinra were generally comparable to healthy controls. In samples from PSO3001 and PSO3002, but not in PSO3003, a reduction in TNFα was seen following icotrokinra treatment, which is probably reflective of the reduction in inflammatory state/improvement in their disease state. This is further supported by the weak, but statistically significant correlation between serum TNF levels and change in PASI90 score from week 0-16 in PSO3001 and PSO3002. Compared to samples of healthy controls, TNF levels are still elevated in study participants, irrespective of treatment allocation.

Th1 cytokines like IFNγ and TNFα are essential for preventing LTBI reactivation, with deficiencies leading to dissemination. The IL-23/Th17 pathway primarily supports mucosal immune responses rather than constituting a core mechanism of LTBI control. IL-23 drives IL-17 and IL-22 production, which in turn promotes CXCL13. CXCL13 is critical for organising B cell follicles and ectopic lymphoid structures within the lungs. These lymphoid structures help contain the bacteria locally, limit dissemination during primary infection, and support vaccine-induced immunity (Khader SA J Immunol 2011; Monin L Semin Immunol 2014). Serum CXCL13 concentrations in patients treated with icotrokinra are comparable to those in healthy individuals, but it is unclear if this reflects the lung mucosal environment. Further, CXCL13 alone does not fully capture the local immune environment. A biologically plausible concern is that suppression of IL-23/Th17 responses could modestly impair mucosal and granuloma-mediated control of *M. tuberculosis* in the lungs, potentially facilitating LTBI reactivation.

IL-23R deficiency has not been associated with the severe mycobacterial susceptibility that is classically observed in IFNγ axis defects. However, IL-23R deficiency is rare, and the available human data are therefore insufficient to draw firm conclusions regarding its role in tuberculosis pathogenesis. The SmPC section 4.3 contraindicates icotrokinra in clinically important active infections (e.g. active tuberculosis), while section 4.4 contains relevant warning that treatment should not be initiated in

patients with any clinically important active infection until the infection resolves or is adequately treated.

Immunological events

The development of antibodies to icotrokinra was overall low and had no clinically relevant impact on the safety/efficacy in the clinical studies (SmPC section 5.1 and 5.2).

QTc prolongation

The applicant did not perform a thorough QT study. E-R analysis was performed based on SAD and MAD data from the FIH study PN-235-01 (doses of 10-1000 mg) to determine the relationship between the plasma concentrations of icotrokinra and the QTc interval. According to ICH E14 Q&A section *Use of concentration response modeling of QTc data*, concentration-response analysis, in which all relevant data across all doses are used to characterise the potential for a drug to influence QTc, can serve as an alternative to the by-time-point analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug. The performed analyses and results are in accordance with ICH E14 guidance. e.g., the upper bound of the two-sided 90% confidence interval for the QTc effect as estimated by exposure-response analysis was <10 ms at the highest clinically relevant exposure allowing the conclusion that an expanded ECG safety evaluation is not needed. A population-based correction method was used because the primary pre-specified method, i.e. Fridericia's correction, failed the pre-specified criteria for selection of the method of correction. Absence of a separate positive control is acceptable as the data are characterising the response at a sufficient multiple of the high clinical exposure of about 3-4x (geo mean C_{max} of 16.6 ng/mL for 1000 mg dose vs 4.84 ng/ml in severe RI). Based on these data, there is no indication for a prolongation of the QTc interval by the proposed 200 mg QD dose of icotrokinra.

Interactions

The applicant has not performed studies on PD drug interactions of icotrokinra. As no data are available, a warning to avoid live vaccines within 3 days after discontinuation of icotrokinra is included in sections 4.4 and 4.5 and 4.6 of the proposed SmPC and the corresponding sections of the PL as a precautionary measure (as it is the case for the previously authorised IL-17/23 inhibitors).

Genetic differences in PD response

In total, blood samples of 826 icotrokinra-treated subjects from studies PSO2001, PSO3001, PSO3002, PSO3003 and PSO3004 were used for pharmacogenomic analyses, i.e. testing for association of genotype with PASI90 response at Week 16 with a logistic regression model. No genome-wide significant (P<5E-08) associations or significant associations of IL23R coding variants were identified for Week 16 PASI90 response.

Exposure-response relationship

Efficacy

Response rates of PASI90 and IGA0/1 increased with C_{avg} and C_{trough}. At 100 mg BID / 200 mg QD the response rate is nearly maximal. This is confirmed by the fact that no exposure-response relationship was visible among the quartiles within the patient group receiving a 200 mg QD dose. The exposure-response analyses indicate that no relevant difference in efficacy is expected between the 100 mg BID regimen and the 200 mg QD regimen. Slightly higher response rates were observed for subjects with body weight < 90 kg compared to those weighing ≥ 90 kg. Response rates were also somewhat higher for adolescents than for adults. The exposure was also slightly higher in adolescents. This is likely due to differences in body weight between adolescents and adults. Further, there was a slightly higher placebo effect in adolescents.

Safety

No exposure-safety relationship was observed among patients treated with 200 mg QD.

Overall, the exposure-response analyses support the efficacy and safety at a dose of 200 mg QD in adults and adolescents.

5.2.6.2. Conclusions

The clinical pharmacology of icotrokinra has been sufficiently described to support the current application and the recommended daily dose of 200 mg. The SmPC appropriately reflects these conclusions.

5.3. Clinical efficacy

5.3.1. Dose response studies

PSO2001 – phase 2b dose-ranging study in subjects with plaque psoriasis

Study 77242113**PSO2001** was a Phase 2b multicenter, randomised, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, PK, and immunogenicity of icotrokinra treatment over 16 weeks, in adults with moderate to severe plaque psoriasis. Participants were randomised to treatment with icotrokinra once daily (25, 50, 100 mg), twice daily (25, 100 mg), or placebo twice daily.

Methods

Participants included had a diagnosis of moderate to severe plaque psoriasis, defined by a PASI≥12, IGA≥3 and BSA ≥10%, with or without PsA, who were candidates for phototherapy or systemic treatment. They were naïve to IL-23 inhibitors and must have discontinued IL-12/23 inhibitors, IL-17 inhibitors, and anti-TNFα therapy at least 12 weeks or 5 half-lives (whichever is longer) prior to the first dose of study medication. Participants must have discontinued immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine) for at least 4 weeks, and topical therapies at least 2 weeks prior to the first dose of study medication.

A total of 255 participants was randomised in a 1:1:1:1:1:1 ratio to placebo, 25 mg, 50 mg, or 100 mg icotrokinra once daily, or 25 mg or 100 mg icotrokinra twice daily.

Study medication had to be taken orally, in the morning and evening, on an empty stomach (e.g., no food for ≥2 hours prior). Concomitant medications (topical, systemic, phototherapy) for the treatment of psoriasis were not allowed, with the exception of shampoos containing salicylic acid only, and topical moisturizers (except on the day of study visit, as this could interfere with the evaluation of psoriasis). The short-term (≤2 weeks) use of corticosteroids for indications other than psoriasis was to be limited to situations for which there were no adequate alternatives in the investigators' opinion.

The primary objective was to evaluate the dose-response relationship of oral administration of icotrokinra (once daily: 25, 50, 100 mg or twice daily: 25 mg, 100 mg) or placebo, for 16 weeks in patients with moderate-to-severe plaque psoriasis. The primary endpoint was the proportion of participants with PASI75 (≥75% improvement from baseline in PASI) at Week 16. Secondary endpoints included the change from baseline in PASI total score, the proportion of participants with PASI90, PASI100, IGA0/1, IGA0, and the change from baseline in BSA, all at Week 16.

For the primary analysis, composite strategy (non-responder imputation) was applied to address intercurrent event (ICE) 1 (discontinuation due to lack of efficacy or AE worsening of psoriasis) and ICE 2 (initiation of a protocol-prohibited therapy that could improve psoriasis) and treatment policy strategy (observed data) was applied to ICE 3 (discontinuation of intervention due to other reasons).

Participants with missing data after application of ICEs were also considered as non-responders. No adjustments for multiple comparisons were made for the secondary endpoints and nominal p-values were provided.

To assess the primary objective of the dose response profile of icotrokinra and facilitate the selection of icotrokinra dose and dosing regimen for future studies, Multiple Comparison Procedures with modelling (MCP-Mod) techniques were used to analyse the primary endpoint. In addition, for binary response endpoints, comparisons between each of the groups versus placebo were performed using a Cochran-Mantel-Haenszel (CMH) test stratified by the baseline weight (≤90 kg, >90 kg). For continuous endpoints, comparisons were performed using a MMRM model, with treatment group, baseline weight (≤90 kg, >90 kg), and baseline value for the corresponding endpoint as explanatory factors. The MMRM model also included visit, treatment group by visit interaction, baseline weight (≤90 kg, >90 kg) by visit interaction, and baseline value by visit interaction as additional explanatory factors.

Results

Of the 336 participants who were screened, a total of 255 participants was randomised into the study from 60 centers across countries/territories: 49% was from Europe (including 24% from Poland, 18% from Germany, 4% from Spain, 3% from France, and 1% from Great Britain), 33% was from North America, and 17% from Asia Pacific.

A total of 24 participants (9%) discontinued study intervention prior to Week 16: 8% in the combined icotrokinra groups and 16% in the placebo group. A numerically higher percentage of participants discontinued from study intervention in the placebo group and the 25 mg QD group (16% in each group) compared with the other groups (range 2% to 10%). Overall, the most common reasons for discontinuation were withdrawal by subject (3%), lack of efficacy, and 'lost to follow-up' (2% each). The most common reason for discontinuation in the placebo group was lack of efficacy and in the 25 mg QD group 'lost to follow-up'. Similar proportions of participants discontinued study participation.

The mean age was 44 years (range: 19 to 73 years), and the majority of participants were white (75%), and male (69%). The weight and BMI were comparable across all groups, with a mean (±SD) weight of 88 kg (±20) and a mean (±SD) BMI of 30 kg/m2 (±7).

At baseline 79% had moderate (IGA score of 3) and 21% severe (IGA score of 4) psoriasis. A slightly higher proportion of participants in the 25 mg QD group (30%) and the 100 mg BID group (29%) had an IGA score of 4 at baseline compared with the placebo group (12%) and other treatment groups (range 16% to 20%). Mean (SD) PASI total score was 19 (5.8), and mean (SD) BSA was 23% (13). Mean (SD) duration of psoriasis was 18.2 (12.8) years. In total 90%, 61%, 48%, and 37% of participants had a history of scalp, nail, hand and/or foot, and genital psoriasis, respectively. Prior to enrollment, 93% of participants had received topical therapies, 43% phototherapy, 48% conventional systemic treatments, 22% biologics, and 7% nonbiologic systemic agents such as apremilast, deucravacitinib, or tofacitinib. Demographics and baseline characteristics were generally similar among groups.

Through Week 16, 73% of participants used concomitant medications. The most frequently used concomitant medications were anti-inflammatory and antirheumatic products (18%), agents acting on the renin-angiotensin system (17%), and analgesics (16%). During the study, 13% of participants received concomitant treatment of moisturisers.

The proportion of participants with PASI75 at Week 16 was statistically significantly higher in each of the groups treated with icotrokinra compared with the placebo group. The 100 mg BID group had the highest proportion of participants with PASI75 response at Week 16 (Table 11). These data were confirmed by two sensitivity analyses and by the Per Protocol analysis. Efficacy was further supported

by secondary endpoints, including PASI90, PASI100, IGA response (see clinical AR section 3.2), change in BSA, Psoriasis Signs Symptoms Diary (PSSD), and Dermatological Life Quality Index (DLQI).

A statistically significant dose-response relation was detected across all groups for the primary endpoint.

Table 11. Primary endpoint: Proportion of participants with PASI75 at Week 16 (FAS PSO2001)

		JNJ-77242113				
	Placebo	25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID
Analysis set: Full analysis set	43	43	43	41	43	42
Subjects achieving ≥ 75% Improvement at Week 16[a]	4 (9.3%)	16 (37.2%)	25 (58.1%)	21 (51.2%)	28 (65.1%)	33 (78.6%)
Treatment difference (95% CI)[b]		27.9% (11.2%, 44.6%)	48.8% (31.9%, 65.8%)	41.9% (24.5%, 59.3%)	55.8% (39.3%, 72.3%)	69.4% (54.7%, 84.1%)
p-value[c]		0.002	< 0.001	< 0.001	< 0.001	< 0.001

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI were calculated adjusting for baseline weight category (≤ 90 kg, > 90 kg) using Mantel-Haenszel (MH) weights.
[c] The p-values are based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline weight category (≤ 90 kg, > 90 kg).

PSO2002 – Long-term extension dose-ranging study in participants with plaque psoriasis

Study 77242113**PSO2002** was the long-term extension (LTE) study for patients who completed PSO2001. All eligible participants from the initial study were given the option to enrol. Participants continued on their initial dose of icotrokinra (in Study PSO2001) while participants in the placebo group transitioned to 100 mg icotrokinra QD. The objective was to evaluate the long-term efficacy and safety of an additional 36 weeks of icotrokinra treatment (maximum total duration of exposure 52 weeks). The primary endpoint was the proportion of participants with PASI75 at Week 36. Methodology was generally similar to Study PSO2001.

A total of 227 participants entered the study. Of these, 36 participants (16%) discontinued the study intervention between week 16 (LTE Week 0) and Week 52 (LTE Week 36).

Efficacy was generally maintained from Week 16 through week 52. The 100 mg BID group showed the highest response rate (76%) at Week 52 compared to the lower doses (range 49% to 70%). The response rate in the placebo → 100 mg QD group was similar to the rate observed in the 100 mg QD group (66% and 65%) (Table 12). Maintenance of efficacy was further supported by secondary endpoints, including clinician-reported outcomes (PASI, IGA, BSA), as well as patient-reported outcomes (PSSD and DLQI).

Table 12. Proportion of participants with PASI75 at week 52 (FAS PSO2001 and PSO2002)

		JNJ-77242113				
	Placebo → 100 mg QD	25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID
Analysis set: Full analysis set	35	43	43	41	43	42
Subjects achieving ≥ 75% Improvement at Week 52[a]	23 (65.7%)	21 (48.8%)	30 (69.8%)	24 (58.5%)	28 (65.1%)	32 (76.2%)
95% CI[b]	(50.0%, 81.4%)	(33.9%, 63.8%)	(56.0%, 83.5%)	(43.5%, 73.6%)	(50.9%, 79.4%)	(63.3%, 89.1%)

[a] For subjects who were randomized to placebo at Week 0, only include those subjects who crossed over to JNJ-77242113 at or after Week 16.
[b] 95% CIs were calculated based on Wald method.
Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.

5.3.2. Main studies

5.3.2.1. Studies PSO3001, PSO3002 and PSO3004

Studies PSO3001, PSO3002, and PSO3004 were conducted in the same patient population. The design of these studies shares many similarities; the design of studies PSO3002 and PSO3004 is almost identical. This report provides a summary of the common methodology, highlighting individual differences where applicable. The results are presented together for all three studies.

5.3.2.1.1. Study titles

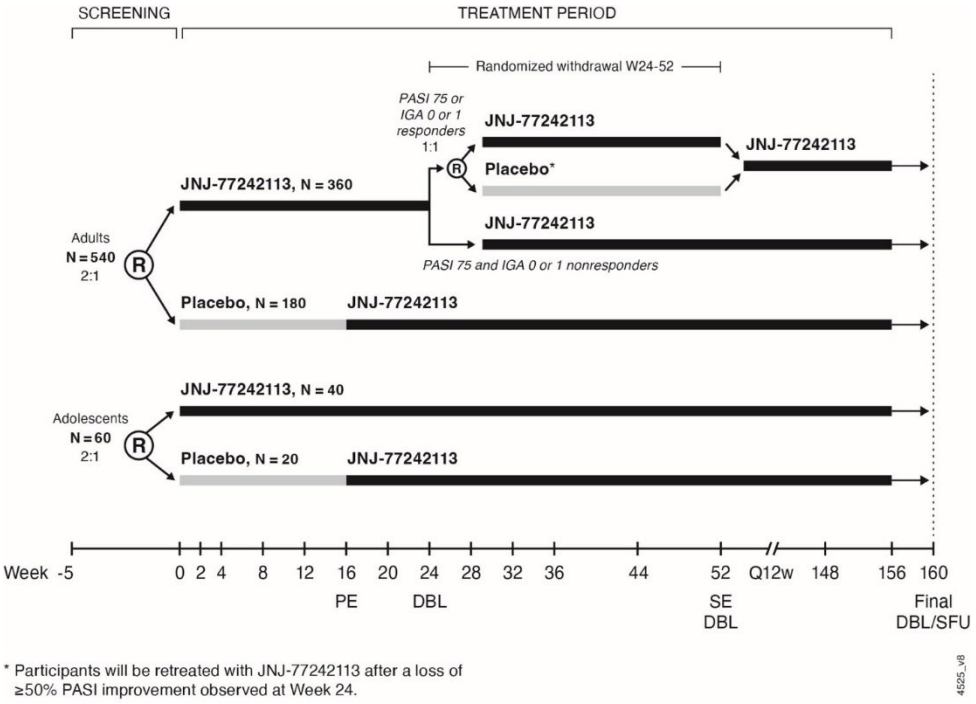
PSO3001: A phase 3 multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of JNJ-77242113 for the treatment of participants with moderate to severe plaque psoriasis with randomised withdrawal and retreatment.

PSO3002 and PSO3004: A phase 3 multicentre, randomised, double-blind, placebo-controlled and deucravacitinib active comparator-controlled study to evaluate the efficacy and safety of JNJ-77242113 for the treatment of participants with moderate to severe plaque psoriasis.

5.3.2.1.2. Study design

PSO3001 consisted of a 5-week screening period, a double-blind (DB) placebo-controlled period from week 0 to week 16, a randomised withdrawal and retreatment period from week 24 through week 52 (completed), and an open-label extension period from week 52 to week 156 (ongoing) (Figure 13).

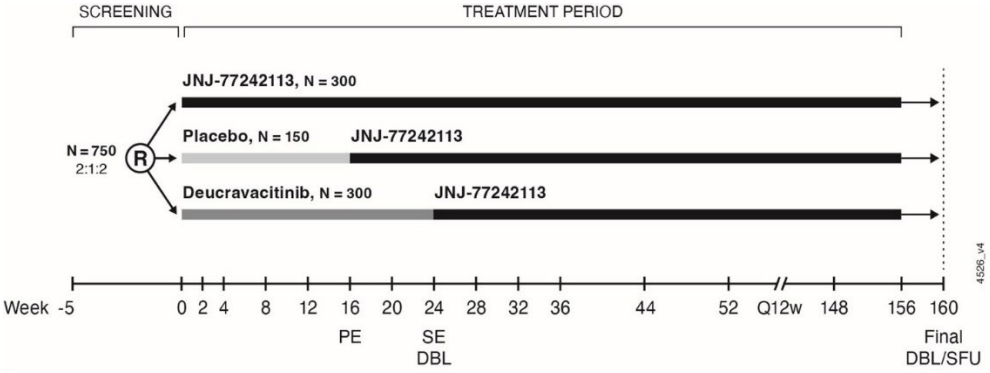
Figure 13. Schematic overview of Study PSO3001



Similar to Study PSO3001, Study **PSO3002** and **PSO3004** consisted of a 5-week screening period and a DB placebo-controlled period from week 0 to week 16. In addition, the studies comprised a DB active comparator-controlled arm from week 0 to week 24 (completed), followed by an open-label period from week 24 onwards (Figure 14). The randomisation ratio and number of placebo-treated participants differ per study. PSO3002 planned to recruit 750 participants, of which 150 were to be randomised to placebo, 300 to icotrokinra, and 300 to deucravacitinib. PSO3004 planned to recruit 675

participants, of which 75 were to be randomised to placebo, 300 to icotrokinra, and 300 to deucravacitinib.

Figure 14. Schematic overview of Study PSO3002



Treatment

In **Study PSO3001,** icotrokinra was provided as a 200 mg film-coated tablet for oral administration. The matching placebo was identical to the icotrokinra tablet, except there was no active ingredient in the placebo formulation. Participants were instructed to take one tablet of study intervention at approximately the same time everyday upon waking, with 240 ml water on an empty stomach (no food intake for at least 2 hours before and for at least 30 minutes after taking the study intervention). Adolescent participants with difficulty swallowing tablets could suspend the tablets in at least 240 ml water.

In **PSO3002** and **PSO3004**, icotrokinra and the matching placebo were similar to Study PSO3001. The deucravacitinib capsules were encapsulated by the applicant. The matching placebo was identical to that of the deucravacitinib capsule, except there was no active ingredient in the placebo formulation. From week 0 to week 24 participants had to take 1 tablet of icotrokinra 200 mg or matching placebo, and 1 capsule of (over-encapsulated) deucravacitinib 6 mg or matching placebo once daily.

The method of administration (swallowed as whole, with water, no food) was similar to Study PSO3001.

Across studies: Concomitant medications (topical, systemic, phototherapy) for the treatment of psoriasis were not permitted up to week 52. The only exceptions were medicated shampoos containing salicylic acid and bland emollients; these were allowed on all body regions, but not within 24 hours before study, as this could interfere with the evaluation of psoriasis. No rescue therapies were permitted.

Randomisation

In **PSO3001** 600 participants were planned to be enrolled; approximately 540 adults and 60 adolescents were randomised in a 2:1 randomisation ratio to icotrokinra 200 mg QD or placebo QD at Week 0. Assignment to study intervention was based on a computer-generated randomisation schedule. Permuted block randomisation was performed with stratification by age group (adolescents <18 years and adults ≥18 years), baseline weight category (for adults only: ≤90kg, >90kg), and geographic region (North and South America, European Union, Asia Pacific). The Interactive Web Response System (IWRS) assigned a unique intervention code, which dictated the intervention assignment and matching study intervention kit for the participant.

Adult participants randomised to the icotrokinra group at Week 0 who reached a PASI75 or IGA 0/1 at

Week 24 were re-randomised 1:1 to either continued icotrokinra or transitioned to placebo. Rerandomisation was stratified by PASI90 status and geographic region. Participants who were re-randomised to placebo were retreated upon loss of ≥50% of their Week 24 PASI improvement or until Week 52 if loss of response was not observed.

All adolescent and adult participants who were randomised to placebo at Week 0 or who were randomised to icotrokinra at Week 0 but did not reach IGA 0/1 or PASI75 at Week 24 continued to receive icotrokinra.

In **PSO3002 and PSO3004** participants were assigned in a 2:1:2 and a 4:1:4 ratio, respectively, to icotrokinra, placebo, or deucravacitinib. Similar methods for randomisation were applied, except that there was no re-randomisation at week 24, since this study did not include a randomised withdrawal period.

Blinding

The sponsor, participants, caregivers, and investigators were blinded to treatment assignment. The investigator was allowed to break the blind in case of a specific emergency where intervention/course of action would be dictated by knowing the intervention status of the participant.

Additionally, in PSO3002 and PSO3004, deucravacitinib was encapsulated by the sponsor to ensure proper blinding.

Patient population

The patient population in Study **PSO3001** consisted of adults and adolescents (≥12 years and weighing ≥40 kg) with moderate to severe plaque psoriasis (with or without PsA) defined by a total PASI ≥12, a total IGA ≥3, and a total BSA ≥10%, who were candidates for phototherapy or systemic treatment.

Participants were not allowed to have a history of treatment with icotrokinra or a primary efficacy failure/clinically significant AE related to agents targeting IL-23. Participants had to have discontinued IL-23 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and anti-TNFα biologic therapy at least 12 weeks or 5 half-lives prior to the first administration of study intervention. Participants had to have discontinued systemic medications for psoriasis including immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine) for at least 4 weeks, and topical therapies for at least 2 weeks, prior to the first dose of study intervention.

Patients with current or history of malignancy, a history of chronic or recurrent infectious diseases, known or suspected immunodeficiency, a serious infection or a history of active TB were excluded.

Participants were recruited from sites in Europe, US, and Asia.

The patient population in Studies **PSO3002 and PSO3004** was similar to study PSO3001, except that no adolescents were included in these studies because deucravacitinib is not approved in this population. Further, participants were not allowed to have a history of deucravacitinib treatment, or primary efficacy failure/a clinically significant AE related to agents targeting TYK2.

Study assessments and endpoints

The co-primary efficacy endpoints in **PSO3001** were an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline at Week 16, and a PASI90 response at Week 16.

Key secondary endpoints included the proportion of participants with

- an IGA score of cleared (0) at Week 16
- a PASI75 response at Week 4

- a PASI90 response at Week 8
- a PASI75 response at Week 16
- a PASI100 response at Week 16
- an scalp-specific (ss-)IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline at Week 16
- Psoriasis Symptoms and Signs Diary (PSSD) score of 0 at Week 8
- at least a 4-point improvement from baseline in PSSD Itch score at Week 4
- at least a 4-point improvement from baseline in PSSD Itch score at Week 16
- PSSD symptom score of 0 at Week 16
- a PASI75 response at Week 52
- a PASI90 response at Week 52

Other secondary endpoints were related to the assessment of special site psoriasis (including the static Physician's Global Assessment of Genitalia (sPGA-G), PGA of hands and feet (hf-PGA), modified nail psoriasis severity index (mNAPSI), and fingernail PGA (f-PGA) and patient reported outcomes (including PSSD, and dermatology life quality index (DLQI).

The co-primary efficacy endpoints in **PSO3002** and **PSO3004** were the same as for study PSO3001: An IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline at Week 16, and a PASI90 response at Week 16. Key secondary endpoints were also largely similar, except for some differences in the hierarchy and some additional endpoints to evaluate the difference between icotrokinra and deucravacitinib (at week 16 and week 24).

Key secondary endpoints were the proportion of participants with:

- an IGA score of cleared (0) at Week 16
- a PASI75 response at Week 4
- a PASI90 response at Week 8
- a PASI75 response at Week 16
- a PASI100 response at Week 16
- an ss-IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline at Week 16
- PSSD symptom score of 0 at Week 8
- PSSD symptom score of 0 at Week 16
- at least a 4-point improvement from baseline in PSSD Itch score at Week 4
- at least a 4-point improvement from baseline in PSSD Itch score at Week 16
- IGA score of 0 or 1 and a 2-grade improvement from baseline at Week 16 and 24
- IGA score of 0 at Week 16 and 24
- PASI75 at Week 16 and 24
- PASI90 at Week 16 and 24

- PASI100 at Week 16 and 24
- PSSD symptom score of 0 at week 15.

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective was to evaluate the efficacy of icotrokinra in participants with moderate to severe plaque psoriasis.

The primary hypothesis of studies PSO3001, PSO3002 and PSO3004 was that icotrokinra is superior to placebo in the treatment of participants with moderate to severe plaque psoriasis as assessed by the proportion of participants who achieve an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline at Week 16, and the proportion of participants who achieve a PASI90 response at Week 16. If superiority for both endpoints had been achieved, the study was considered positive.

Estimands for the primary objective

Table 13. Estimands for primary objective

Population	Study PSO3001: Patients ≥12 years of age with moderate to severe plaque psoriasis. Studies PSO3002 and PSO3004: Adult patients with moderate to severe plaque psoriasis.
Treatment condition<s>	Assignment to experimental treatment icotrokinra 200 mg QD, compared to assignment to placebo, regardless of discontinuation due to ICE 3.
Endpoint (variable)	Achieving a PASI90 response at Week 16, where a PASI 90 responder is defined as a patient meeting the PASI90 criteria at Week 16 and not experiencing either ICE 1 or 2. Achieving an IGA 0 or 1 response at Week 16, where an IGA 0 or 1 responder is defined as a patient meeting the IGA 0 or 1 criteria at Week 16 and not experiencing either ICE 1 or 2.
Population-level summary	Difference in proportions.
Intercurrent events and strategy to handle them	
1. Discontinuation of treatment due to lack of efficacy, or due to an AE of worsening of psoriasis.	Composite Strategy: The occurrence of this ICE is captured in the variable definition as patients with these ICEs are considered non-responders.
2. Initiation of other medication or therapy that could improve psoriasis.	Composite Strategy: The occurrence of this ICE is captured in the variable definition as patients with these ICEs are considered non-responders.
3. Discontinuation of treatment for other reasons than ICE 1.	Treatment Policy: Strategy targeting the effect of treatment assignment, regardless of the occurrence of this ICE.

Note: For patients experiencing multiple ICEs, ICE 2 will override ICE 3 and the composite strategy will be applied.

Study PSO3001: For an adult or adolescent patient with moderate to severe psoriasis, what would be the expected effect of being assigned icotrokinra on the likelihood of experiencing a treatment response at Week 16 where patients discontinuing treatment due to lack of efficacy, or AE of worsening of psoriasis are considered non-responders and regardless of other discontinuations?

Studies PSO3002 and PSO3004: For an adult patient with moderate to severe psoriasis, what would be the expected effect of being assigned icotrokinra on the likelihood of experiencing a treatment response at Week 16 where patients discontinuing treatment due to lack of efficacy, or AE of worsening of psoriasis are considered non-responders and regardless of other discontinuations?

Statistical methods for estimation and sensitivity analysis on primary estimands

For purposes of analysis, the following analysis sets were defined:

Population	Description
Enrolled	All participants who signed the ICF
Randomised	All participants who were randomised in the study.
FAS	All participants who were randomised in the study.
Per-protocol Analysis Set	A subset of participants in the full FAS who were in general compliance with the protocol elements that could affect the efficacy assessments.
Safety Analysis Set	All randomised participants who took at least 1 dose of study intervention.
PK Analysis Set	All randomised participants who received at least 1 dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra
Immunogenicity Analysis Set	All randomised participants who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.

In detail: For the efficacy analyses in studies PSO3001, PSO3002 and PSO3004, the FAS was used according to the participants' assigned treatment to which they were randomised, regardless of the treatment they received. The FAS included all randomised participants.

Safety analyses included all randomised participants who received at least 1 administration of study intervention and participants were analysed based on the treatment they actually received, regardless of the treatment groups to which they were assigned.

In the co-primary analyses, the proportion of PASI90 responders and IGA 0 or 1 responders at Week 16 was summarised by treatment group. To address the primary objective, a 2-sided (α=0.05) CMH Chi-square test stratified by age group (adults, adolescents, study PSO3001 only), baseline weight category for adults (≤90kg in adults, >90kg in adults, adolescents), and geographic region (AMER, EU, APAC) was used. Difference in response rates between the icotrokinra group and the placebo group at Week 16 and their corresponding 95% CIs (using Miettinen-Nurminen method) were calculated.

To address the robustness of the co-primary endpoints analyses, 2 sensitivity analyses and a supplementary analysis, as specified below, were conducted.

- Sensitivity Analysis 1 (MI): After accounting for the ICEs as in the primary analysis, missing data were imputed using multiple imputation method by fully conditional specification.
- Sensitivity Analysis 2 (Tipping Point analysis): After the occurrence of ICEs as in the primary analysis, Bernoulli draws over a range of possible scenarios (i.e., 0% to 100% in increment of 10%, for the placebo group and the icotrokinra group independently) for the treatment effects

were used to impute missing IGA 0/1 and PASI90 response status at Week 16. For this tipping point analysis, the analysis allowed for assumptions about the response rates in the 2 arms to vary independently; furthermore, it included scenarios where imputed missing values on the icotrokinra group had worse outcomes than those in the placebo group.

In two supplementary analyses, the co-primary endpoints was also analysed utilising the treatment policy estimand and in the per protocol population based on the primary estimand.

For each of the subgroups defined below, the difference between the icotrokinra treatment group and placebo/deucravacitinib group on the proportion of participants with an IGA 0 or 1 and PASI90 response rate and key selected secondary endpoints at Week 16, and their 95% confidence intervals were calculated. No p-values would be provided. Subgroup analyses for adolescents were only performed in study PSO3001.

Table 14. Subgroups definition criteria for statistical analysis

Subgroup	Definition
Baseline demographics:	
Region	Define based on UN guidance as per the M49 standard • AMER • EU • APAC
Sex	• male • female • other
Race	• American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or Other Pacific Islander • White • Multiple • Unknown • Not reported
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino • Not Reported • Unknown
Age Group (years)	• <18 • 18-<45 • 45-<65 • ≥ 65 years
BMI	• normal <25 kg/m^2 • overweight 25-<30 kg/m^2 • obese ≥30 kg/m^2
Body Weight Group (kg)	• ≤90kg, >90kg
Baseline disease characteristics:	
Age at diagnosis (years) (adults)	• <median (adults) • ≥median (adults)
Age at diagnosis (years) (adolescents)	• <median (adolescents) • ≥median (adolescents)
Psoriasis disease duration (years) (adults)	• <median (adults) • ≥median (adults)
Psoriasis disease duration (years) (adolescents)	• <median (adolescents) • ≥median (adolescents)
Baseline PASI	• <20 • ≥20
Baseline IGA	• =4 • ≤3
Baseline BSA	• <20% • ≥20%
Baseline DLQI, CDLQI	• <10 • ≥10
Psoriatic arthritis	• Yes • No
Psoriasis medication history:	
Phototherapy (ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA])	• Never used • Ever used

Subgroup	Definition
Systemics (Conventional non-biologic systemics, Novel non-biologic systemics, systemic 1,25-dihydroxy vitamin D3 and analogues, phototherapy, biologics)	• Never used • Ever used
Conventional non-biologic systemics (PUVA, MTX, cyclosporine, acitiretin, azathioprine, or fumarate)	• Never used • Ever used
Novel non-biologic systemics (apremilast, deucravacitinib, or tofacitinib)	• Never used • Ever used
Biologics (etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, certolizumab pegol)	• Never used • Ever used
Anti-TNFα agent (etanercept, infliximab, certolizumab pegol, or adalimumab)	• Never used • Ever used
IL-12/23 inhibitors (ustekinumab, briakinumab)	• Never used • Ever used
IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab)	• Never used • Ever used
IL-17 inhibitors (secukinumab, ixekizumab, or brodalumab)	• Never used • Ever used

Sample size

For study PSO3001, the assumptions for the sample size and power calculations were based on placebo response rates from the historical psoriasis clinical studies and data from the Phase 2b Study PSO2001.

- The proportion of participants in the placebo group who achieve an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline and a PASI90 response at Week 16 are 8% and 5%, respectively.
- The proportion of participants in the icotrokinra group who achieve an IGA score of cleared (0) or minimal (1) at least a 2-grade improvement from baseline and a PASI90 response at Week 16 are 64% and 59%, respectively.

Based on the above assumptions, a total of approximately 600 participants to be randomised in a 2:1 ratio to icotrokinra 200 mg once daily (n=400) or placebo (n=200) at Week 0 would provide >99% power to detect significant differences at a 2-sided significance level of 0.05 for both co-primary endpoints at Week 16.

The sample size was also chosen to ensure a reasonable safety database to assess the overall safety of icotrokinra.

In addition, assuming approximately 75% of the adult participants originally randomised to icotrokinra group are PASI75 responders and will be randomised in a 1:1 ratio to either continue or undergoing withdrawal at Week 24. This portion of the study would ensure at least 95% power to detect a 20 percentage points of difference in PASI75 response rates at Week 52 between these 2 groups.

For studies PSO3002 and PSO3004, additional assumptions for the sample size and power calculations were based data from the Phase 2b study PSO2001 and 2 deucravacitinib Phase 3 studies (POETYK PSO-1 and POETYK PSO-2) that evaluated the safety and efficacy of deucravacitinib in the treatment of adult participants with moderate to severe psoriasis.

- The proportion of participants in the icotrokinra who achieve PASI75 response at Week 16 is 75%.
- The proportion of participants in the deucravacitinib group who achieve an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline and a PASI75 response and a PASI90 response at Week 16 is 51%, 55%, and 30%, respectively.

Based on the above assumptions, with a total of approximately 750 participants to be randomised in a 2:1:2 ratio to icotrokinra (n=300), placebo (n=150), and deucravacitinib (n=300) at Week 0:

- There will be >99% power at a 2-sided significance level of 0.05 to detect significant differences for both coprimary endpoints in the proportion of participants achieving an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline and the proportion of participants who achieve a PASI90 response between the placebo and icotrokinra groups at Week 16.
- There will be >99% power to detect a 20-percentage difference respectively in the proportion of participants achieving a PASI75 response between the deucravacitinib and icotrokinra groups at Week 16 at a 2-sided significance level of 0.05.

There will be approximately 90% power at a 2-sided significance level of 0.05 to detect a true 13% difference in the proportion of participants with an IGA score of cleared (0) or minimal (1) between the icotrokinra and deucravacitinib groups at Week 16 or Week 24.

Secondary objectives

Study PSO3001: Secondary objectives were to further evaluate the general and special area psoriasis efficacy of icotrokinra in participants with moderate to severe plaque psoriasis; to evaluate the effect of icotrokinra on PROs in participants with moderate to severe plaque psoriasis; and to evaluate the maintenance of efficacy of icotrokinra compared with treatment withdrawal during the randomised withdrawal period.

Studies 3002 and 2004: Secondary objectives were to further evaluate the general and special area psoriasis efficacy of icotrokinra compared with placebo in participants with moderate to severe plaque psoriasis; to evaluate the effect of icotrokinra compared with placebo on PROs in participants with moderate to severe plaque psoriasis; and to evaluate the efficacy and effect of icotrokinra compared with deucravacitinib on ClinROs and a PRO in participants with moderate to severe plaque psoriasis.

Estimands for the secondary objectives

The main estimands for key secondary endpoints at or prior to Week 16 had same attributes as co-primary estimands, except for attributes of variable and population. For the endpoints based on ss-IGA score the population was limited to patients with a baseline ss-IGAQ score >= 2, for PSSD symptom scores, the population was limited to those with baseline score > 0 and for PSSD-itch score to patients with a baseline score >=4. In studies PSO3002 and 3004, the treatment condition attribute also included comparison to deucravacitinib.

In study 3001, the main estimands for key secondary endpoints at Week 52 had same attributes as co-primary estimands, except for attributes of variable, population, and population level summary. The populations were restricted to PASI75 responders at week 24, and the population level summary for time to loss of PASI endpoints was the hazard ratio versus placebo. In addition, ICE 4 was defined as meeting criteria of loss of ≥50% Week 24 PASI improvement. Patients with this ICE were handled using the composite strategy.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The proportions of participants achieving a key secondary efficacy response were summarised and compared between treatment groups in the same manner as the co-primary endpoints, using appropriate stratification factors. In case of rare events for the binary endpoint, Fisher's exact test was used.

For the analyses related to the time-to-event key secondary endpoints in study PSO3001, the life table method was used to estimate the distribution of time to loss of PASI response for the intervention group. The median time to loss of PASI response was provided. The comparison of the distribution of loss of response between icotrokinra and placebo group was based on a stratified log-rank test. Hazard ratio and its 95% CI were estimated based on a stratified Cox's regression model with intervention as the explanatory variable. Stratification factors used in these analyses included PASI90 response status at Week 24 (if applicable) and geographic region. Missing data was not imputed for time to event endpoints.

For the following 4 key secondary analyses in studies PSO3002 and 3004, non-inferiority was assessed before superiority (the non-inferiority margin for these comparisons is predefined as 12%), and superiority was assessed after non-inferiority was established:

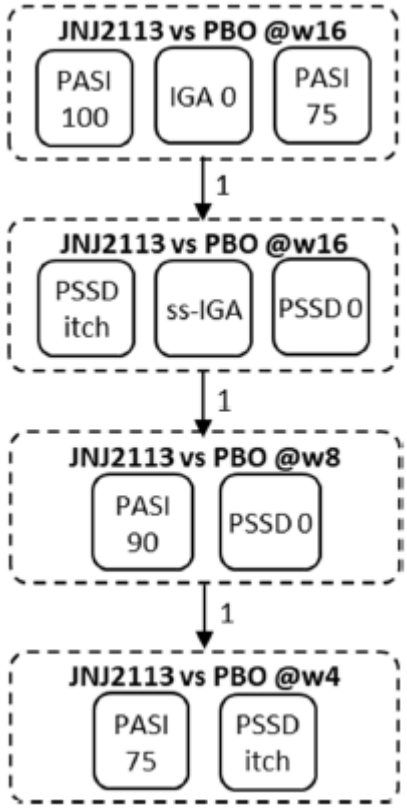
- Proportion of participants achieving PASI75 at Week 16 and at Week 24
- Proportion of participants achieving an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline at Week 16 and Week 24.

The non-inferiority margin for these comparisons was predefined as 12%. This margin was determined based on the historical data from placebo-controlled deucravacitinib Phase 3 studies (Armstrong 2023). Based on the meta-analyses of these 2 Phase 3 studies, the lower bound of the 95% CI for the treatment effect on the IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline and PASI75 response at Week 16 between the deucravacitinib and placebo groups was approximately 38.8% and 40.0%, respectively. Therefore, a non-inferiority margin of 12% was chosen to preserve approximately 70% of deucravacitinib benefit.

In study PSO3001, a multiplicity adjustment procedure was used to control the overall Type I error rate for the 2 coprimary and 14 key secondary endpoints. Since there were 2 randomisations utilised in the study (i.e., 2 different experiments), the endpoints prior to or at Week 16, and the endpoints related to the randomised withdrawal will each be assigned with a 2-sided significance level of 0.05. The testing procedure began with the test of superiority of icotrokinra group compared with placebo group in the co-primary endpoints. Key secondary endpoints would only be tested if both coprimary endpoints are significant. Otherwise, all subsequent p-values for all the key secondary endpoints were considered nominal.

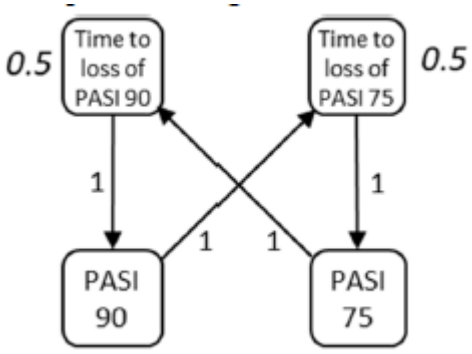
The secondary endpoints during the first 16 weeks of placebo-controlled period were grouped in 4 tiers. Within each tier, the Bonferroni–Holm's (Holm S 1979) procedure (Figure 15) was used to test all endpoints in that tier with an overall type I error rate of 0.05 (2-sided). If any test within a tier is not significant, the other tests in the same tier could still be declared significant if they meet the Holm thresholds, but the formal testing stopped and all p-values in subsequent tiers were considered nominal. If all tests within a tier were significant, then testing continued to the next tier.

Figure 15. Testing procedure for the key secondary endpoints during the placebo-controlled period



Additionally, if the co-primary endpoints were significant, the following endpoints during the randomised withdrawal portion were also tested using the graphical approach at a 2-sided overall alpha of 0.05 (Figure 16): time to loss of PASI75, time to loss of PASI90, PASI75 response at Week 52 and PASI90 response at Week 52.

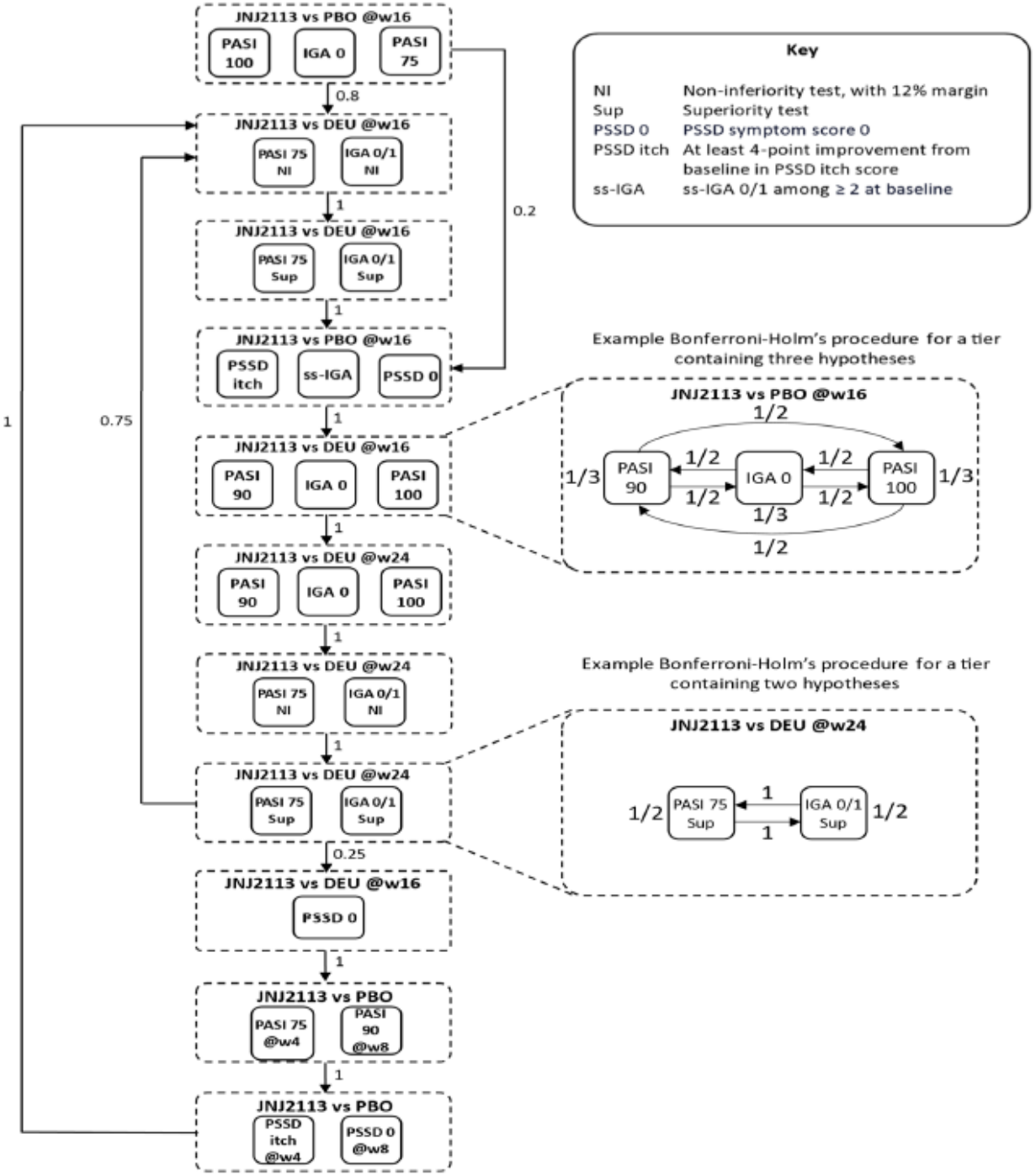
Figure 16. Testing procedure for the key secondary endpoints during the placebo-controlled period



In studies PSO3002 and PSO3004, a multiplicity adjustment procedure will be used to control the overall Type I error rate of α=0.05 (2-sided) for the primary and 21 key secondary endpoints. The testing procedure begins with the test of superiority of the icotrokinra group compared with the placebo group in the coprimary endpoints. Key secondary endpoints will only be tested if both co-primary endpoints are significant. If at least one of the coprimary endpoints is not significant (i.e., p>0.05), all subsequent p-values in the testing hierarchy will be considered nominal. After testing of the coprimary endpoints, and if both p-values are ≤0.05, the testing procedure will continue with tests

for the key secondary endpoints, which are grouped into different tiers as presented below by using the graphical approach with Type I error -propagation (Figure 17).

Figure 17. Testing procedure for the key secondary endpoints



5.3.2.1.4. Results

Participant flow and numbers analysed

PSO3001

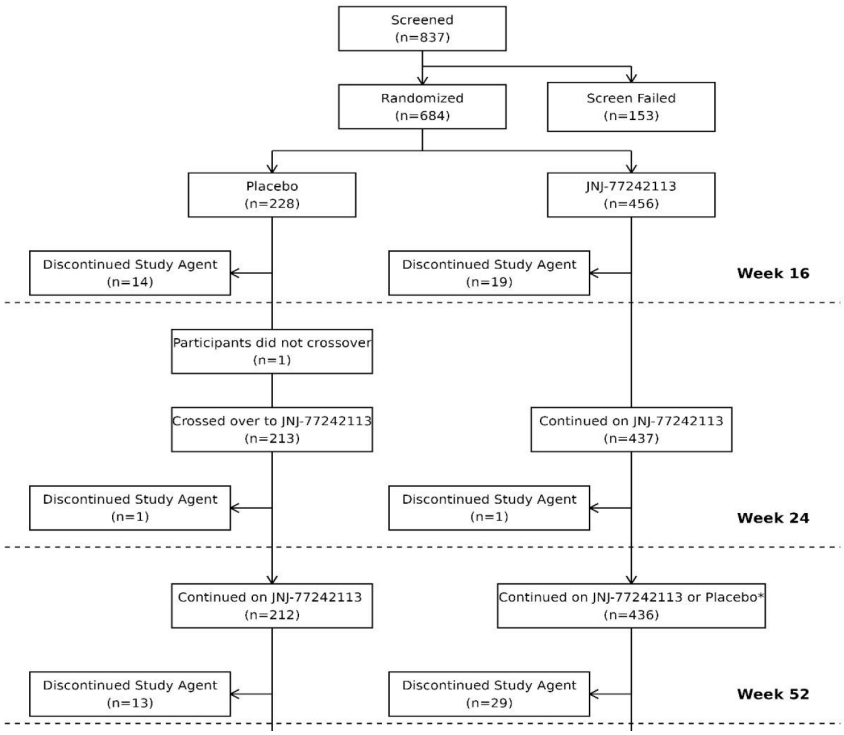
Of the 837 participants who were screened, 684 participants were randomised into the study and all received their allocated treatment. A total of 66/684 participants were adolescents (age ≥12 to <18 years of age). The study was conducted across 138 sites in 15 countries/territories.

Through week 16 a total of 33 (5%) participants discontinued study intervention (4% in the placebo group; 6% in the icotrokinra group). Most common reasons were withdrawal by subject (2%) in the icotrokinra group and lack of efficacy (4%) in the placebo group.

Through week 52 a total of 49 (11%) participants in the icotrokinra group (including discontinuations during the withdrawal period) and 14 (7%) participants in the placebo --> icotrokinra group, discontinued study intervention. The most common reasons in the icotrokinra group were lack of efficacy and adverse event (3% each). The most common reasons in the placebo --> icotrokinra group were lack of efficacy, adverse event, and withdrawal by subject (3% each).

The participant flow is shown in Figure 18.

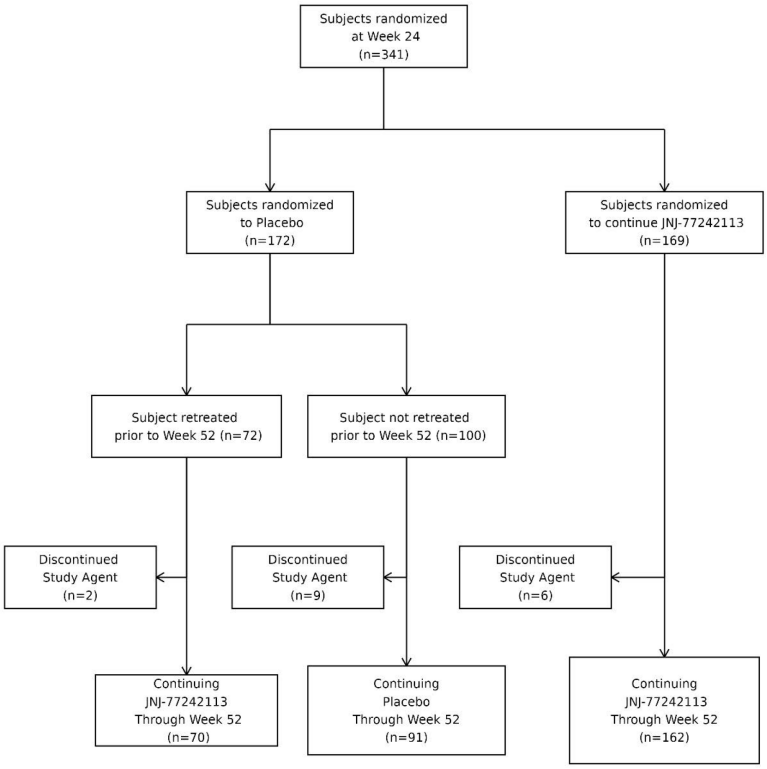
Figure 18. Participant flow PSO3001



Randomised withdrawal phase (Week 24 to Week 52)

At week 24 in total 341 adult participants in the icotrokinra group were reported as PASI75 or IGA 0/1 responders and were re-randomised to either placebo or icotrokinra. Participants were to be retreated upon loss of ≥50% of their Week 24 PASI improvement; in total 72 participants re-randomised to placebo were retreated (Figure 19).

Figure 19. Treatment disposition from Week 24 through week 52 PSO3001



Among the participants that were re-randomised to placebo and icotrokinra, in total 17 participants discontinued study intervention from week 24 through week 52. In those re-randomised to placebo 11 (6%) discontinued; most common reasons were lack of efficacy (3%) and adverse event (2%). In those re-randomised to icotrokinra 6 (4%) discontinued; the most common reason was withdrawal by subject (2%).

Due to entry errors into the IWRS:

- 1 participant who was not reported as a Week 24 PASI75 or IGA 0/1 responder was incorrectly rerandomised at Week 24 (rerandomised placebo group) and 2 participants who were reported as Week 24 responders were not rerandomised when they were required to be rerandomised per protocol.
- 10 participants were in the incorrect randomisation stratum with respect to PASI90 response category at Week 24.
- Retreatment for 12 participants was not correctly handled. Ten participants were retreated at a visit when loss of response [≥50% loss of Week 24 PASI improvement] was not observed and 2 participants were not retreated at the visit when loss of response was observed.

PSO3002

Of the 986 participants who were screened, 774 participants were randomised into the study, and 772 received their allocated treatment. The study was conducted across 149 sites in 13 countries/territories.

Through week 52 a total of 60 (8%) participants discontinued study intervention (9% in the placebo --> icotrokinra group, 5% in the deucravacitinib --> icotrokinra group, and 11% in the icotrokinra group). The most common reason was withdrawal by subject.

PSO3004

Of the 917 participants who were screened, 731 participants were randomised into the study, and all received their allocated treatment. The study was conducted across 114 sites in 11 countries/territories.

Through week 52 a total of 55 (8%) participants discontinued study intervention (3% in the placebo --> icotrokinra group, 5% in the deucravacitinib --> icotrokinra group, and 12% in the icotrokinra group)

After approval of the Week 52 CSR, multiple GCP concerns were identified at one site (CB4-US10098). The site enrolled 8 participants (1 placebo, 2 icotrokinra, and 5 deucravacitinib).

Note to reader: The applicant provided an updated CSR in which these 8 participants were excluded from the efficacy analyses. The results and conclusions were consistent with the original results and conclusions. It was determined that safety data from these participants were not impacted, and all safety data from participants at this site were retained in the study analyses.

Deviations from study plan

Study protocol for PSO3001 was amended twice (03 August 2023 and 12 October 2023). The first amendment was prior to the study start; the second amendment was following regulatory feedback and pertained to minor clarifications of the protocol.

Study protocol for PSO3002 was amended twice (24 July 2023 and 06 December 2023). The first amendment was prior to the study start; the second amendment was following regulatory feedback and pertained to minor clarifications of the protocol.

Study protocol for PSO3004 was amended once (21 February 2024) following regulatory feedback and pertained to minor clarifications of the protocol.

Major protocol deviations occurred in 12 participants in PSO3001, 49 in PSO3002, and 37 in PSO3004.

Baseline data

Across studies PSO3001, PSO3002, PSO3004 demographic and baseline disease characteristics were overall balanced between treatment groups (Table 15).

Table 15. Summary of baseline demographics PSO3001, PSO3002, PSO3004 (FAS)

	Moderate to Severe Plaque Psoriasis Studies				
	77242113PSO3001	77242113PSO3002	77242113PSO3004	77242113PSO3002 and 77242113PSO3004	Combined[a]
Analysis set: Full analysis set	684	774	731	1505	2189
Age, years					
N	684	774	731	1505	2189
Mean (SD)	42.6 (16.38)	46.7 (13.37)	46.1 (13.56)	46.4 (13.46)	45.2 (14.54)
Median	43.0	47.0	45.0	46.0	45.0
Range	(12; 85)	(18; 81)	(18; 86)	(18; 86)	(12; 86)
IQ range	(30.5; 56.0)	(37.0; 57.0)	(35.0; 56.0)	(36.0; 57.0)	(35.0; 56.0)
<18 years	66 (9.6%)	0	0	0	66 (3.0%)
≥18 to <45 years	300 (43.9%)	344 (44.4%)	350 (47.9%)	694 (46.1%)	994 (45.4%)
≥45 to <65 years	253 (37.0%)	346 (44.7%)	307 (42.0%)	653 (43.4%)	906 (41.4%)
≥65 years	65 (9.5%)	84 (10.9%)	74 (10.1%)	158 (10.5%)	223 (10.2%)
Sex					
N	684	774	731	1505	2189
Female	237 (34.6%)	246 (31.8%)	235 (32.1%)	481 (32.0%)	718 (32.8%)
Male	447 (65.4%)	528 (68.2%)	496 (67.9%)	1024 (68.0%)	1471 (67.2%)
Undifferentiated	0	0	0	0	0
Unknown	0	0	0	0	0
Race					
N	684	774	731	1505	2189
American Indian or Alaska Native	1 (0.1%)	3 (0.4%)	2 (0.3%)	5 (0.3%)	6 (0.3%)
Asian	167 (24.4%)	180 (23.3%)	89 (12.2%)	269 (17.9%)	436 (19.9%)
Black or African American	8 (1.2%)	11 (1.4%)	22 (3.0%)	33 (2.2%)	41 (1.9%)
Native Hawaiian or Other Pacific Islander	2 (0.3%)	2 (0.3%)	5 (0.7%)	7 (0.5%)	9 (0.4%)
White	494 (72.2%)	570 (73.6%)	604 (82.6%)	1174 (78.0%)	1668 (76.2%)
Multiple	1 (0.1%)	0	3 (0.4%)	3 (0.2%)	4 (0.2%)
Not Reported	7 (1.0%)	5 (0.6%)	5 (0.7%)	10 (0.7%)	17 (0.8%)
Unknown	4 (0.6%)	3 (0.4%)	1 (0.1%)	4 (0.3%)	8 (0.4%)
Ethnicity					
N	684	774	731	1505	2189
Hispanic or Latino	88 (12.9%)	132 (17.1%)	102 (14.0%)	234 (15.5%)	322 (14.7%)
Not Hispanic or Latino	585 (85.5%)	636 (82.2%)	628 (85.9%)	1264 (84.0%)	1849 (84.5%)
Not Reported	4 (0.6%)	4 (0.5%)	0	4 (0.3%)	8 (0.4%)
Unknown	7 (1.0%)	2 (0.3%)	1 (0.1%)	3 (0.2%)	10 (0.5%)
Weight, kg					
N	684	774	730	1504	2188
Mean (SD)	86.2 (22.23)	87.5 (22.69)	89.0 (20.58)	88.2 (21.70)	87.6 (21.88)
Median	84.5	84.5	86.6	85.7	85.0
Range	(41; 200)	(39; 211)	(43; 181)	(39; 211)	(39; 211)
IQ range	(70.9; 97.5)	(72.5; 98.6)	(75.0; 100.9)	(73.6; 99.8)	(72.6; 99.2)
≤90 kg	410 (59.9%)	466 (60.2%)	422 (57.8%)	888 (59.0%)	1298 (59.3%)
>90 kg	274 (40.1%)	308 (39.8%)	308 (42.2%)	616 (41.0%)	890 (40.7%)
Height, cm					
N	682	774	730	1504	2186
Mean (SD)	171.3 (9.63)	171.8 (9.46)	172.7 (9.47)	172.2 (9.47)	171.9 (9.53)
Median	171.5	172.0	173.0	172.1	172.0
Range	(147; 203)	(147; 204)	(143; 203)	(143; 204)	(143; 204)
IQ range	(164.0; 178.0)	(165.0; 178.0)	(167.0; 180.0)	(166.0; 179.0)	(165.0; 179.0)
Body mass index, kg/m^2					
N	682	774	729	1503	2185
Mean (SD)	29.3 (6.97)	29.5 (7.08)	29.8 (6.52)	29.7 (6.81)	29.6 (6.86)
Median	28.3	28.5	28.8	28.6	28.5
Range	(16; 64)	(16; 83)	(15; 58)	(15; 83)	(15; 83)
IQ range	(24.8; 32.8)	(24.8; 32.7)	(25.6; 33.4)	(25.2; 33.1)	(25.1; 33.0)
Normal <25 kg/m^2	181 (26.5%)	202 (26.1%)	160 (21.9%)	362 (24.1%)	543 (24.9%)
Overweight ≥25 to <30 kg/m^2	234 (34.3%)	268 (34.6%)	256 (35.1%)	524 (34.9%)	758 (34.7%)
Obese ≥30 kg/m^2	267 (39.1%)	304 (39.3%)	313 (42.9%)	617 (41.1%)	884 (40.5%)
Geographic region					
N	684	774	731	1505	2189
North America	195 (28.5%)	208 (26.9%)	200 (27.4%)	408 (27.1%)	603 (27.5%)
USA	124 (18.1%)	124 (16.0%)	124 (17.0%)	248 (16.5%)	372 (17.0%)
Canada	71 (10.4%)	84 (10.9%)	76 (10.4%)	160 (10.6%)	231 (10.6%)
South America	26 (3.8%)	58 (7.5%)	25 (3.4%)	83 (5.5%)	109 (5.0%)
European Union	315 (46.1%)	344 (44.4%)	430 (58.8%)	774 (51.4%)	1089 (49.7%)
Asia-Pacific	148 (21.6%)	164 (21.2%)	76 (10.4%)	240 (15.9%)	388 (17.7%)

[a] Includes subjects in 77242113PSO3001, 77242113PSO3002, and 77242113PSO3004 studies.
Note: N's for each parameter reflect non-missing values.

Table 16. Summary of baseline disease characteristics PSO3001, PSO3002, PSO3004 (FAS)

	77242113PSO3001	77242113PSO3002	77242113PSO3004	77242113PSO3002 and 77242113PSO3004	Combined[a]
Analysis set: Full analysis set	684	774	731	1505	2189
Psoriasis disease duration, years					
N	684	774	731	1505	2189
Mean (SD)	17.09 (13.521)	17.31 (12.128)	17.58 (13.061)	17.44 (12.587)	17.33 (12.884)
Median	14.00	15.00	15.00	15.00	14.58
Range	(0.4; 69.1)	(0.5; 56.0)	(0.4; 68.0)	(0.4; 68.0)	(0.4; 69.1)
IQ range	(6.00; 25.00)	(8.00; 24.15)	(7.00; 25.00)	(7.36; 25.00)	(7.00; 25.00)
Age at diagnosis, years					
N	684	774	731	1505	2189
Mean (SD)	25.7 (14.90)	29.5 (15.22)	28.6 (15.27)	29.1 (15.25)	28.0 (15.22)
Median	23.0	27.0	25.0	26.0	25.0
Range	(0; 77)	(0; 73)	(0; 74)	(0; 74)	(0; 77)
IQ range	(14.0; 35.0)	(18.0; 40.0)	(17.0; 39.0)	(17.0; 40.0)	(16.0; 38.0)
IGA score					
N	684	774	731	1505	2189
Severe (4)	170 (24.9%)	158 (20.4%)	145 (19.8%)	303 (20.1%)	473 (21.6%)
Moderate (3)	514 (75.1%)	616 (79.6%)	586 (80.2%)	1202 (79.9%)	1716 (78.4%)
Mild (2)	0	0	0	0	0
PASI total score (0-72)					
N	684	774	731	1505	2189
Mean (SD)	19.89 (7.493)	20.10 (7.270)	19.82 (6.912)	19.96 (7.097)	19.94 (7.221)
Median	17.45	18.00	17.80	18.00	18.00
Range	(12.0; 58.3)	(11.6; 62.4)	(10.8; 51.6)	(10.8; 62.4)	(10.8; 62.4)
IQ range	(14.70; 22.40)	(15.20; 22.70)	(15.10; 22.10)	(15.10; 22.30)	(15.00; 22.30)
<20	449 (65.6%)	480 (62.0%)	487 (66.6%)	967 (64.3%)	1416 (64.7%)
≥20	235 (34.4%)	294 (38.0%)	244 (33.4%)	538 (35.7%)	773 (35.3%)
BSA (%)					
N	684	774	731	1505	2189
Mean (SD)	25.5 (14.99)	26.1 (15.60)	25.8 (14.22)	26.0 (14.94)	25.8 (14.95)
Median	20.0	20.2	21.0	20.8	20.5
Range	(10; 83)	(10; 90)	(10; 85)	(10; 90)	(10; 90)
IQ range	(15.0; 31.0)	(15.0; 32.0)	(15.0; 32.0)	(15.0; 32.0)	(15.0; 32.0)
<20%	318 (46.5%)	361 (46.6%)	336 (46.0%)	697 (46.3%)	1015 (46.4%)
≥20%	366 (53.5%)	413 (53.4%)	395 (54.0%)	808 (53.7%)	1174 (53.6%)
ss-IGA score					
N	678	770	727	1497	2175
Severe Disease (4)	125 (18.4%)	105 (13.6%)	85 (11.7%)	190 (12.7%)	315 (14.5%)
Moderate Disease (3)	384 (56.6%)	428 (55.6%)	393 (54.1%)	821 (54.8%)	1205 (55.4%)
Mild Disease (2)	96 (14.2%)	130 (16.9%)	141 (19.4%)	271 (18.1%)	367 (16.9%)
Very Mild Disease (1)	33 (4.9%)	40 (5.2%)	46 (6.3%)	86 (5.7%)	119 (5.5%)
Absence of Disease (0)	40 (5.9%)	67 (8.7%)	62 (8.5%)	129 (8.6%)	169 (7.8%)
sPGA-G score					
N	678	769	727	1496	2174
Very Severe (5)	3 (0.4%)	4 (0.5%)	3 (0.4%)	7 (0.5%)	10 (0.5%)
Severe (4)	41 (6.0%)	45 (5.9%)	46 (6.3%)	91 (6.1%)	132 (6.1%)
Moderate (3)	92 (13.6%)	124 (16.1%)	124 (17.1%)	248 (16.6%)	340 (15.6%)
Mild (2)	66 (9.7%)	67 (8.7%)	74 (10.2%)	141 (9.4%)	207 (9.5%)
Minimal (1)	49 (7.2%)	49 (6.4%)	76 (10.5%)	125 (8.4%)	174 (8.0%)
Clear (0)	427 (63.0%)	480 (62.4%)	404 (55.6%)	884 (59.1%)	1311 (60.3%)
hf-PGA score					
N	678	769	727	1496	2174
Severe (4)	26 (3.8%)	20 (2.6%)	48 (6.6%)	68 (4.5%)	94 (4.3%)
Moderate (3)	125 (18.4%)	139 (18.1%)	170 (23.4%)	309 (20.7%)	434 (20.0%)
Mild (2)	111 (16.4%)	122 (15.9%)	118 (16.2%)	240 (16.0%)	351 (16.1%)
Almost Clear (1)	45 (6.6%)	63 (8.2%)	80 (11.0%)	143 (9.6%)	188 (8.6%)
Clear (0)	371 (54.7%)	425 (55.3%)	311 (42.8%)	736 (49.2%)	1107 (50.9%)
f-PGA score					
N	678	769	727	1496	2174
Severe (4)	8 (1.2%)	15 (2.0%)	13 (1.8%)	28 (1.9%)	36 (1.7%)
Moderate (3)	82 (12.1%)	96 (12.5%)	90 (12.4%)	186 (12.4%)	268 (12.3%)
Mild (2)	113 (16.7%)	132 (17.2%)	130 (17.9%)	262 (17.5%)	375 (17.2%)
Minimal (1)	97 (14.3%)	105 (13.7%)	108 (14.9%)	213 (14.2%)	310 (14.3%)
Cleared (0)	378 (55.8%)	421 (54.7%)	386 (53.1%)	807 (53.9%)	1185 (54.5%)
mNAPSI total score (0-130)[b]					
N	299	348	341	689	988
Mean (SD)	17.9 (15.58)	17.0 (16.59)	20.0 (17.70)	18.5 (17.20)	18.3 (16.72)
Median	14.0	12.0	16.0	14.0	14.0
Range	(0; 93)	(0; 105)	(0; 100)	(0; 105)	(0; 105)
IQ range	(6.0; 26.0)	(6.0; 23.0)	(7.0; 28.0)	(6.0; 25.0)	(6.0; 25.0)

The prior psoriasis treatments and concomitant medications were overall well balanced across treatment groups and studies except for a greater proportion of patients in Studies PSO3002 and PSO3004 using concomitant medications, compared to PSO3001.

PSO3001

In the overall study population 86% had received prior topical therapy, 72% of participants had received prior systemic therapy, 30% had received prior phototherapy, and 34% had received prior biologic therapy. In the adolescent subgroup 91% of adolescent participants had received prior topical therapy, 52% had received prior systemic therapy, 20% had received prior phototherapy, and 23% had received prior biologic therapy.

Among the 48 (7%) participants with LTBI at or prior to screening, 16 (33%) were treated for LTBI prior to the study, 12 (25%) received concomitant LTBI treatment during the study, and 20 (42%) did not receive treatment for LTBI.

In the overall study population 42% of participants used concomitant medications. Most frequently used ones were analgesics (10%), antibacterials for systemic use (10%), and anti-inflammatory and antirheumatic products (9%).

PSO3002 and PSO3004

In Study PSO3002 and PSO3004, 86% and 89% had received prior topical therapy, 74% and 70% of participants had received prior systemic therapy, 34% and 33% had received prior phototherapy, and 27% and 25% had received prior biologic therapy, respectively.

In the overall study population 76% and 74% of participants used concomitant medications. Most frequently used ones were Agents acting on the renin-angiotensin system (24% in both studies), anti-inflammatory and antirheumatic products (19% and 17%), and analgesics (17% in both studies).

Outcomes and estimation

Through week 16

A statistically significant difference between icotrokinra and placebo was seen for the co-primary endpoint (IGA 0/1 and/or PASI90). The proportion of participants with an IGA score of 0 or 1 with a ≥2-grade improvement from baseline, and those with a PASI90 response, at week 16, are presented in Table 17, Table 18 and Table 19 for studies PSO3001, PSO3002, and PSO3004, respectively.

Table 17. Co-Primary endpoint at week 16 (FAS PSO3001)

	Placebo	JNJ-77242113
Analysis set: Full analysis set	228	456
Subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16[a]	19 (8.3%)	295 (64.7%)
Treatment difference (95% CI)[b]		56.4% (50.4%, 61.7%)
p-value[c]		< 0.001
Subjects achieving a PASI90 response at Week 16[a]	10 (4.4%)	226 (49.6%)
Treatment difference (95% CI)[b]		45.1% (39.5%, 50.4%)
p-value[c]		< 0.001

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for age group, baseline weight category for adult, and geographic region using Mantel-Haenszel weights.
[c] Based on the CMH chi-square test stratified by age group, baseline weight category for adults, and geographic region.

Table 18. Co-Primary endpoint at week 16 (FAS PSO3002)

	Placebo	JNJ-77242113
Analysis set: Full analysis set	156	311
Subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16[a]	17 (10.9%)	213 (69%)
Treatment difference (95% CI)[b]		57.6% (49.9%, 64.2%)
p-value[c]		< 0.001
Subjects achieving a PASI90 response at Week 16[a]	6 (3.8%)	171 (55.0%)
Treatment difference (95% CI)[b]		51.2% (44.5%, 57.3%)
p-value[c]		< 0.001

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights.
[c] Based on the CMH chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

Table 19. Co-Primary endpoint at week 16 (FAS PSO3004)

	Placebo	JNJ-77242113
Analysis set: Full analysis set	82	322
Subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16[a]	7 (8.5%)	227 (70.5%)
Treatment difference (95% CI)[b]		62.1% (52.9%, 69.1%)
p-value[c]		< 0.001
Subjects achieving a PASI90 response at Week 16[a]	1 (1.2%)	184 (57.1%)
Treatment difference (95% CI)[b]		56.0% (48.5%, 62.0%)
p-value[c]		< 0.001

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights.
[c] Based on the Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

For the primary endpoint analyses in Studies PSO3001, PSO3002, and PSO3004, the proportion of participants with an ICE through week 16 or missing IGA/PASI data at week 16, was low (4-12%). Sensitivity analyses for missing data assumptions were consistent with the main co-primary endpoint results, with no tipping point observed. Results remained statistically significant across imputed missing values.

A statistically significant difference between icotrokinra and placebo was seen for all key secondary endpoints (incl. PASI, IGA, PSSD), from week 4 onwards, through week 16. Key secondary endpoint results are presented in Table 20, Table 21, and Table 22 for studies PSO3001, PSO3002, and PSO3003, respectively.

Table 20. Key secondary endpoints through week 16 (FAS PSO3001)

	Placebo	JNJ-77242113	Treatment Difference (95% CI)	Adjusted P-values[a] (Unadjusted P-value)
Analysis set: Full analysis set	228	456		
Psoriasis Improvement				
IGA score of 0 at Week 16[b]	1.3% (3/228)	33.3% (152/456)	31.9% (27.2%, 36.6%)	<0.001 (< 0.001)
PASI100 response at Week 16[b]	0.4% (1/228)	27.0% (123/456)	26.5% (22.4%, 30.8%)	<0.001 (< 0.001)
PASI75 response at Week 16[b]	11.0% (25/228)	69.1% (315/456)	58.1% (51.9%, 63.6%)	<0.001 (< 0.001)
PASI90 response at Week 8[b]	1.3% (3/228)	21.5% (98/456)	20.1% (15.9%, 24.5%)	<0.001 (< 0.001)
PASI75 response at Week 4[c]	2.2% (5/228)	14.9% (68/456)	12.7% (8.8%, 16.6%)	0.002 (< 0.001)
Scalp-specific Psoriasis Improvement at Week 16				
ss-IGA score of 0 or 1 and ≥2-grade improvement from baseline[b,d]	15.0% (30/200)	72.3% (293/405)	57.0% (49.9%, 63.1%)	<0.001 (< 0.001)
Psoriasis PROs				
PSSD symptom score of 0 at Week 16[c,e]	1.0% (2/208)	20.1% (82/408)	19.2% (15.0%, 23.6%)	<0.001 (< 0.001)
≥4-point improvement from baseline in PSSD itch score at Week 16[b,f]	13.1% (23/176)	58.0% (203/350)	45.2% (37.5%, 52.0%)	<0.001 (< 0.001)
PSSD symptom score of 0 at Week 8[e,g]	1.4% (3/208)	7.1% (29/408)	5.7% (2.0%, 8.9%)	0.002 (0.002)
≥4-point improvement from baseline in PSSD itch score at Week 4[c,f]	5.1% (9/176)	19.1% (67/350)	14.1% (8.6%, 19.3%)	0.002 (< 0.001)

[a] Multiple testing procedure specified in Section 2.1 of the Statistical Analysis Plan is used. Statistical significance can be claimed if the adjusted p-value is ≤0.05.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for age group, baseline weight category for adult, and geographic region using Mantel-Haenszel weights. P-value was based on CMH chi-square test stratified by age group, baseline weight category for adult, and geographic region.
[c] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for age group and baseline weight category for adult using Mantel-Haenszel weights. P-value was based on CMH chi-square test stratified by age group and baseline weight category for adult.
[d] Among subjects with a baseline ss-IGA score ≥2
[e] Among subjects with a baseline PSSD symptom score >0
[f] Among subjects with a baseline PSSD Itch score ≥4
[g] Treatment difference and 95% CI were calculated based on exact method. P-value was based on Fisher's exact test.
Note: Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.

Table 21. Key secondary endpoints through week 16 (FAS PSO3002)

	Placebo	JNJ-77242113	Treatment Difference (95% CI)	Adjusted P-values[a] (Unadjusted P-value)
Analysis set: Full analysis set	156	311		
Psoriasis Improvement				
IGA score of 0 at Week 16[b]	1.9% (3/156)	36.7% (114/311)	34.8% (28.7%, 40.7%)	< 0.001 (< 0.001)
PASI100 response at Week 16[b]	1.3% (2/156)	31.2% (97/311)	29.9% (24.2%, 35.7%)	< 0.001 (< 0.001)
PASI75 response at Week 16[b]	11.5% (18/156)	74.3% (231/311)	62.7% (55.1%, 69.1%)	< 0.001 (< 0.001)
PASI90 response at Week 8[b]	1.3% (2/156)	19.9% (62/311)	18.6% (13.5%, 23.5%)	< 0.001 (< 0.001)
PASI75 response at Week 4[b]	2.6% (4/156)	12.2% (38/311)	9.6% (4.8%, 14.3%)	< 0.001 (< 0.001)
Scalp-specific Psoriasis Improvement at Week 16				
ss-IGA score of 0 or 1 and ≥2-grade improvement from baseline[b,c]	20.9% (28/134)	72.4% (189/261)	51.2% (41.8%, 59.4%)	< 0.001 (< 0.001)
Psoriasis PROs				
PSSD symptom score of 0 at Week 16[b,d]	2.8% (4/142)	23.8% (68/286)	21.3% (15.3%, 27.2%)	< 0.001 (< 0.001)
≥4-point improvement from baseline in PSSD itch score at Week 16[b,e]	16.5% (19/115)	61.8% (155/251)	45.1% (35.2%, 53.5%)	< 0.001 (< 0.001)
PSSD symptom score of 0 at Week 8[d,f]	2.1% (3/142)	8.4% (24/286)	6.3% (0.7%, 10.5%)	0.011 (0.011)
≥4-point improvement from baseline in PSSD itch score at Week 4[b,e]	7.0% (8/115)	22.3% (56/251)	15.2% (7.6%, 22.1%)	< 0.001 (< 0.001)

[a] Multiple testing procedure specified in Section 2.1 of the Statistical Analysis Plan is used. Statistical significance can be claimed if the adjusted p-value is ≤0.05.

[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights. P-value was based on Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

[c] Among subjects with a baseline ss-IGA score ≥2.

[d] Among subjects with a baseline PSSD symptom score >0.

[e] Among subjects with a baseline PSSD Itch score ≥ 4

[f] Treatment difference and 95% CI were calculated based on exact method. P-value was based on Fisher's exact test.

Note: Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.

Table 22. Key secondary endpoints through week 16 (FAS PSO3004)

	Placebo	JNJ-77242113	Treatment Difference (95% CI)	Adjusted P-values[a] (Unadjusted P-value)
Analysis set: Full analysis set	82	322		
Psoriasis Improvement				
IGA score of 0 at Week 16[b]	1.2% (1/82)	36.6% (118/322)	35.6% (28.5%, 41.7%)	< 0.001 (< 0.001)
PASI100 response at Week 16[b]	1.2% (1/82)	31.7% (102/322)	30.4% (23.6%, 36.0%)	< 0.001 (< 0.001)
PASI75 response at Week 16[b]	9.8% (8/82)	77.3% (249/322)	67.7% (58.3%, 74.5%)	< 0.001 (< 0.001)
PASI90 response at Week 8[b]	0.0% (0/82)	25.2% (81/322)	25.1% (19.5%, 30.2%)	0.004 (< 0.001)
PASI75 response at Week 4[b]	3.7% (3/82)	16.1% (52/322)	12.5% (5.2%, 18.0%)	0.004 (0.003)
Scalp-specific Psoriasis Improvement at Week 16				
ss-IGA score of 0 or 1 and ≥2-grade improvement from baseline[b,c]	18.3% (13/71)	73.7% (199/270)	55.5% (44.1%, 64.7%)	< 0.001 (< 0.001)
Psoriasis PROs				
PSSD symptom score of 0 at Week 16[b,d]	0.0% (0/71)	21.5% (64/298)	21.5% (15.1%, 26.6%)	< 0.001 (< 0.001)
≥4-point improvement from baseline in PSSD itch score at Week 16[b,e]	14.8% (9/61)	60.1% (155/258)	46.3% (34.2%, 55.6%)	< 0.001 (< 0.001)
PSSD symptom score of 0 at Week 8[d,f]	1.4% (1/71)	9.1% (27/298)	7.7% (-0.5%, 12.0%)	0.025 (0.025)
≥4-point improvement from baseline in PSSD itch score at Week 4[b,e]	4.9% (3/61)	20.9% (54/258)	15.7% (6.3%, 22.3%)	0.008 (0.004)

[a] Multiple testing procedure specified in Section 2.1 of the Statistical Analysis Plan is used. Statistical significance can be claimed if the adjusted p-value is ≤0.05.

[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights. P-value was based on Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

[c] Among subjects with a baseline ss-IGA score ≥2.

[d] Among subjects with a baseline PSSD symptom score >0.

[e] Among subjects with a baseline PSSD itch score ≥4.

[f] Treatment difference and 95% CI were calculated based on exact method. P-value was based on Fisher's exact test.

Note: Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.

Other relevant endpoints included severity outcomes for special site psoriasis, and patient-reported outcomes, including DLQI.

Higher response rates were seen for icotrokinra in scalp, genital, hand/foot, and nail psoriasis compared with placebo across the three studies (PSO3001, PSO3002, PSO3004). Consistent improvements were observed among participants with at least mild special area psoriasis (baseline scores ≥2).

Improvements in health-related quality of life, assessed by change from baseline in DLQI, were numerically larger in adults receiving icotrokinra compared with those receiving placebo at week 18, across the three studies (PSO3001, PSO3002, PSO3004).

Through week 52 (randomised at week 24 analysis set), PSO3001.

At week 24 in total 341 participants were IGA 0/1 or PASI75 responders and were re-randomised to placebo (n=172) or icotrokinra (n=169). Clinical response rates, including PASI90, and PASI75 declined over time among participants in whom icotrokinra was withdrawn at week 24, whereas the response was generally maintained among participants continuing icotrokinra from week 24 to week 52 (Table 23). Median time to loss of PASI75 response was 16.9 and of PASI90 response - 10.1 weeks after withdrawal of icotrokinra, respectively.

Table 23. Key secondary endpoints week 52 (randomised at week 24 analysis set PSO3001)

	Week 24 Treatment Assignment			
	Placebo	JNJ-77242113	Treatment Difference[a]/ Hazard ratio[a] (95% CI)	Adjusted P-value[b] (Unadjusted P-value)
Analysis set: Randomised at Week 24 analysis set	172	169		
At Week 52				
PASI75 response at Week 52[c, d]	29.5% (49/166)	89.4% (144/161)	59.6% (50.9%, 67.3%)	< 0.001 (< 0.001)
PASI90 response at Week 52[e, f]	20.9% (27/129)	84.4% (108/128)	63.5% (53.1%, 72.0%)	< 0.001 (< 0.001)
Through Week 52				
Median time (weeks) to loss of PASI75 response[c, g]	16.9	NA	0.08 (0.05,0.13)	< 0.001 (<0.001)
Median time (weeks) to loss of PASI90 response[e, h]	10.1	NA	0.13 (0.08,0.20)	< 0.001 (<0.001)

[a] For the PASI response endpoints at Week 52, treatment difference and 95% CI are presented. For the time to event endpoints, hazard ratio and 95% CI are presented.
[b] Multiple testing procedure specified in Section 2.1 of the Statistical Analysis Plan is used. Statistical significance can be claimed if the adjusted p-value is ≤0.05.
[c] Among PASI75 responders at Week 24.
[d] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for Week 24 PASI90 response status and geographic region using Mantel-Haenszel weights. P-value was based on CMH chi-square test stratified by Week 24 PASI90 response status and geographic region.
[e] Among PASI90 responders at Week 24.
[f] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for geographic region using Mantel-Haenszel weights. P-value was based on CMH chi-square test stratified by geographic region.
[g] P-value was from log-rank test stratified by Week 24 PASI90 response status and geographic region. Hazard ratio (95% CI) was from Cox's regression model stratified by Week 24 PASI90 response status and geographic region.
[h] P-value was from log-rank test stratified by geographic region. Hazard ratio (95% CI) was from Cox's regression model stratified by geographic region.
Note: Subjects with ICE 1,2,4 (for subjects randomised to placebo at Week 24) after Week 24 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders for binary endpoints and not imputed for time to event endpoints.

For the through Week 52 endpoint analyses, the proportion of participants who experienced an ICE from Week 24 through Week 52 or who had missing IGA/PASI data at Week 52 was low in the re-randomised icotrokinra group (4%). Among the re-randomised placebo participants, there were 47% of participants who had ICEs, and most ICEs were ICE 4 (loss of ≥50% PASI improvement in 56%).

The results of sensitivity analyses to assess the impact of incorrect IWRS entry errors for loss of response (≥50% loss of Week 24 PASI improvement), which caused 10 participants re-randomised to placebo at Week 24 to be incorrectly retreated with icotrokinra per protocol, were consistent with the results of the main analyses.

For adult participants randomised to icotrokinra at Week 0, who were reported as IGA 0/1 or PASI75 non-responders at Week 24 (n=51) and continued icotrokinra treatment the proportion of participants who achieved an IGA score of 0/1 was 33% (n=17) at Week 32 and was overall maintained through Week 52 (31%, n=16). The proportion of participants who achieved a PASI75 score was 51% (n=26) at Week 36 and was maintained through Week 52 (51%, n=26).

Among participants rerandomised at Week 24, the number of participants experiencing a relapse (loss of ≥50% of the week 24 PASI improvement) through week 52 was 97/172 with placebo and 6/169 with icotrokinra.

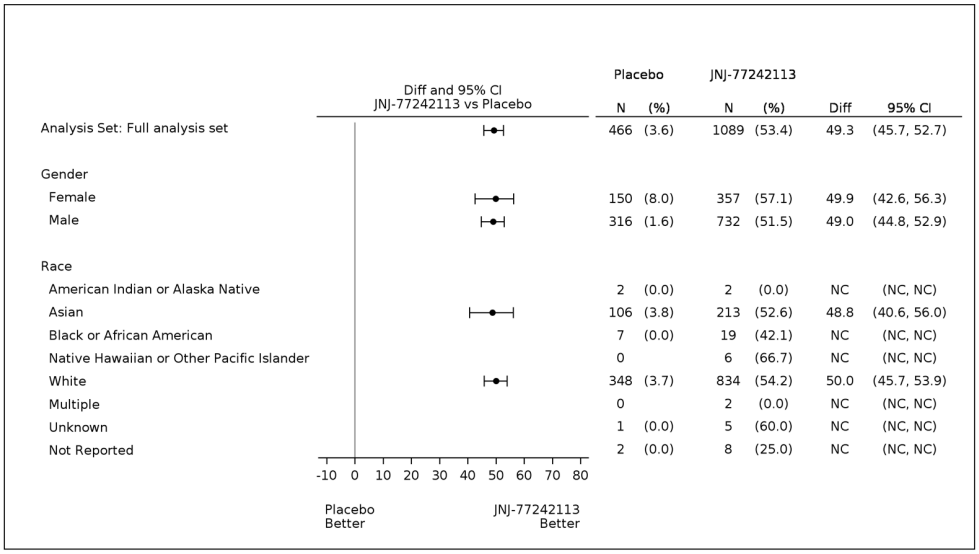
Among participants rerandomised to placebo at week 24, three of 172 patients (1.7%) met the criteria for rebound within 2 months after discontinuation of icotrokinra according to the EMA psoriasis guideline. The events occurred 29, 41 and 60 days after treatment discontinuation and included one case of new-onset pustular psoriasis with widespread skin involvement and two cases of worsening psoriasis (>125% of baseline PASI).

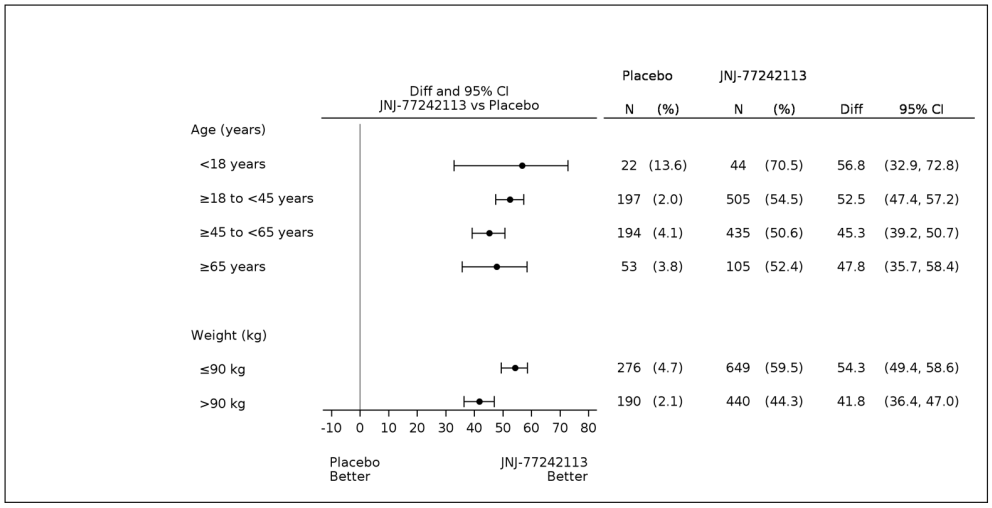
Pre-defined and post-hoc subgroup analyses

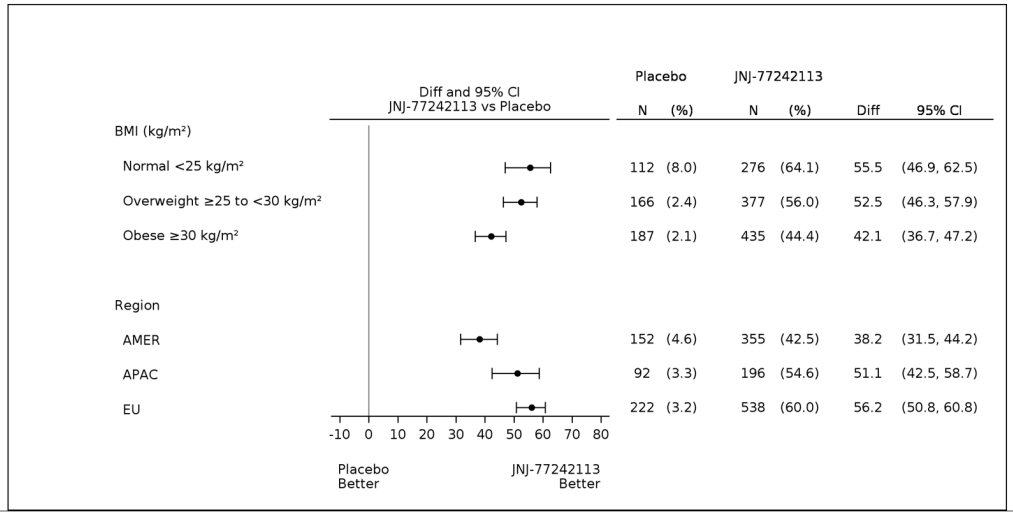
icotrokinra demonstrated overall consistent efficacy in clinical endpoints at Week 16 compared with placebo and compared with deucravacitinib across subgroups of participants based on baseline demographics (gender, race, ethnicity, age, bodyweight, BMI, geographic region), disease characteristics (age at diagnosis, disease duration, baseline PASI, IGA, BSA, and presence of PsA), and psoriasis medication history (phototherapy, systemics including conventional and novel nonbiologic systemics, and biologics including anti-TNF agents, IL-12/23, IL-23, and IL-17 inhibitors).

PASI90 response rates for icotrokinra versus placebo, from PSO3001, PSO3002, and PSO3004 were pooled to increase the number of patients per subgroup (Figure 20 , Figure 21, Figure 22).

Figure 20. PASI90 at week 16 in subgroups based on baseline demographics (pooled PSO3001, 3002, 3004)

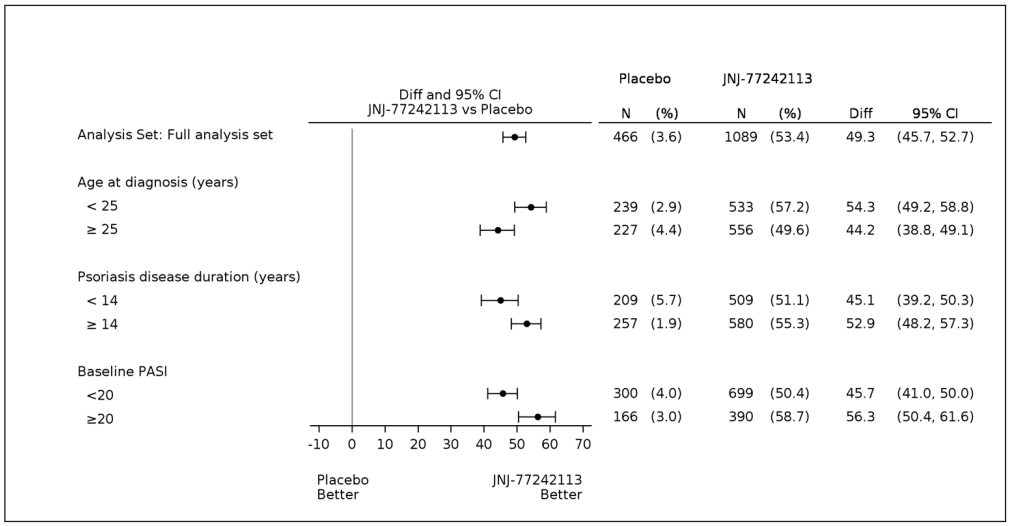


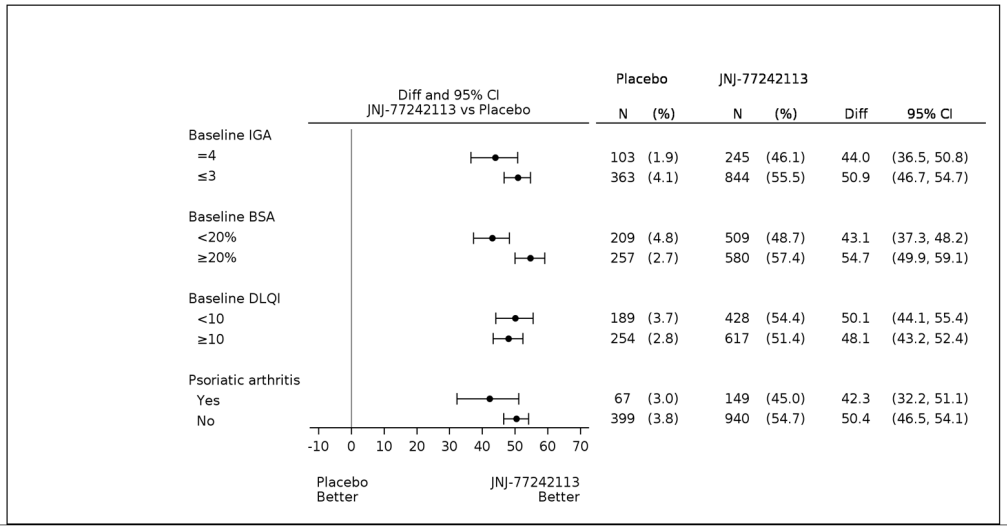




Key: NC = not calculated when sample size in either treatment group is less than 10.
Note: 95% confidence interval for difference in proportions was based on Miettinen-Nurminen method using Mantel-Haenszel weights adjusted by study.
[gefpasi02a.rtf] [PROD/xcp_immunology/jnj-77242113_sce/dbr_pso_2025/re_nda_week_24/gefpasi02a.sas] 22APR2025, 11:01

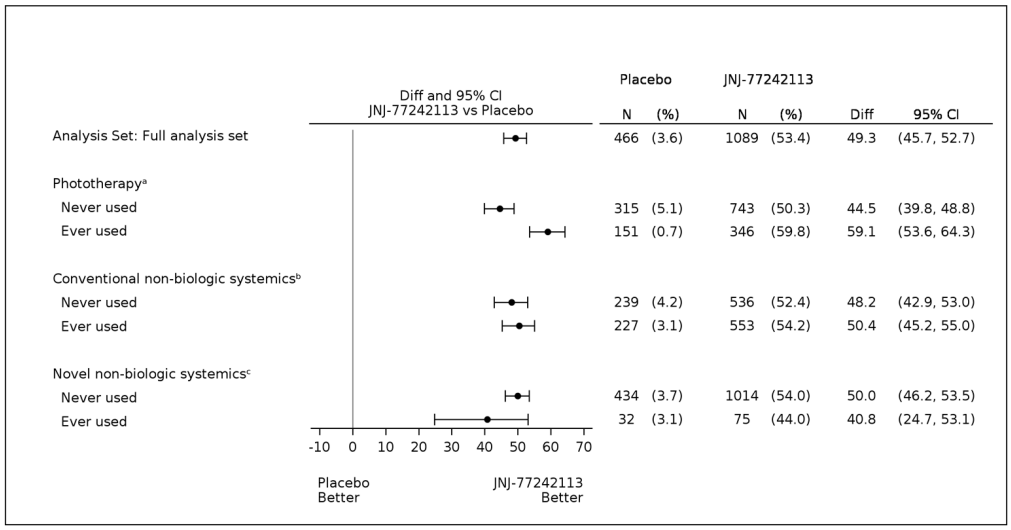
Figure 21. PASI90 at week 16 in subgroups based on baseline disease characteristics (Pooled PSO3001, 3002, 3004)

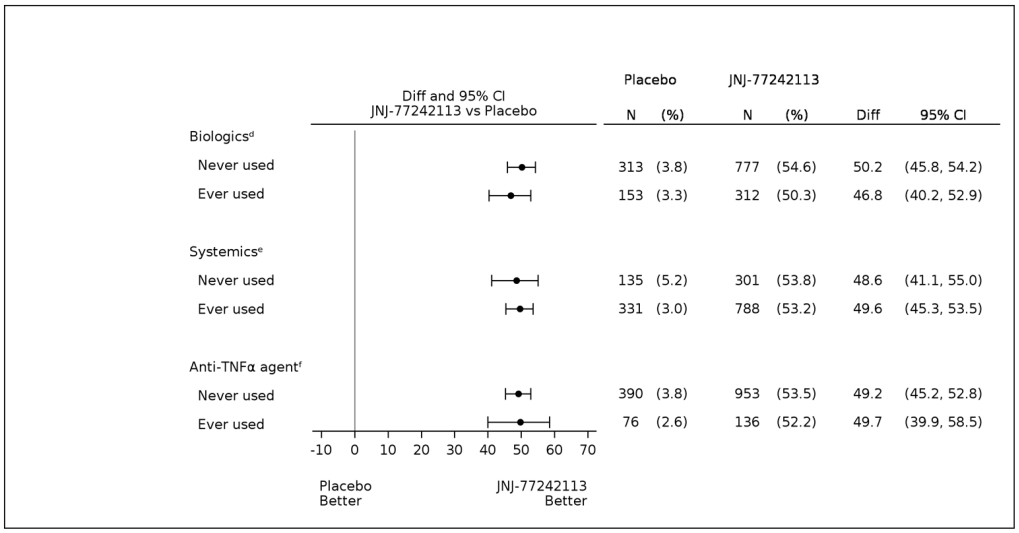


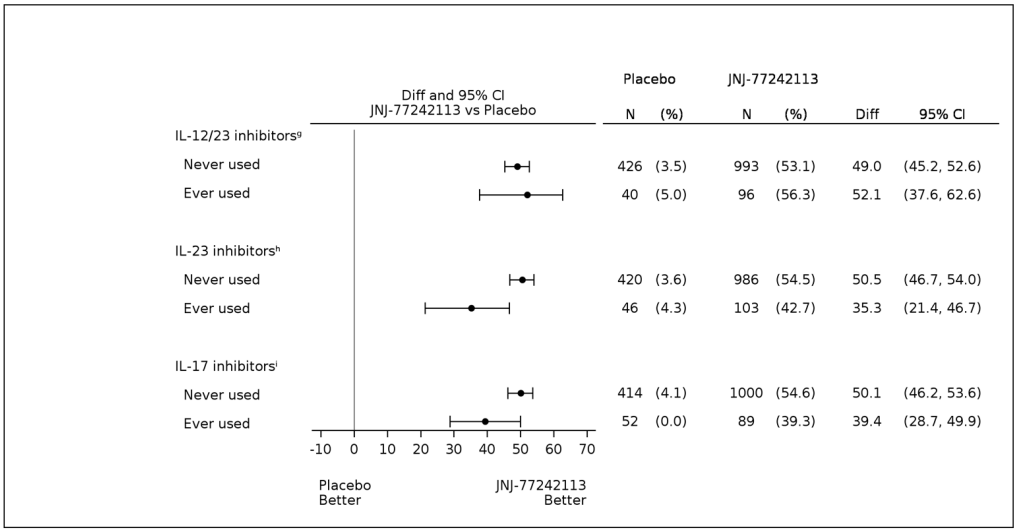


Key: NC = not calculated when sample size in either treatment group is less than 10.
Note: 95% confidence interval for difference in proportions was based on Miettinen-Nurminen method using Mantel-Haenszel weights adjusted by study.

Figure 22. PASI90 at week 16 in subgroups based on prior therapies (Pooled PSO3001, 3002, 3004)







Key: NC = not calculated when sample size in either treatment group is less than 10.
[a] Phototherapy includes PUVB or PUVA.
[b] Conventional non-biologic systemics include PUVA, methotrexate, cyclosporine, acitretin, azathioprine, or fumarate.
[c] Novel non-biologic systemics include apremilast, deucravacitinib, or tofacitinib.
[d] Biologics include etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, or certolizumab pegol.
[e] Systemics include conventional non-biologic systemics, novel non-biologic systemics, 1,25-vitamin D3 and analogs, phototherapy, or biologics.
[f] Anti-TNFα agents include etanercept, infliximab, certolizumab pegol, or adalimumab.
[g] IL-12/23 inhibitors include ustekinumab or briakinumab.
[h] IL-23 inhibitors include guselkumab, tildrakizumab, or risankizumab.
[i] IL-17 inhibitors include secukinumab, ixekizumab, or brodalumab.
Note: 95% confidence interval for difference in proportions was based on Miettinen-Nurminen method using Mantel-Haenszel weights adjusted by study.

5.3.2.2. Study PSO3003

5.3.2.2.1. Study title

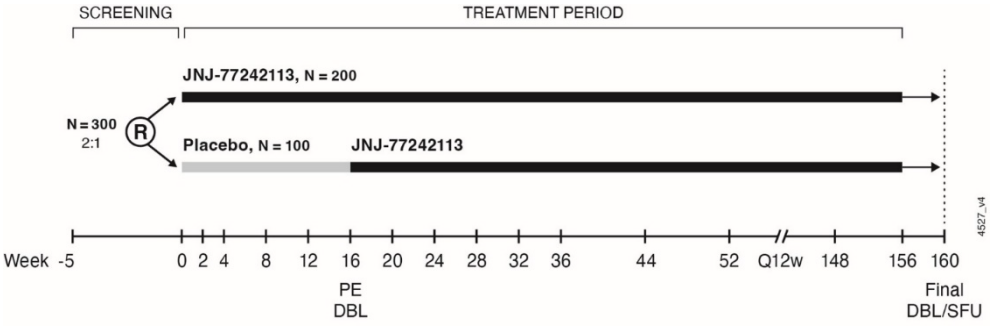
A phase 3 multicenter, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of JNJ-77242113 for the treatment of participants with plaque psoriasis involving special areas.

5.3.2.2.2. Study design

Study PSO3003 is an ongoing at the time of submission Phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel group, interventional study to evaluate the clinical efficacy and safety of icotrokinra treatment compared with placebo in adult and adolescent participants with plaque psoriasis involving special areas (scalp, genital, and/or hand/foot). The study consisted of a 5-week screening period, a DB placebo-controlled period from week 0 to 16 (completed), and an open-label treatment period up to week 156 (ongoing). At the time of submission efficacy data were provided up to 52 weeks.

A schematic overview of this study is shown in Figure 23.

Figure 23. Schematic overview of Study PSO3003



Treatment

icotrokinra was provided as a 200 mg film-coated tablet for oral administration. The matching placebo was identical to the icotrokinra tablets except there was no active ingredient in the placebo formulation. Participants were instructed to take one tablet of study intervention at approximately the same time everyday upon waking, with 240 ml water on an empty stomach (no food intake for at least 2 hours before and for at least 30 minutes after taking the study intervention). Adolescent participants with difficulty swallowing tablets could suspend the tablets in at least 240 ml water.

Through Week 52 of the study:

- Participants in the icotrokinra group received icotrokinra for a maximum of 52 weeks.
- Participants in the placebo → icotrokinra group received placebo for a maximum of 16 weeks and icotrokinra for a maximum of 36 weeks.

Concomitant treatment with topical therapies or systemic medications that could affect psoriasis evaluations, or treatment with phototherapy, was not permitted during the study up to week 52. The only exceptions were medicated shampoos containing salicylic acid and bland emollients, these were allowed on all body regions, but not within 24 hours before study visits. No rescue therapies were permitted.

Randomisation

Participants were assigned to 1 of 2 intervention groups based on a computer-generated randomisation schedule prepared before the study. Permuted block randomisation with icotrokinra stratification by special area involvement (with the order of baseline hf-PGA ≥3, sPGA-G ≥3, and ss-IGA ≥3), geographic region, and BSA category (<10%, ≥10%) was be used. The IWRS assigned a unique intervention code, which dictated the intervention assignment and matching study intervention kit for the participant.

Randomisation codes were disclosed to select sponsor individuals only after the clinical database was closed after the Week 16 DBL. The randomisation codes were not to be disclosed to the investigators and participants until all participants completed the Week 52 visit.

Blinding

The sponsor, participants, caregivers, and investigators were blinded to treatment assignment. The investigator was allowed to break the blind in case of a specific emergency where intervention/course of action would be dictated by knowing the intervention status of the participant.

Patient population

The study population in Study **PSO3003** consisted of adults and adolescents (≥12 years and weighing ≥40 kg) with plaque psoriasis who were candidates for phototherapy or systemic treatment and had failed to respond to ≥1 topical therapy for the treatment of psoriasis. Participants must have met the following disease criteria at screening and baseline: Total BSA ≥1% and IGA (overall) ≥2 and at least 1 of the following: ss-IGA score ≥3, and/or sPGA-G ≥3, and/or hf-PGA score ≥3. A maximum of 40% of the total population was permitted to have BSA<10%.

Participants must have had discontinued IL-23 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and anti-TNFα biologic therapy at least 12 weeks or 5 half-lives, whichever is longer, prior to the first administration of study intervention. Participants must have had discontinued systemic medications for psoriasis including immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine) for at least 4 weeks prior to the first dose of study intervention and must have discontinued topical therapies at least 2 weeks prior to the first dose of study intervention.

Patients with current or history of malignancy, a history of chronic or recurrent infectious diseases, known or suspected immunodeficiency, a serious infection or a history of active TB were excluded.

Participants were recruited from sites in Europe, America, and Asia.

Endpoints

The primary efficacy endpoint was an IGA (overall) score of 0/1 and a ≥2-grade improvement from baseline at Week 16.

Key secondary endpoints at week 16 were the proportion of participants with: ss-IGA score 0/1, PSSI 90, sPGA-G score of 0/1, hf-PGA score of 0/1, IGA (overall) score of 0, PSSD symptom score of 0, ≥4-point improvement from baseline in PSSD Itch score, GenPs-SFQ item 2 score of 0/1, ≥4-point improvement from baseline in Scalp Itch NRS score, ≥4-point improvement from baseline in GPSS Genital Itch NRS score (Item 1 from the GPSS).

5.3.2.2.3. Objectives and estimands

Primary objective

The primary objective was to evaluate the efficacy of icotrokinra in participants with plaque psoriasis involving special areas.

Estimand for the primary objective

Table 24. Estimand for primary objective

Population	Participants ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar)
Treatment condition<s>	Assignment to experimental treatment icotrokinra 200 mg QD, compared to assignment to placebo, regardless of discontinuation due to ICE 3
Endpoint (variable)	Binary response variable, where a responder is defined as a participant with an IGA (overall) score of cleared (0) or minimal (1) and a ≥2-grade improvement from baseline at Week 16 who does not have ICE 1 or 2
Population-level summary	Difference in proportions
Intercurrent events and strategy to handle them	
1. Discontinuation of study intervention due to lack of efficacy or due to an AE of worsening psoriasis prior to Week 16	Composite Strategy: The occurrence of this ICE is captured in the variable definition as patients with these ICEs are considered non-responders
2. Initiation of a protocol-prohibited medication or therapy during the study that could improve psoriasis prior to Week 16	Composite Strategy: The occurrence of this ICE is captured in the variable definition as patients with these ICEs are considered non-responders
3. Discontinuation of study intervention for reasons other than ICE 1 prior to Week 16	Treatment Policy: Strategy targeting the effect of treatment assignment, regardless of the occurrence of this ICE.

Note: For patients experiencing multiple ICEs, ICE 2 will override ICE 3 and the composite strategy will be applied.

For an adult or adolescent patient ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar), what would be the expected effect of being assigned icotrokinra compared to placebo on the likelihood of experiencing a treatment response at Week 16 where patients discontinuing treatment due to lack of efficacy, or AE of worsening of psoriasis are considered non-responders and regardless of other discontinuations?

Statistical methods for estimation and sensitivity analysis on primary estimands

For purposes of analysis, the following analysis sets were defined:

Population	Description
Enrolled	All participants who signed the ICF
Randomised	All participants who were randomised in the study.
FAS	All participants who were randomised in the study.
Safety Analysis Set	All randomised participants who took at least 1 dose of study intervention.
PK Analysis Set	All randomised participants who received at least 1 dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra
Immunogenicity Analysis Set	All randomised participants who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.

For the efficacy analyses in studies PSO3003, the FAS was used according to the participants' assigned treatment to which they were randomised, regardless of the treatment they received. The FAS included all randomised participants.

Safety analyses included all randomised participants who received at least 1 administration of study intervention and participants were analysed based on the treatment they actually received, regardless of the treatment groups to which they were assigned.

The comparison of response rates between treatment groups was performed using a 2-sided CMH chi-square test with a significance level of 0.05. The test was stratified by special area involvement (baseline hf-PGA ≥3, sPGA-G ≥3, and ss-IGA ≥3) and BSA category (i.e., <10%, ≥10%). To estimate the difference in response rates between the icotrokinra and placebo groups at Week 16, 95% CIs were calculated using the Miettinen-Nurminen method, adjusted for the stratification factors of special area involvement (baseline hf-PGA ≥3, sPGA-G ≥3, and ss-IGA ≥3) and BSA category (i.e., <10%, ≥10%) using Mantel-Haenszel weights.

To address the robustness of the co-primary endpoints analyses, 2 sensitivity analyses and a supplementary analysis, as specified below, were conducted.

- Sensitivity Analysis 1 (MI): After accounting for the ICEs as in the primary analysis, missing data were imputed using multiple imputation method by fully conditional specification.
- Sensitivity Analysis 2 (Tipping Point analysis): After the occurrence of ICEs as in the primary analysis, Bernoulli draws over a range of possible scenarios (i.e., 0% to 100% in increment of 10%, for the placebo group and the icotrokinra group independently) for the treatment effects were used to impute missing IGA 0/1 and PASI90 response status at Week 16. For this tipping point analysis, the analysis allowed for assumptions about the response rates in the 2 arms to vary independently; furthermore, it included scenarios where imputed missing values on the icotrokinra group had worse outcomes than those in the placebo group.

In a supplementary analysis, the co-primary endpoints were also analysed utilising the treatment policy estimand.

For each of the subgroups defined below, the difference between the icotrokinra treatment group and placebo group in the proportion of the IGA (overall) 0) or 1 responders, and select key secondary endpoints for IGA 0 and special areas (ss-IGA score of 0 or 1, PSSI 90 response, sPGA-G score of 0 or

1, and hf-PGA score of 0 or 1) at Week 16, and their 95% confidence intervals will be calculated.

Table 25. Subgroups definition criteria for statistical analysis

Subgroup	Definition
Baseline demographics:	
Region	Define based on UN guidance as per the M49 standard • AMER • EU • APAC
Sex	• male • female • other
Race	• American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or other Pacific Islander • White • Multiple • Not Reported • Unknown
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino • Not Reported • Unknown
Age Group (years)	• <18 • ≥18 to <45 years • ≥45 to <65 years • ≥65 years
BMI	• normal <25 kg/m^2 • overweight 25-<30 kg/m^2 • obese ≥30 kg/m^2
Body Weight Group (kg)	• ≤90 kg • >90 kg
Baseline disease characteristics:	
Age at diagnosis (years)	• <median • ≥median
Psoriasis disease duration (years)	• <median • ≥median
Baseline PASI	• <12 • ≥12 to <20 • ≥20
Baseline IGA	• =4 • =3 • =2
Baseline BSA	• <10% • ≥10% to <20% • ≥20%
Baseline DLQI	• <10 • ≥10
Psoriatic arthritis	• Yes

	• No
Psoriasis medication history:	
Phototherapy (ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA])	• Never used • Ever used
Systemics (Conventional non-biologic systemics, novel non-biologic systemics, 1,25-vitamin D3 and analog, phototherapy, biologics)	• Never used • Ever used
Conventional non-biologic systemics (PUVA, MTX, cyclosporine, acitiretin, azathioprine, or fumarate)	• Never used • Ever used
Novel non-biologic systemics (apremilast, deucravacitinib, or tofacitinib)	• Never used • Ever used
Biologics (etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, certolizumab pegol)	• Never used • Ever used
Anti-TNFα agent (etanercept, infliximab, certolizumab pegol, or adalimumab)	• Never used • Ever used
IL-12/23 inhibitors (ustekinumab, briakinumab)	• Never used • Ever used
IL-23 inhibitors (guselkumab, tildrakizumab, Risankizumab)	• Never used • Ever used
IL-17 inhibitors (secukinumab, ixekizumab, or brodalumab)	• Never used • Ever used

Sample size

The assumptions of the sample size and power calculations for the primary endpoint were based on placebo response rates from the historical psoriasis clinical studies and response rates observed from the icotrokinra Phase 2b study.

- The proportion of placebo participants achieving an IGA (overall) score of 0 or 1 and at least 2-grade improvement from baseline at Week 16 is 8%.
- The proportion of icotrokinra participants achieving an IGA (overall) score of 0 or 1 and at least 2-grade improvement from baseline at Week 16 is 64%.

Based on the above assumptions, a total of approximately 300 participants to be randomised in a 2:1 ratio to icotrokinra (n=200) or placebo (n=100) at Week 0 would provide >99% power to detect significant difference for the primary endpoint at a 2-sided significance level of 0.05.

The assumptions of the sample size and power calculations for select key secondary endpoints were based on the data from guselkumab Phase 3 psoriasis studies (VOYAGE 1 and VOYAGE 2), icotrokinra Phase 2b psoriasis study and the secukinumab SCALP psoriasis study for scalp psoriasis, the ixekizumab IXORA-Q and study PSO2001 studies for genital psoriasis, and PSO3001, PSO3002, and PSO2001 studies for hand/foot psoriasis.

To achieve at least a 90% power at a two-sided significance level of 0.05, approximately 75 participants were needed for each subpopulation (i.e., baseline hf-PGA score ≥3, baseline sPGA-G score ≥3, or baseline ss-IGA score ≥3). Of note, these 3 subpopulations are not mutually exclusive.

Secondary objectives

Secondary objectives were to evaluate the general psoriasis and special areas psoriasis efficacy of icotrokinra in participants with plaque psoriasis involving special areas and to evaluate the effect of icotrokinra on PROs in participants with plaque psoriasis involving special areas.

The proportions of participants achieving a key secondary efficacy response were summarised and compared between treatment groups in the same manner as the primary endpoint, using the appropriate stratification factors.

Estimands for the secondary objectives

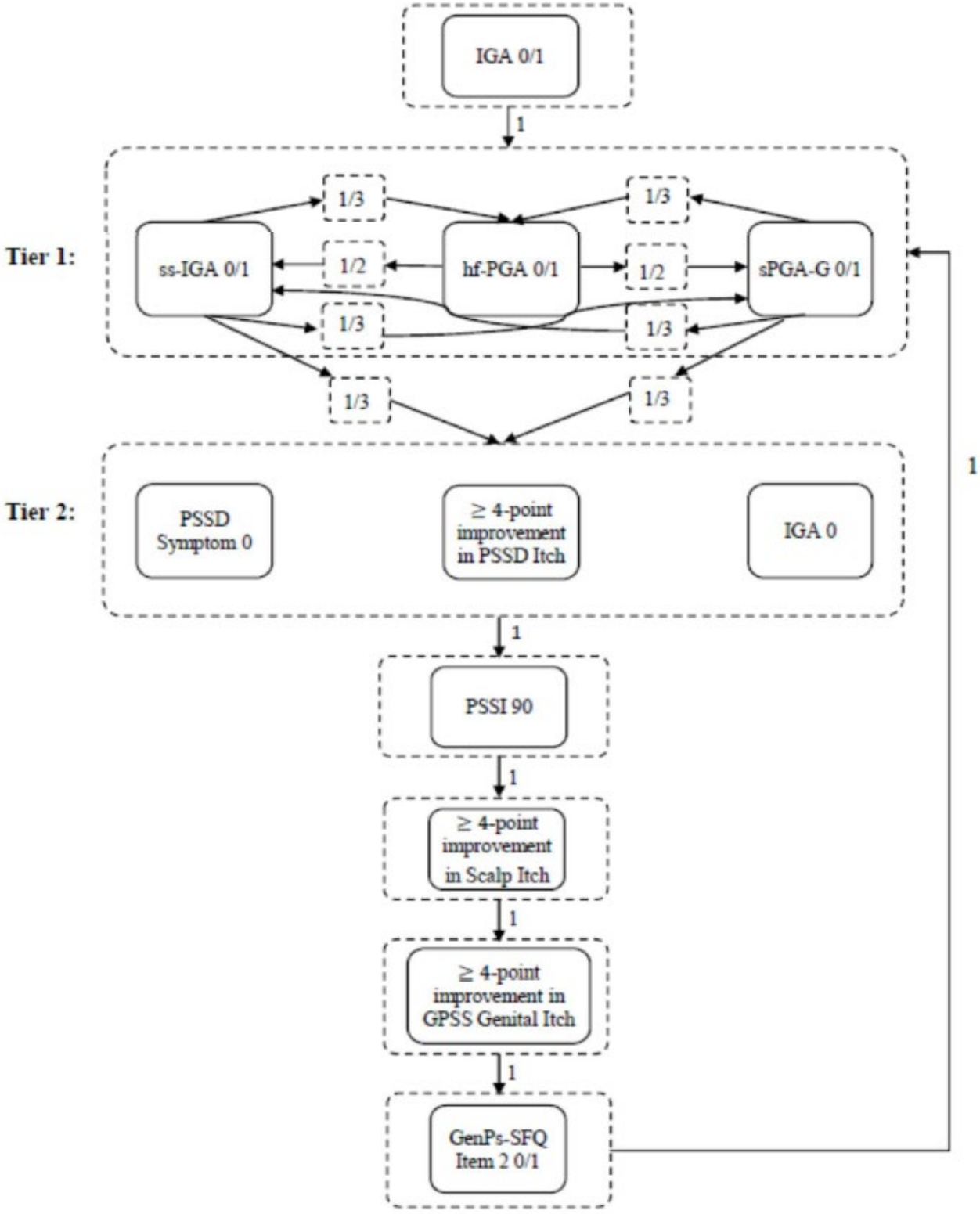
The proportions of participants achieving a key secondary efficacy response were summarised and compared between treatment groups in the same manner as the primary endpoint, using the appropriate stratification factors.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

A multiplicity adjustment procedure was used to control the overall Type I error rate of $\alpha=0.05$ (2-sided) for the primary and 10 key secondary endpoints. The testing procedure began with the test of superiority of the JNJ-77242113 group compared with the placebo group in the primary endpoint. Key secondary endpoints were only tested if the primary endpoint was significant. Otherwise, all subsequent p-values in the testing hierarchy were considered nominal.

When the primary endpoint is positive, a truncated Bonferroni-Holm procedure (Holm, 1979) as shown in Figure 24 was applied to the key secondary endpoints at Week 16 in Tier 1. In this truncated version, if ss-IGA 0/1 or sPGA-G 0/1 was significant at their assigned alpha levels, 1/3 of the assigned alpha level was passed down to the endpoints in Tier 2. The Bonferroni-Holm procedure was used to test endpoints in Tier 2 at an alpha level propagated from Tier 1. If any test within this tier was not significant, the other tests in the same tier could still be declared significant if they meet the Bonferroni-Holm's thresholds, but the formal testing would stop and all p-values from the endpoints in subsequent tiers were considered nominal. If all tests in Tier 2 were significant based on Bonferroni-Holm's procedure, then testing continued to the remaining endpoints in a fixed sequence ordered below. If GenPs-SFQ was significant at its assigned alpha level, its assigned alpha level was passed back with equal weights to the Tier 1 endpoints.

Figure 24. Testing procedure for the primary endpoint and key secondary endpoints



5.3.2.2.4. Results

Participant flow and numbers analysed

Of the 366 participants who were screened, 311 were randomised into the study (all received their allocated treatment). A total of 6/311 were adolescents (age ≥12 to <18 years of age). The study was conducted across 69 sites, across 7 regions, in 10 countries/territories.

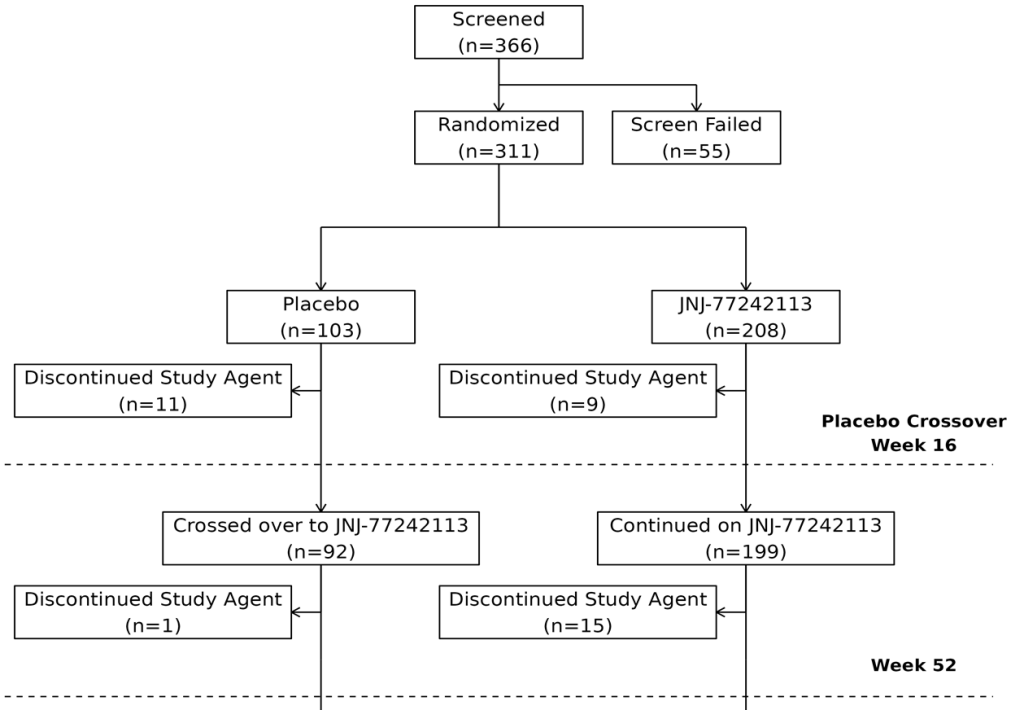
Through week 16 a total of 20 (6%) participants discontinued study intervention (11% in the placebo group; 4% in the icotrokinra group). Most common reasons were adverse event (2%) in the icotrokinra group and lack of efficacy/worsening of psoriasis (6%) and adverse event (3%) in the placebo group.

Through week 52 a total of 25 (8%) participants in total (icotrokinra group + the placebo --> icotrokinra group after week 16), discontinued study intervention. The most common reasons were lack of efficacy (4%) and adverse event (2%).

The participant flow through week 52 is shown in Figure 25.

Most participants who discontinued study intervention also discontinued study participation.

Figure 25. Participant flow PSO3003



Deviations from study plan

Study protocol was amended twice (24 July 2023, 31 October 2023). The first amendment was prior to the study start; the second amendment was following regulatory feedback and pertained to minor clarifications of the protocol. Major protocol deviations occurred in 20 participants.

Baseline data

Demographic characteristics were overall balanced between treatment groups. In the overall populations the majority was white (78%) and male (65%). The mean age was 45 (range: 12-87) years, mean weight was 86 kg, and mean BMI was 29.2. Six of the 311 randomised participants were adolescents (Table 26).

Baseline disease characteristics were comparable between groups, except that in the hand/foot subpopulation, a greater proportion of participants in the icotrokinra group (35%) had severe hand/foot psoriasis at baseline (based on a hf-PGA score of 4) compared with the placebo group (17%). Baseline disease characteristics for the overall population are shown in (Table 27).

In total 252 participants had moderate to severe scalp psoriasis (ss-IGA ≥3), 140 had moderate to severe genital psoriasis (sPGA-G ≥3), and 71 had moderate to severe hand/foot psoriasis (hf-PGA ≥3). Approximately 16% of participants had a diagnosis of PsA.

Table 26. Summary of demographics (FAS PSO3003)

	Placebo	JNJ-77242113	Total
Analysis set: Full analysis set	103	208	311
Age, years			
N	103	208	311
Mean (SD)	43.5 (13.78)	45.3 (14.58)	44.7 (14.33)
Median	44.0	45.0	44.0
Range	(12; 87)	(13; 82)	(12; 87)
IQ range	(35.0; 53.0)	(34.0; 55.0)	(34.0; 55.0)
<18 years	3 (2.9%)	3 (1.4%)	6 (1.9%)
≥18 to <45 years	50 (48.5%)	100 (48.1%)	150 (48.2%)
≥45 to <65 years	45 (43.7%)	85 (40.9%)	130 (41.8%)
≥65 years	5 (4.9%)	20 (9.6%)	25 (8.0%)
Sex			
N	103	208	311
Female	40 (38.8%)	71 (34.1%)	111 (35.7%)
Male	63 (61.2%)	137 (65.9%)	200 (64.3%)
Undifferentiated	0	0	0
Unknown	0	0	0
Race			
N	103	208	311
American Indian or Alaska Native	0	0	0
Asian	20 (19.4%)	41 (19.7%)	61 (19.6%)
Black or African American	0	2 (1.0%)	2 (0.6%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	82 (79.6%)	161 (77.4%)	243 (78.1%)
Multiple	0	1 (0.5%)	1 (0.3%)
Not Reported	1 (1.0%)	3 (1.4%)	4 (1.3%)
Unknown	0	0	0
Ethnicity			
N	103	208	311
Hispanic or Latino	5 (4.9%)	16 (7.7%)	21 (6.8%)
Not Hispanic or Latino	96 (93.2%)	184 (88.5%)	280 (90.0%)
Not Reported	2 (1.9%)	8 (3.8%)	10 (3.2%)
Unknown	0	0	0
Weight, kg			
N	101	204	305
Mean (SD)	86.3 (25.67)	85.3 (20.21)	85.6 (22.13)
Median	85.7	83.8	84.0
Range	(40; 246)	(45; 166)	(40; 246)
IQ range	(70.5; 101.2)	(72.7; 96.6)	(71.0; 97.6)
≤90 kg	59 (58.4%)	133 (65.2%)	192 (63.0%)
>90 kg	42 (41.6%)	71 (34.8%)	113 (37.0%)
Height, cm			
N	102	205	307
Mean (SD)	170.9 (10.26)	171.4 (8.61)	171.2 (9.18)
Median	170.7	172.5	172.0
Range	(150; 194)	(152; 196)	(150; 196)
IQ range	(162.0; 178.0)	(166.0; 178.0)	(164.0; 178.0)
Body mass index, kg/m^2			
N	101	203	304
Mean (SD)	29.4 (8.06)	29.0 (6.64)	29.2 (7.13)
Median	27.6	28.3	28.2
Range	(16; 78)	(17; 67)	(16; 78)
IQ range	(24.3; 33.5)	(24.4; 32.4)	(24.4; 32.8)
Normal <25 kg/m^2	31 (30.7%)	60 (29.6%)	91 (29.9%)
Overweight ≥25 to <30 kg/m^2	33 (32.7%)	65 (32.0%)	98 (32.2%)
Obese ≥30 kg/m^2	37 (36.6%)	78 (38.4%)	115 (37.8%)

Note: N's for each parameter reflect non-missing values.

Table 27. Summary of psoriasis disease characteristics (FAS PSO3003)

	Placebo	JNJ-77242113	Total
Analysis set: Full analysis set	103	208	311
Psoriasis disease duration, years			
N	103	208	311
Mean (SD)	15.15 (10.547)	16.79 (13.319)	16.25 (12.476)
Median	13.00	13.33	13.00
Range	(0.9; 53.0)	(0.7; 65.0)	(0.7; 65.0)
IQ range	(7.00; 21.00)	(6.00; 24.00)	(6.25; 24.00)
Age at diagnosis, years			
N	103	208	311
Mean (SD)	28.5 (14.59)	28.7 (15.43)	28.6 (15.13)
Median	26.0	26.0	26.0
Range	(0; 70)	(0; 71)	(0; 71)
IQ range	(17.0; 39.0)	(17.0; 39.0)	(17.0; 39.0)
IGA score			
N	103	208	311
Severe (4)	22 (21.4%)	46 (22.1%)	68 (21.9%)
Moderate (3)	73 (70.9%)	153 (73.6%)	226 (72.7%)
Mild (2)	8 (7.8%)	9 (4.3%)	17 (5.5%)
Minimal (1)	0	0	0
Cleared (0)	0	0	0
PASI total score (0-72)			
N	103	208	311
Mean (SD)	14.03 (6.994)	14.60 (7.610)	14.41 (7.405)
Median	13.80	13.35	13.60
Range	(1.7; 41.8)	(1.8; 37.3)	(1.7; 41.8)
IQ range	(8.70; 18.60)	(8.40; 19.25)	(8.40; 18.90)
<12	42 (40.8%)	88 (42.3%)	130 (41.8%)
≥12	61 (59.2%)	120 (57.7%)	181 (58.2%)
BSA (%)			
N	103	208	311
Mean (SD)	14.8 (11.67)	16.6 (13.51)	16.0 (12.94)
Median	13.0	12.0	12.3
Range	(1; 60)	(1; 78)	(1; 78)
IQ range	(6.5; 19.5)	(7.0; 22.9)	(6.8; 21.0)
<10%	38 (36.9%)	74 (35.6%)	112 (36.0%)
≥10%	65 (63.1%)	134 (64.4%)	199 (64.0%)
ss-IGA score			
N	103	208	311
Severe disease (4)	21 (20.4%)	33 (15.9%)	54 (17.4%)
Moderate disease (3)	64 (62.1%)	134 (64.4%)	198 (63.7%)
Mild disease (2)	11 (10.7%)	22 (10.6%)	33 (10.6%)
Very mild disease (1)	0	6 (2.9%)	6 (1.9%)
Absence of disease (0)	7 (6.8%)	13 (6.3%)	20 (6.4%)
PSSI total score (0-72)[a]			
N	96	195	291
Mean (SD)	26.4 (16.23)	24.1 (15.01)	24.9 (15.43)
Median	24.0	21.0	21.0
Range	(4; 72)	(2; 72)	(2; 72)
IQ range	(14.0; 36.0)	(12.0; 32.0)	(12.0; 33.0)
sPGA-G score			
N	103	208	311
Very severe (5)	1 (1.0%)	1 (0.5%)	2 (0.6%)
Severe (4)	12 (11.7%)	22 (10.6%)	34 (10.9%)
Moderate (3)	29 (28.2%)	75 (36.1%)	104 (33.4%)
Mild (2)	5 (4.9%)	13 (6.3%)	18 (5.8%)
Minimal (1)	3 (2.9%)	6 (2.9%)	9 (2.9%)
Clear (0)	53 (51.5%)	91 (43.8%)	144 (46.3%)
hf-PGA score			
N	103	208	311
Severe (4)	4 (3.9%)	17 (8.2%)	21 (6.8%)
Moderate (3)	19 (18.4%)	31 (14.9%)	50 (16.1%)
Mild (2)	8 (7.8%)	18 (8.7%)	26 (8.4%)
Almost clear (1)	4 (3.9%)	8 (3.8%)	12 (3.9%)
Clear (0)	68 (66.0%)	134 (64.4%)	202 (65.0%)

Outcomes and estimation

Through week 16

A statistically significant difference between icotrokinra and placebo was seen for the primary endpoint (IGA 0/1). The proportion of participants with an IGA score of 0 or 1 with a ≥2-grade improvement from baseline at week 16 is presented in Table 28.

Table 28. Primary endpoint at week 16 PSO3003 (FAS)

	Placebo	JNJ-77242113
Analysis set: Full analysis set	103	208
Subjects achieving an IGA (overall) score of 0/1 and ≥2-grade improvement from baseline[a]	6 (5.8%)	118 (56.7%)
Treatment difference (95% CI)[b]		51.1% (42.1%, 58.8%)
p-value[c]		< 0.001

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.

[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for special area involvement and BSA category using Mantel-Haenszel weights.

[c] The p-value was based on the CMH chi-square test stratified by special area involvement and BSA category.

For the primary endpoint analysis, the proportion of participants with an ICE through week 16 or missing data at week 16, was low (10% with placebo and 3% with icotrokinra). Sensitivity analyses for missing data assumptions were consistent with the main result, with no tipping point observed. Results remained statistically significant across imputed missing values.

A statistically significant difference between icotrokinra and placebo was seen in 9 out of 10 key secondary endpoints. These key secondary endpoints compared icotrokinra with placebo at Week 16 in participants with at least moderate scalp, genital, and/or hand/foot psoriasis (Table 29).

Table 29. Summary of Key secondary endpoints PSO3003 (FAS)

	Placebo	JNJ-77242113	Treatment Difference (95% CI)	Adjusted P-value[a] (Unadjusted P-value)
Analysis set: Full analysis set	103	208		
Scalp Psoriasis Endpoints at Week 16				
ss-IGA score of 0 or 1[b,c]	10.6% (9/85)	65.9% (110/167)	55.5% (44.8%, 64.4%)	<0.001 (<0.001)
PSSI 90[b,c]	5.9% (5/85)	57.5% (96/167)	51.8% (41.7%, 60.3%)	0.008 (<0.001)
≥4-point improvement from baseline in Scalp Itch NRS score[c,d]	8.6% (5/58)	58.8% (77/131)	50.2% (37.8%, 60.6%)	0.008 (<0.001)
Genital Psoriasis Endpoints at Week 16				
sPGA-G score of 0 or 1[e,f]	21.4% (9/42)	76.5% (75/98)	55.4% (39.1%, 68.0%)	<0.001 (<0.001)
≥4-point improvement from baseline in GPSS Genital Itch NRS score[f,g]	12.9% (4/31)	63.8% (44/69)	49.8% (31.3%, 64.3%)	0.008 (<0.001)
GenPs-SFQ Item 2 score of 0 or 1[f,h]	36.0% (9/25)	80.0% (44/55)	43.2% (20.2%, 62.4%)	0.008 (<0.001)
Hand/Foot Psoriasis Endpoints at Week 16				
hf-PGA score of 0 or 1[f,i]	26.1% (6/23)	41.7% (20/48)	16.7% (-6.2%, 36.8%)	0.144 (0.144)
Overall Psoriasis Endpoints at Week 16				
IGA (overall) score of 0[j]	1.0% (1/103)	25.5% (53/208)	24.8% (17.4%, 31.5%)	<0.001 (<0.001)
≥4-point improvement from baseline in PSSD Itch score[j,k]	13.5% (10/74)	59.5% (100/168)	45.2% (33.4%, 55.3%)	<0.001 (<0.001)
PSSD symptom score of 0[f,l]	3.4% (3/87)	16.2% (31/191)	12.8% (5.5%, 19.4%)	0.008 (0.003)

[a] Multiple testing procedure specified in Section 2.1 of the Statistical Analysis Plan is used. Statistical significance can be claimed if the adjusted p-value is ≤0.05.
[b] Among subjects with a baseline ss-IGA score ≥3.
[c] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for geographic region and BSA category using Mantel-Haenszel weights. P-value was based on the CMH chi-square test stratified by geographic region and BSA category.
[d] Among subjects with a baseline ss-IGA score ≥3 and a baseline Scalp Itch NRS score ≥4.
[e] Among subjects with a baseline sPGA-G score ≥3.
[f] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for BSA category using Mantel-Haenszel weights. P-value was based on the CMH chi-square test stratified by BSA category.
[g] Among subjects with a baseline sPGA-G score ≥3 and a baseline GPSS Genital Itch NRS score (item 1 from the GPSS) ≥4.
[h] Among subjects with a baseline sPGA-G score ≥3 and a baseline GenPs-SFQ Item 2 score ≥2.
[i] Among subjects with a baseline hf-PGA score ≥3.
[j] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for special area involvement and BSA category using Mantel-Haenszel weights. P-value was based on the CMH chi-square test stratified by special area involvement and BSA category.
[k] Among subjects with a baseline PSSD Itch score ≥4.
[l] Among subjects with a baseline PSSD symptom score >0.
Note: Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.

Pre-defined and post-hoc subgroup analyses

Subgroup analyses were based on baseline demographic characteristics, baseline disease characteristics, and psoriasis medication history. Among subgroups with at least 10 participants in each treatment group, the proportions of participants with ss-IGA 0/1 or PSSI 90, sPGA-G 0/1, hf-PGA 0/1 or IGA 0/1 at Week 16 were generally consistent with the main outcome in the relevant population.

5.3.3. Clinical studies in special populations

Table 30. Clinical studies in special populations

	Controlled Trials	*Non-controlled trials*
Renal impairment* patients (Subjects number /total number)	0	NA
Hepatic impairment** patients (Subjects number /total number)	0	NA
Paediatric patients <18 years (Subjects number /total number)	72/2500	NA
Older patients; Age 65-74 (Subjects number /total number)	211/2500	NA
Age 75-84 (Subjects number /total number)	34/2500	NA
Age 85+ (Subjects number /total number)	3/2500	NA

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

** Hepatic impairment is defined as having Child-Pugh score B or C

Adolescents

The efficacy of icotrokinra in adolescent participants of 12 years of age and older and weighing at least 40 kg is primarily based on the 66 adolescent participants with moderate to severe plaque psoriasis enrolled in PSO3001. Due to the small sample size in PSO3003 (n=6), adolescents in this study were only included in the subgroup analysis for the primary endpoint (IGA 0/1 at Week 16).

Study design and methods were overall similar for adults and adolescents, except that an alternative method of administration was included in the protocol: If adolescent participants had difficulty swallowing tablets, the study intervention could be suspended in a glass of water.

PSO3001

Adolescent participants were randomised and treated with icotrokinra for 52 weeks or placebo for 16 weeks and then icotrokinra through Week 52.

Baseline demographics and disease characteristics were generally consistent between the adolescents and overall study population except for expected differences including shorter psoriasis disease duration and lower mean body weight. The range of body weight in adolescents was 41 to 130 kg and in adults 41 to 200 kg. The frequency of severe and moderate plaque psoriasis, median affected BSA and median PASI scores at baseline were comparable in adults and adolescents. Prior psoriasis therapies in adolescents included systemic therapy in 51%, phototherapy in 20%, and biologic therapy in 23% and was less compared to adults, as expected. More adults, 46.6% had hand/feet psoriasis at baseline compared to adolescents (33.3%). Involvement of scalp psoriasis (97% resp. 93.8%) or genital psoriasis (37.9% resp. 36.9%) at baseline was comparable in adolescents and adults. More adolescents than adults had facial psoriasis (33.3% resp. 23.3%). More adult patients, 55.3%, had a moderate to severe impairment of their quality of life (DLQI resp. CDLQI ≥ 10) compared to 24.6% of the adolescent patients.

A statistically significant difference between icotrokinra and placebo was seen for the co-primary endpoint (IGA 0/1 and/or PASI90). The proportions of adolescent participants with an IGA score of 0/1 with a ≥2-grade improvement from baseline, and those with a PASI90 response, at week 16 are shown in Table 31. A statistically significant difference between icotrokinra and placebo was seen for most key secondary endpoints, from week 4 onwards, through week 16. Key secondary endpoint results are presented in Table 32.

The proportion of adolescents in the icotrokinra group achieving responses continued to increase through Week 24 and was maintained through Week 52. After crossing over from placebo to icotrokinra at Week 16, adolescents in the placebo → icotrokinra group had a similar response as adolescents in the icotrokinra group, at week 52.

Table 31. Co-Primary endpoint in adolescent participants (FAS PSO3001)

Table 6: Summary of Primary Endpoints Among Adolescents; Full Analysis Set (Study 77242113PSO3001)	Placebo	JNJ-77242113
Analysis set: Full analysis set	228	456
Adolescent subjects	22	44
Subjects achieving an IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 16[a]	6 (27.3%)	37 (84.1%)
Treatment difference (95% CI)[b]		56.2% (33.2%, 74.1%)
p-value[b]		< 0.001
Subjects achieving a PASI 90 response at Week 16[a]	3 (13.6%)	31 (70.5%)
Treatment difference (95% CI)[b]		56.3% (32.5%, 73.0%)
p-value[b]		< 0.001

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] The p-values, treatment difference and 95% CI were calculated adjusting for geographic region.

Table 32. Key secondary endpoints in adolescents (FAS PSO3001)

	Placebo	JNJ-77242113
Analysis set: Full analysis set	228	456
Adolescent subjects	22	44
Subjects achieving a PASI 75 response at Week 16[a]	5 (22.7%)	38 (86.4%)
Treatment difference (95% CI)[b]		63.3% (39.7%, 79.7%)
p-value[b]		< 0.001
Subjects achieving a PASI 100 response at Week 16[a]	1 (4.5%)	13 (29.5%)
Treatment difference (95% CI)[b]		24.4% (4.9%, 40.6%)
p-value[b]		0.021
Subjects achieving an IGA score of 0 at Week 16[a]	1 (4.5%)	18 (40.9%)
Treatment difference (95% CI)[b]		35.7% (14.6%, 51.9%)
p-value[b]		0.002
Subjects with baseline PSSD symptom score >0	20	37
Subjects achieving a PSSD symptom score of 0 at Week 16[a]	0	13 (35.1%)
Treatment difference (95% CI)[b]		34.5% (13.7%, 51.1%)
p-value[b]		0.002
Subjects with baseline PSSD itch score ≥4	17	27
Subjects achieving a ≥4-point improvement from baseline in PSSD itch score at Week 16[a]	2 (11.8%)	15 (55.6%)
Treatment difference (95% CI)[b]		47.5% (20.2%, 67.8%)
p-value[b]		0.002
Subjects with baseline ss-IGA score ≥2	21	43
Subjects achieving an ss-IGA score of 0 or 1 and a ≥2 grade improvement at Week 16[a]	3 (14.3%)	35 (81.4%)
Treatment difference (95% CI)[b]		65.0% (42.6%, 80.5%)
p-value[b]		< 0.001
Subjects achieving a PASI 90 response at Week 8[a]	1 (4.5%)	14 (31.8%)
Treatment difference (95% CI)[b]		26.7% (6.9%, 43.1%)
p-value[b]		0.014
Subjects with baseline PSSD symptom score >0	20	37
Subjects achieving a PSSD symptom score of 0 at Week 8[a]	0	5 (13.5%)
Treatment difference (95% CI)[c]		13.5% (-4.3%, 28.8%)
p-value[c]		0.151
Subjects achieving a PASI 75 response at Week 4[a]	2 (9.1%)	10 (22.7%)
Treatment difference (95% CI)[c]		13.6% (-9.4%, 30.8%)
p-value[c]		0.310
Subjects with baseline PSSD itch score ≥4	17	27
Subjects achieving a ≥4-point improvement from baseline in PSSD itch score at Week 4[a]	0	6 (22.2%)
Treatment difference (95% CI)[c]		22.2% (1.0%, 42.3%)
p-value[c]		0.067

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] The p-values, treatment difference and 95% CI were calculated adjusting for geographic region.
[c] The p-values, treatment difference and 95% CI were based on exact method.

At baseline and at week 16, 96% (n=42) of adolescent participants in the icotrokinra group swallowed the study intervention whole and 5% (n=2) suspended the study intervention in water. All adolescent participants (n=22) in the placebo group swallowed the study intervention whole.

PSO3003

Due to the small sample size in PSO3003 (n=6), adolescents in this study were analysed in a subgroup analysis for the primary endpoint (overall IGA 0 or 1 with a 2-grade improvement from baseline at Week 16).

Elderly

Treatment differences observed in participants ≥65 years of age were comparable to those observed in the younger participants.

Renal and Hepatic Impairment

No dose adjustment is recommended for patients with renal or hepatic impairment.

Antibodies to icotrokinra

The development of antibodies to icotrokinra, or the titers of antibodies to icotrokinra were not associated with a reduction in IGA 0/1, IGA 0, PASI100, PASI90, or PASI75 response rates. Among participants with antibodies to icotrokinra across the Phase 3 studies, none were positive for NAbs.

5.3.4. In vitro biomarker test for patient selection for efficacy

Not Applicable.

5.3.5. Supportive studies

Not Applicable.

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

Results for key endpoints across studies PSO3001, PSO3002, and PSO3004 through week 16 were pooled (Table 33). Study design and methodology were comparable for the 16-week placebo-controlled period in these three studies, justifying pooling of these data.

Table 33. Pooled summary of Key Endpoints through week 16 (PSO3001, PSO3002 and PSO3004)

	Placebo		JNJ-77242113		Difference (JNJ-77242113 - Placebo)
	No.(%) of Subjects With Event	95% CI[a]	No.(%) of Subjects With Event	95% CI[a]	Difference per 100 Subjects[b] (95% CI)[c]
Full Analysis set: Pooled	466		1089		
Efficacy at Week 16					
IGA score 0 or 1 and ≥2-grade improvement from BL	43/466 (9.2%)	(6.6%, 11.9%)	735/1089 (67.5%)	(64.7%, 70.3%)	57.9 (53.8, 61.6)
PASI90	17/466 (3.6%)	(1.9%, 5.4%)	581/1089 (53.4%)	(50.4%, 56.3%)	49.3 (45.7, 52.7)
IGA score 0	7/466 (1.5%)	(0.6%, 3.1%)	384/1089 (35.3%)	(32.4%, 38.1%)	33.6 (30.4, 36.7)
PASI75	51/466 (10.9%)	(8.1%, 13.8%)	795/1089 (73.0%)	(70.4%, 75.6%)	61.5 (57.4, 65.3)
PASI100	4/466 (0.9%)	(0.2%, 2.2%)	322/1089 (29.6%)	(26.9%, 32.3%)	28.4 (25.5, 31.4)
ss-IGA score 0 or 1 and ≥2-grade improvement from BL among those with a BL ss-IGA score ≥2	71/405 (17.5%)	(13.8%, 21.2%)	681/936 (72.8%)	(69.9%, 75.6%)	55.1 (50.1, 59.6)
PRO: PSSD symptom score 0 among those with a BL PSSD symptom score >0	6/421 (1.4%)	(0.5%, 3.1%)	214/992 (21.6%)	(19.0%, 24.1%)	20.2 (17.3, 23.1)
PRO: ≥4-point improvement from BL in PSSD Itch score among those with a BL PSSD Itch score ≥4 points	51/352 (14.5%)	(10.8%, 18.2%)	513/859 (59.7%)	(56.4%, 63.0%)	45.1 (39.9, 49.9)
Efficacy at Week 8					
PASI90	5/466 (1.1%)	(0.4%, 2.5%)	241/1089 (22.1%)	(19.7%, 24.6%)	20.7 (18.0, 23.4)
PRO: PSSD symptom score 0 among those with a BL PSSD symptom score >0	7/421 (1.7%)	(0.7%, 3.4%)	80/992 (8.1%)	(6.4%, 9.8%)	6.3 (4.0, 8.4)
Efficacy at Week 4					
PASI75	12/466 (2.6%)	(1.1%, 4.0%)	158/1089 (14.5%)	(12.4%, 16.6%)	11.7 (9.0, 14.3)
PRO: ≥4-point improvement from BL in PSSD Itch score among those with a BL PSSD Itch score ≥4 points	20/352 (5.7%)	(3.3%, 8.1%)	177/859 (20.6%)	(17.9%, 23.3%)	14.9 (11.0, 18.4)

Key: CI=Confidence Interval, BL=Baseline.

[a] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided.

[b] Difference = 100 * difference between event rates.

Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for study using Mantel-Haenszel weights.

5.3.7. Observational data or data from registries

Not Applicable.

5.3.8. Patient experience data (PED)

See above.

5.3.9. Healthcare professional engagement

HCP engagement

Current systemic treatments for moderate-to-severe plaque psoriasis include biologics such as TNF-α inhibitors, IL-12/23p40 inhibitor, IL-17 inhibitors, and IL-23 inhibitors. Although biologics are very effective, showing excellent skin clearance and durability, the injectable route remains a barrier for many patients. There is a need for better oral treatment options, as currently available oral treatments like PDE4 inhibitor (apremilast) and TYK2 inhibitor (deucravacitinib), are less effective or may have tolerability concerns.

Important unmet needs in psoriasis treatment include the lack of curative treatments, limited effective oral systemic treatment options, and the need for alternatives for patients who decline or cannot use injectable treatments. icotrokinra appears to address several unmet needs, offering a similar response to approved injectable IL-23 inhibitors and a favourable short-term safety profile. Its safety profile resembles that of already licensed injectable anti-IL-23 biologics.

Ideal treatments should achieve high levels of skin clearance, rapid onset of action, long-term control of the disease, and meaningful efficacy in hard-to-treat areas. They should also improve quality of life, reduce the socio-economic burden, and be effective in patients with common comorbidities such as psoriatic arthritis, metabolic syndrome and cardiovascular disease. Simple administration, minimal laboratory monitoring and predictable dosing are also important factors to consider in routine care.

Long-term data are needed to understand the durability of response, safety, and real-world adherence to daily treatment. The development of treatments with disease-modifying potential, reducing the need for continuous life-long therapy, would be highly desirable.

Overall, icotrokinra has the potential to meaningfully expand systemic treatment options for plaque psoriasis, particularly for patients who require high efficacy yet strongly prefer an oral route of administration. Continued long-term follow-up, real-world effectiveness data, and comparative assessments versus injectable IL-23 inhibitors will be essential to fully characterise its long-term benefit–risk profile.

Patient organisation engagement

Current systemic treatments for plaque psoriasis, including oral and injectable options, present challenges in long-term adherence due to side effects, monitoring requirements, and administration

barriers. While oral therapies are generally more acceptable to patients, treatment preferences are influenced by social determinants such as cost, access, and cultural attitudes. Unmet needs remain significant: patients seek rapid and sustained skin clearance, convenience, and holistic care addressing comorbidities and psychosocial impact. Special populations, including pregnant individuals and children, face critical gaps in safe and effective options. icotrokinra hydrochloride, combining biologic-like efficacy with oral convenience and safety, could fulfil these needs, particularly for patients desiring needle-free alternatives and younger populations. Patients prioritise efficacy and quality of life, tolerating minor side effects but rejecting severe risks.

5.3.10. Overall discussion and conclusions on clinical efficacy

5.3.10.1. Discussion

The **clinical development program** for icotrokinra is adequate to support the indication. It is consistent with the guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr) and provided scientific advice (EMA/SA/0000131317). The applicant proposed an indication for the '*…treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy' (for more details please see section 1.3).*

Efficacy is substantiated by a comprehensive data package including four phase 3 studies PSO3001, PSO3002, PSO3003, and PSO3004 (all ongoing at the time of submission), and supported by a phase 2 dose-ranging study and its extension (PSO2001 and PSO2002). In the phase 3 studies 2500 patients were included, 72 of them were adolescents (66 in PSO3001 and 6 in PSO3004).

Design and conduct of clinical studies

PSO2001 and PSO2002 evaluated 5 dose groups of icotrokinra for up to 1 year of continuous treatment in adult participants with moderate to severe plaque psoriasis.

The study **designs** of the **dose-ranging studies PSO2001** and **PSO2002** are adequate and in line with the guideline (CHMP/EWP/2454/02 corr). PSO2001 was a 20-week (16-week treatment, 4-week follow-up), randomised, double blind, placebo controlled, parallel group, dose ranging Phase 2 study. At week 16 of PSO2001, eligible participants had the option to enrol in a 40-week LTE (36-week treatment period and a 4-week safety follow-up period) study. Maximum treatment duration was 52 weeks, which is in line with recommendations of ICH E1.

The study **designs** of the **pivotal studies** are adequate regarding the patient population, randomisation, blinding, chosen comparators, and efficacy endpoints. **PSO3001** was a randomised, double-blind, placebo-controlled study, including a randomised withdrawal phase, for which at time of submission data up to week 52 were provided. **PSO3002** and **PSO3004** were both randomised, double-blind, placebo-, and active comparator-controlled studies, of similar design, for which at time of submission data up to week 44 and week 24 were provided, respectively.

The 16-week double-blind placebo-controlled treatment period is adequate to evaluate short-term efficacy of icotrokinra in moderate to severe plaque psoriasis. Placebo is considered an appropriate comparator. PSO3002 and PSO3004 additionally included a double-blind 24-week deucravacitinib-controlled phase; deucravacitinib is considered an appropriate active comparator with proven efficacy and a similar route of administration to icotrokinra.

The icotrokinra arm in PSO3001 included a **randomised withdrawal** phase. Adult responders (PASI75 or IGA 0/1) at week 24 were re-randomised to placebo or icotrokinra, allowing evaluation of durability of response up to week 52. Non-responders continued treatment with icotrokinra. In line

with the agreed PIP, adolescent patients did not participate in the randomised withdrawal phase and remained on icotrokinra, from week 16 on through Week 52 uncontrolled and open label.

The **study populations** are in line with the target population in the indication. The studies enrolled participants with a PASI ≥12, a total IGA ≥3, and a total BSA ≥10%, who were candidates for phototherapy or systemic therapy. While the study population captures the broader spectrum of patients, including those who were candidates for phototherapy, the proposed indication is limited to those who are candidates for systemic therapy. This approach aligns with previously approved therapies for moderate to severe psoriasis (e.g., guselkumab, risankizumab, tildrakizumab).

PSO3001 also included adolescents (≥12 years of age weighing ≥40 kg) who fitted the above criteria. No adolescents were included in PSO3002 and PSO3004 because deucravacitinib is not approved in this age group. Stratification by age group (PSO3001), weight group, and geographic region ensured similar distribution of participants across groups. Re-randomised responders (PSO3001) were stratified by PASI90 status and geographic region.

Both **primary** (PASI90 and IGA0/1 response) and **key secondary endpoints** including PASI100 and IGA 0 are adequate; they are stringent and clinically relevant. Further, they are in line with the primary endpoints used in clinical studies of other approved psoriasis therapies, including IL-23p19 targeting monoclonal antibodies (EPARs guselkumab, risankizumab, tildrakizumab). Outcomes related to the Psoriasis Symptom and Sign Diary (PSSD) were the only PROs included as key endpoints. This tool to self-evaluate psoriasis signs and symptoms has been previously developed and validated by the applicant (EPAR guselkumab). DLQI is a frequently used and validated endpoint (Basra MKA 2008), yet this endpoint was only included as 'other secondary endpoint' and was not part of the hierarchical testing strategy. Special site psoriasis was evaluated with site specific outcome measures; only the ss-IGA to evaluate scalp psoriasis was included as key secondary endpoint. Outcome measures to evaluate genitals, hands/feet, and nails were included as other endpoints. This is acceptable as the indication does not specifically reference special sites, and a dedicated study (PSO3003) was conducted to assess the treatment response in these difficult-to-treat areas. PSO3002 and PSO3004 included key secondary endpoints to test non-inferiority and superiority of icotrokinra versus deucravacitib.

In the defined primary estimand **analysis** for studies PSO3001, PSO3002 and PSO3004, discontinuation due to lack of efficacy or worsening of psoriasis and initiation of other medication are handled with a composite strategy, considering the patients non-responder. As these events are considered signs of treatment failure, this is agreed. Other discontinuations will be handled with a treatment strategy. A supplementary estimand was defined using a treatment policy strategy for all intercurrent events. The estimand definitions are considered acceptable.

The definitions of the analysis populations and the use of FAS for the efficacy analysis are acceptable.

The analysis of the co-primary endpoints used Cochran-Mantel-Haenszel Chi-square test, adjusted for stratification factors used in randomisation. This is considered acceptable for responder endpoints. After accounting for the intercurrent events, patients with missing data were considered a non-responder, which is acceptable as the amount of missing data is minimal. Two sensitivity analyses were performed to address the missing data handling, multiple imputation and tipping point analysis, which will allow assessment of the impact of missing data.

Binary secondary endpoints were analysed in a similar way as the co-primary endpoint, time to event endpoints were analysed using a stratified log-rank test and Cox regression, which is acceptable.

In study PSO3001, multiplicity across the co-primary and key secondary endpoints prior or at week 16 was handled using a combination of hierarchical testing of groups of endpoints, and Bonferroni-Holm procedure within the groups, with statistical significance on both co-primary endpoints as

gatekeeper. Together this will protect the type I error rate. For the randomised withdrawal part, the co-primary endpoints were gatekeeper as well, followed by a graphical approach for testing the re-randomisation endpoints, which also protects the type I error rate. The minor concerns regarding the study-wise type I error inflation have been clarified by the applicant and accepted by the CHMP.

Studies PSO3002 and PSO3004 used a similar approach for handling multiplicity across the co-primary and key secondary endpoints, combining hierarchical testing and Bonferroni-Holm, which will protect the overall type I error rate.

The assumptions of treatment effect for the sample size calculation were based on phase 2 data and for studies PSO3002 and PSO3004 on deucravacitinib Phase 3 studies. In hindsight the assumptions were accurate, and the calculation can be followed. The sample size was also chosen to ensure collection of sufficient safety data; hence the studies were somewhat overpowered for efficacy.

For studies PSO3002 and PSO3004, a non-inferiority margin for comparisons versus deucravacitinib was defined based on a meta-analysis of data from placebo-controlled deucravacitinib phase 3 studies. A margin of 12% was chosen to preserve 70% of the observed deucravacitinib effect. The calculation of the margin can be followed from a statistical perspective even without clinical justification of the margin since the studies showed superiority versus deucravacitinib.

PSO3003 was a randomised, double blind, placebo-controlled study, for which at time of submission data up to week 52 were provided.

The **study population** supports the target population in the indication. This study aimed to address efficacy of icotrokinra in a somewhat different psoriasis population, compared to the other three phase 3 studies. Plaque psoriasis with at least moderate special site involvement (defined as overall BSA ≥1% and IGA ≥2, and at least one of the following: ss-IGA≥3, sPGA-G≥3, and/or hf-PGA≥3) may according to treatment guidelines (*Nast et al 2020*) be classified as more severe. Because involvement of these areas disproportionately affects quality of life. Even when the affected body surface area is small, it can cause substantial physical and emotional distress, contribute to social isolation, and is often more difficult to treat. Stratification by special site (with the order of baseline hf-PGA ≥3, sPGA-G ≥3, and ss-IGA ≥3), BSA category (<10%, ≥10%), and geographic region ensured similar distribution of participants across groups.

The **primary endpoint** (IGA 0/1 with ≥2 point improvement from baseline) is agreed, although it can be questioned whether a primary endpoint addressing overall IGA is relevant, since the aim of the study is to focus on effects in specific body areas. This is not considered a problem since special sites are not specifically mentioned in the indication. In contrast to the other phase 3 studies, PASI90 was not additionally included as a co-primary endpoint. This is considered reasonable for a population with overall less severe psoriasis, the quantitative improvement in this population may be less clear. Key secondary endpoints included specific scoring systems (both ClinROs and PROs), to evaluate the impact on special site psoriasis (e.g., scalp, hand/foot, genitals). Endpoints were generally endorsed in a Scientific Advice (EMA/SA/0000131317). Although not formally validated, ss-IGA, hf-IGA, sPGA-G are adapted from general physician/investigator global assessment scales and are considered pragmatic tools for special site involvement. ss-IGA and hfPGA were previously accepted in regulatory approval (e.g., EPAR guselkumab).

The statistical **analysis** plan for study PSO3003 was very similar as the plan for the other pivotal studies and is acceptable.

The assumptions of treatment effect for the sample size calculation were based on phase 2 data and findings from guselkumab and ixekizumab phase 3 studies. In hindsight the assumptions were accurate, and the calculation can be followed.

Efficacy data and additional analyses

PSO2001 and PSO2002: Dose-ranging studies

Overall, the dose-ranging studies provide sufficient support for the recommended dose of icotrokinra 200 mg QD, which was also the dose selected for evaluation of safety and efficacy in phase 3 studies and reflects the claimed posology.

PSO2001 evaluated 255 adults with moderate to severe plaque psoriasis (IGA score of ≥3, PASI total score of ≥12, BSA ≥10%). Evaluated doses were icotrokinra 25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD, 100 mg BID and these were compared with placebo. Treatment with icotrokinra, irrespective of dose, resulted in a statistically significant higher PASI75 response, compared with placebo. The proportion of patients with PASI75 at week 16 increased in a dose-dependent manner, with the highest response observed at the highest dose of 100 mg BID.

Following PSO2001, 227 subjects subsequently entered the extension study PSO2002, for an additional treatment period of 36 weeks. Participants continued on their initial dose of icotrokinra while participants in the placebo group transitioned to 100 mg icotrokinra QD. Results provided preliminary support for a sustained clinical response, with a PASI75 response rate that was generally maintained up to week 52, across doses.

In line with the SmPC, the recommended dose of 200 mg once daily is considered appropriate. The rationale that a once daily dose is more convenient to patients, and could potentially improve adherence, is plausible. E-R analysis indicated similar exposure of icotrokinra 100 mg BID and 200 mg QD, and IL-23R inhibition was predicted to be comparable.

PSO3001, PSO3002, PSO3004: main studies in overall psoriasis

A total of 2189 participants with moderate to severe plaque psoriasis was randomised, of which 66 were adolescents (≥12 years of age weighing ≥40kg). Overall completion rates were high (>90%).

Baseline demographics and disease characteristics were balanced between the studies and reflective of a general patient population with moderate to severe plaque psoriasis. The **study populations** were overall in line with the target population in the indication. There were no major differences in baseline characteristics across treatment groups. Moreover, in study PSO3001 frequency of moderate and severe plaque psoriasis, median PASI and median affected BSA at baseline were comparable in both adults and adolescents.

At week 16, a statistically significant **treatment difference** was observed in the proportion of PASI90 and IGA 0/1 responders (co-primary endpoint) with icotrokinra 200 mg once daily versus placebo. Results were consistent across the three studies. The robustness of the primary outcome was further demonstrated by several sensitivity analyses and supplementary analyses. Key secondary endpoints complemented the observed treatment effect.

The onset of effect was early, with statistically significant differences in PASI75 and PASI90 response between icotrokinra and placebo, observed at week 4 and week 8, respectively.

icotrokinra was also superior to deucravacitinib in PSO3002 and PSO3004. IGA score 0 or 1 and PASI 75 at weeks 16 and 24 were multiplicity-adjusted key secondary efficacy endpoints tested for non-inferiority and subsequently superiority. In addition, confirmatory superiority was demonstrated for PASI90 at weeks 16 and 24.

Improvement in the severity of special site psoriasis was observed with icotrokinra vs placebo, for those with mild psoriasis of the scalp (ss-IGA≥2), genitals (sPGA-G≥2), hands/feet (hfPGA≥), and fingernails (fPGA≥2). icotrokinra demonstrated clinically meaningful improvements in patient-reported outcomes (PSSD and DLQI).

The **short-term effects** observed are robust and clinically relevant. The co-primary endpoints, which reflect clear or almost clear skin (e.g., IGA 0/1) and statistically significant improvements in PASI scores (90% improvement) supported by key secondary endpoints (PASI100, IGA 0, ss-IGA, PROs), provide meaningful measures of treatment success. Results were consistent across three placebo-controlled pivotal studies, each including an adequate number of participants.

In study PSO3001 at week 52 (end of the withdrawal phase) a statistically significant larger proportion of adult patients treated with icotrokinra compared to placebo, **maintained their PASI90** response (84% vs 21%). The median time to loss of PASI90 response in adult patients in whom icotrokinra treatment was withdrawn was 10 weeks.

Relapse, defined as loss of ≥50% of the week 24 PASI response, occurred in 56% (97/172) of adult patients re-randomised to placebo and 4% with icotrokinra. Per protocol these participants were eligible for re-treatment with icotrokinra. In total 72 participants were retreated (of which 10 due to an error in the IRWS) prior to week 52, and 19 others were retreated at week 52. Others did not receive retreatment as they discontinued due to lack of efficacy or initiation of other medication (n=5) or due to a data entry error (n=1).

PASI improvement upon **retreatment** appears to be at least comparable to the initial response with icotrokinra (25% with PASI90 after 8 weeks of retreatment). Yet, the evidence available is limited, given the median time to loss of ≥50% PASI response of 25.7 weeks (from week 24 onwards), and the total follow-up duration at time of MAA of 52 weeks. This is accepted, since no claims on re-treatment after discontinuation are included in the SmPC.

In the randomised withdrawal phase of Study PSO3001, three cases (3/172 patients; 1.7%) fulfilling EMA-defined criteria for rebound were observed within 2 months following discontinuation of icotrokinra. These included one case of new-onset pustular psoriasis with widespread skin involvement and two cases of worsening of psoriasis to 141% and 155% of baseline PASI and occurred 29, 41 and 60 days after treatment discontinuation, respectively. All three cases previously had good to excellent control of psoriasis at the time-point of treatment discontinuation (PASI 75, 90, 100 responses, respectively). It remains uncertain whether the extent of the worsening, the temporal relationship, and the clinical course in these cases are consistent with a gradual worsening of the underlying disease; consequently, a rebound effect cannot be excluded. Based on the limited data available, a causal relationship has not been established. While no established biological mechanism for rebound following IL-23 inhibition has been demonstrated, icotrokinra differs from monoclonal antibodies as the first oral IL-23 receptor antagonist. Its shorter half-time and shorter time to loss of PASI90 after withdrawal indicate reduced pharmacodynamic persistence, thus absence of an established biological mechanism cannot be automatically extrapolated to icotrokinra. Currently, the available data are not considered to indicate a need for changes in treatment practice and to warrant a warning in the SmPC, section 4.4. The findings support inclusion of rebound in the PSUR and continued monitoring through routine pharmacovigilance activities.

Not all patients respond to icotrokinra treatment through a treatment period of up to 52 weeks. There were patients without IGA 0/1 or PASI90 response in the pooled (PSO3001, 3002, 3004) population of participants after 16 weeks of treatment with icotrokinra (e.g., 32% and 47%, respectively). In the randomised withdrawal phase of PSO3001, at week 24, in total 51 **non-responders** continued icotrokinra treatment. Although treatment response increased with longer treatment duration, approximately half of the non-responders at week 24 remained non-responder through week 52, despite treatment continuation with icotrokinra. A recommendation for treatment discontinuation in case of non-response after 24 weeks is included in SmPC section 4.2.

At week 16, icotrokinra was superior to placebo and to deucravacitinib across analysed **subgroups** based on baseline demographics, disease characteristics and prior treatment.

Treatment results in **adolescents** (n=66) were generally comparable to the results in the overall population in PSO3001 in the short-term. In study PSO3001 frequency of moderate and severe plaque psoriasis, median PASI and median affected BSA at baseline were comparable in adolescents and adults.

Statistically significant larger proportions of adolescents had a PASI90 and IGA 0/1 response at week 16 and PASI75/ 100 or IGA 0 response at week 16 with icotrokinra versus placebo.

In accordance with the approved PIP, adolescents did not take part in the randomised withdrawal. Available open-label data support clinically relevant and sustained benefit in adolescents with continued exposure to icotrokinra through Week 52 (study PSO3001)). In the treatment arm, which received icotrokinra continuously from week 0 onwards, the proportion of adolescents achieving IGA 0/1 response and PASI90 response continued to increase through week 24 and was maintained up to week 52 (data-cut off). Data also indicate for all endpoints that adolescents switched from placebo subsequently gained benefit on active treatment, and that a treatment effect with continued exposure was maintained up to week 52. Comparative week 52 across study data support similar long-term efficacy in adolescents and adults. Thus, considering all these aspects extrapolation of findings regarding maintenance of effect, relapse of psoriasis and risk of rebound following discontinuation of treatment in adults to adolescents is acceptable.

Included adolescents were ≥12 years of age weighing ≥40 kg. The **≥40 kg weight cut-off** is acceptable, as it reflects the lower bound of the studied population, and it ensures that the indication remains consistent with the population studied. All available efficacy and safety data originate from participants ≥12 years of age weighing ≥40 kg. icotrokinra has an overall mild safety profile, which was similar in adults and adolescents, despite the ~20% higher exposure in adolescents (probably due to their lower weight).

The response to icotrokinra versus placebo, but not versus deucravacitinib, seemed to be slightly lower in the subgroup of participants with **higher bodyweight** (≥90 kg). Exposure is approximately 20% lower in this subgroup but falls within the flat portion of the E-R curve. The SmPC does not recommend dose adjustment based on body weight (SmPC section 5.2).

Patients who **ever used IL-23 inhibitors** seemed to have a lower response to icotrokinra versus placebo, compared to those not previously exposed to IL-23 inhibitors. Yet, confidence intervals were large, group sizes were small, and the results were not confirmed in the comparison with deucravacitinib. With more stringent endpoints (e.g., PASI100 and IGA 0), the difference in treatment response was especially clear (confidence intervals were not overlapping). These findings may indicate that patients who fail IL-23 inhibitors may not optimally respond to icotrokinra. The literature is nuanced about intraclass switching across anti-IL-23 mAbs in plaque psoriasis (*Grace Hren M et al Clin Exp Dermatol 2024; Reddy R Br J Dermatol 2021*). Some patients do derive benefit from intraclass switching, whereas others may respond better to a therapy with a different mechanism. Whether this is also applicable to icotrokinra, is uncertain, given the distinct target (IL-23R vs IL-23) and the limited evidence available. Despite the potentially lower response to icotrokinra in those priorly exposed to IL-23i, icotrokinra remained superior to placebo.

PSO3003: main study in special site psoriasis

In total 311 participants were randomised of which 6 adolescents. Similar to the other phase 3 studies, the overall completion rate was high (94%). More participants with placebo compared to icotrokinra discontinued through week 16, mainly due to lack of efficacy/worsening of psoriasis.

The **study population** was overall in line with the target population in the indication. Population characteristics were comparable to those in studies PSO3001, 3002, and 3004, and were overall well balanced. Except that more patients in the icotrokinra group (35%) had severe hand-foot psoriasis

compared to the placebo group (17%).

At week 16 a statistically significant **treatment difference** was observed in the proportion of IGA 0/1 responders with icotrokinra 200 mg once daily vs placebo. The robustness of the primary outcome was demonstrated by sensitivity analyses and supplementary analyses. Key secondary endpoints related to overall psoriasis complemented the observed treatment effect.

A statistically significant and clinically relevant treatment difference was observed with icotrokinra versus placebo in **subgroups** with **scalp** (e.g., ss-IGA) and **genital** psoriasis (e.g., sPGA-G), but not with **hand/foot** psoriasis (hf-PGA), where the difference was numerical.

Results were consistent across subgroups based on demographics, disease characteristics and prior psoriasis medication. No separate analyses were performed on data from adolescents, due to the limited number included.

5.3.10.2. Conclusions on the clinical efficacy

Icotrokinra 200 mg demonstrated statistically significant and clinically relevant improvement over placebo, in the treatment of moderate to severe plaque psoriasis in adults and adolescents (≥12 years of age weighing ≥40 kg) who were candidates for systemic therapy. Efficacy was consistently shown across studies, analyses, and subgroups. The indication is adequately substantiated by short-term efficacy data vs placebo and vs deucravacitinib, as well as by data on the maintenance of efficacy up to 52 weeks. The study populations were in line with the target population in the indication. The posology is accepted. The recommended dose of 200 mg once daily is appropriate and is in line with the dose used in the clinical studies.

Hence, the CHMP concluded that the efficacy of icotrokinra is shown in the treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The phase 3 development program (see section 5.3) consists of 4 randomised, controlled studies in which icotrokinra 200 mg orally once daily was administered to patients with plaque psoriasis (PSO) who are candidates for phototherapy or systemic therapy: studies PSO3001, 3002, 3003, and 3004. All 4 phase 3 studies are ongoing to collect safety data for up to 3 years of icotrokinra exposure.

Data of the above pivotal studies (PSO3001, 3002, 3003, and 3004) included comparable patient populations and identical dose and formulation (200 mg QD) and were pooled:

1) **Placebo-controlled** safety data, pooling data from studies PSO3001, PSO3002, PSO3003, and PSO3004 from week 0 through week 16 comparing icotrokinra (n=1296) with placebo (n=568).
2) **Active-controlled** safety data, pooling data from studies PSO3002 and PSO3004 from week 0 through week 24 comparing icotrokinra (n=632) with deucravacitinib (n=634).
3) **Uncontrolled** safety data up to week 52 (safety data through cut-off date), pooling data from studies PSO3001, PSO3002, PSO3003, and PSO3004 from week 0 through the respective safety data cut-off dates (n=2367).

For the four phase 3 studies in Psoriasis, safety data were collected during visits, and at early termination (if applicable). Adverse Events, vital signs, C-SSRS, TB evaluation, and pregnancy tests (female patients) were collected according to protocol during screening, at week 0, week 2, week 4, and every 4 weeks up to week 44, at week 52, and every 12 weeks thereafter until study termination. Clinical laboratory tests (haematology, chemistry, urinalysis) were collected during screening, and every 4 weeks starting at week 0 up to week 36, as well as week 44, 52, 64, and every 24 weeks thereafter up to end of the study; lipid panels and hs-CRP were assessed at weeks 0, 16, and 52 only. ECG's were performed during screening, at weeks 16, 52, 112, and 156. In adolescents, height and weight were documented during screening, at weeks 0, 16, 52, 112, and 156; Tanner stadia at weeks 0, 52, 112, and 156.

Summaries of treatment-emergent AEs were provided for any assessment/event that occurred or worsened between the date of the first application of study drug and the date of last study drug administration plus 4 weeks.

5.4.2. Patient exposure

Overall, 2498 participants with at least one exposure to study drug (placebo, deucravacitinib, icotrokinra) were included in the safety analysis set. At the data cut-off dates, 2367 patients were exposed to icotrokinra, 1849 (78%) for at least 6 months, and 648 (27%) up to 1 year (Table 34). There were 131 participants not exposed to icotrokinra, mainly because they did not cross-over from placebo or deucravacitinib.

Of the included patients, 33% were **female** and 67% were **male**. There were 72 **adolescents** (12<18 years of age) exposed to icotrokinra, all but 1 for at least 6 months (99%) and 45 (63%) for at least 1 year. Of them, 66 adolescents were included in study PSO3001 and 6 adolescents in PSO3003. Of the 2367 patients exposed, 240 (10%) were **≥65 years of age**, 179 (75%) were exposed for at least 6 months and 53 (22%) were exposed for at least one year.

Through the safety data cut-off date, the mean (SD) average daily dose of icotrokinra was 196.1 (10.28) mg and the mean (SD) total duration of treatment was 37.4 (17.15) weeks. Across age groups, the average daily dose and the total duration of treatment were similar.

Table 34. Patient exposure (Cut-off 3 April 2025)

	JNJ-77242113				
	Placebo → JNJ-77242113[a]	JNJ-77242113	Combined[b]	Deucravacitinib → JNJ-77242113[c]	Total[d]
Analysis set: Subjects treated with JNJ-77242113	520	1296	1816	551	2367
All subjects					
Duration of treatment (weeks)					
N	520	1296	1816	551	2367
At least 16 weeks[f]	477 (91.7%)	1240 (95.7%)	1717 (94.5%)	277 (50.3%)	1994 (84.2%)
At least 6 months[g]	428 (82.3%)	1195 (92.2%)	1623 (89.4%)	226 (41.0%)	1849 (78.1%)
At least 1 year[h]	17 (3.3%)	631 (48.7%)	648 (35.7%)	0	648 (27.4%)
Age ≥12 and <18 years[e]					
Duration of treatment (weeks)					
N	25	47	72		72
At least 16 weeks[f]	24 (96.0%)	47 (100.0%)	71 (98.6%)		71 (98.6%)
At least 6 months[g]	24 (96.0%)	47 (100.0%)	71 (98.6%)		71 (98.6%)
At least 1 year[h]	0	45 (95.7%)	45 (62.5%)		45 (62.5%)
Age ≥65 years					
Duration of treatment (weeks)					
N	55	125	180	60	240
At least 16 weeks[f]	50 (90.9%)	120 (96.0%)	170 (94.4%)	30 (50.0%)	200 (83.3%)
At least 6 months[g]	45 (81.8%)	109 (87.2%)	154 (85.6%)	25 (41.7%)	179 (74.6%)
At least 1 year[h]	1 (1.8%)	52 (41.6%)	53 (29.4%)	0	53 (22.1%)

[a] Includes data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113.
[b] Includes data for subjects randomized to JNJ-77242113 and data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113.
[c] Includes data after Week 24 for deucravacitinib subjects who switched over to receive JNJ-77242113.
[d] Includes data for subjects randomized to JNJ-77242113, data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113, and data after Week 24 for deucravacitinib subjects who switched over to receive JNJ-77242113.
[e] Adolescent population enrolled in 77242113PSO3001 and 77242113PSO3003 studies.
[f] The duration between the first and last JNJ-77242113 administration was at least 16 weeks.
[g] The duration between the first and last JNJ-77242113 administration was at least 26 weeks.
[h] The duration between the first and last JNJ-77242113 administration was at least 52 weeks.

5.4.3. Adverse events

Summary of adverse events

In the pooled **placebo-controlled** safety dataset up to week 16 (Table 35), the occurrence of TEAEs was numerically similar or less in the icotrokinra treated group (49%) as compared to placebo (52%), also in terms of the proportions of patients with at least one serious adverse event (1.6% *versus* 2.8%), one or more infections (1.6% *versus* 2.1%), and AEs leading to discontinuation (2.0% *versus* 3.0%). In the icotrokinra group, 2 patients died versus no deaths in the placebo group.

Table 35. Overall Summary of Treatment-emergent Adverse Events Through Week 16; Safety Analysis Set (Pooled PSO3001, 3002, 3003, and 3004)

	Placebo	JNJ-77242113
Analysis set: Safety analysis set	568	1296
Average duration of follow-up (weeks)	15.63	15.92
Subjects with 1 or more adverse events	295 (51.9%)	636 (49.1%)
Subjects with adverse events by maximum intensity[a]		
Mild	162 (28.5%)	364 (28.1%)
Moderate	117 (20.6%)	251 (19.4%)
Severe	16 (2.8%)	21 (1.6%)
Subjects with 1 or more serious adverse events	12 (2.1%)	21 (1.6%)
Subjects with 1 or more infections[b]	148 (26.1%)	311 (24.0%)
Subjects with 1 or more adverse events leading to discontinuation of study agent	17 (3.0%)	26 (2.0%)
Subjects who died	0	2 (0.2%)

	Placebo	JNJ-77242113

[a] Only the maximum severity event experienced by subject is reported.
[b] Infections were defined as any adverse events which were coded to the MedDRA system organ class 'Infections and infestations'.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 27.0.
Note: Crude pooling method was used to calculate the proportions.

During the pooled **active-controlled** safety dataset up to week 24, comparable or numerically lower proportions of patients with TEAEs were observed in the icotrokinra group compared to deucravacitinib treated patients.

In the group of 2367 participants exposed to icotrokinra up in the pooled **uncontrolled** safety data up to the data cut-off, 62% of patients had one or more adverse events, that were mostly of mild (31%) or moderate (28%) intensity while 2.7% were severe. There were 3.2% of participants with at least 1 SAE, and 2.0% with a TEAE that led to a discontinuation of icotrokinra. There were 38% who had at least 1 infection. The comparison of AEIRs in the safety set up to the data cut-off with the placebo-controlled period indicated no increase in risks over time.

Adolescents

In the pooled 16-week **placebo-controlled** period, 25 adolescents were allocated to placebo and 47 to icotrokinra. The proportion of participants with at least 1 TEAE was 72% in the placebo group and 47% in the icotrokinra group. The proportions of patients in the placebo and icotrokinra groups with at least one serious adverse event were (0 *versus* 4.3%), one or more infections (32% *versus* 30%), and AEs leading to discontinuation (0 *versus* 0). The SAEs were pancreatitis (n=1) and arthralgia (n=1).

Common Adverse Events

In the 16-weeks **placebo-controlled** period, most common TEAE per SOC were Infections and infestations (26% *versus* 24%), Investigations (6.5% *versus* 6.8%), GI disorders (6.2% *versus* 6.6%), and Skin and connective tissue disorders (7.6% *versus* 6.2%). TEAEs on PT-level that were numerically more common in icotrokinra compared to placebo (difference with placebo of 0.5% or more) were Nausea (0.5% *versus* 1.2%), Headache (3.3% *versus* 3.9%), Cough (0.2% *versus* 1.2%), Fatigue (0.5% *versus* 1.2%), and Hypertension (1.2% *versus* 1.7%); all these differences were <1% (Table 36).

Table 36. Number of Subjects With 1 or More Treatment-emergent Adverse Events with a Frequency of at Least 1% in Any Treatment Group Through Week 16; Safety Analysis Set (Pooled studies PSO3001, 3002, 3003, and 3004)

	Placebo	JNJ-77242113
Analysis set: Safety analysis set	568	1296
Average duration of follow-up (weeks)	15.63	15.92
Subjects with 1 or more adverse events (crude)	295 (51.9%)	636 (49.1%)
95% CI[a]	(47.9%, 56.2%)	(46.3%, 51.8%)
Risk difference (95% CI)[a]		-3.0% (-8.0%, 2.0%)
System organ class Preferred term		
Infections and infestations	148 (26.1%)	311 (24.0%)
Nasopharyngitis	39 (6.9%)	94 (7.3%)
Upper respiratory tract infection	29 (5.1%)	62 (4.8%)
COVID-19	8 (1.4%)	18 (1.4%)
Urinary tract infection	10 (1.8%)	16 (1.2%)
Influenza	7 (1.2%)	13 (1.0%)
Bronchitis	6 (1.1%)	11 (0.8%)
Pharyngitis	6 (1.1%)	11 (0.8%)
Sinusitis	6 (1.1%)	8 (0.6%)
Gastroenteritis viral	6 (1.1%)	5 (0.4%)
Oral herpes	7 (1.2%)	5 (0.4%)
Gastrointestinal disorders	35 (6.2%)	86 (6.6%)
Diarrhoea	11 (1.9%)	27 (2.1%)
Nausea	3 (0.5%)	15 (1.2%)
Skin and subcutaneous tissue disorders	43 (7.6%)	80 (6.2%)
Pruritus	8 (1.4%)	15 (1.2%)
Psoriasis	18 (3.2%)	10 (0.8%)
Nervous system disorders	28 (4.9%)	73 (5.6%)
Headache	19 (3.3%)	51 (3.9%)
Musculoskeletal and connective tissue disorders	37 (6.5%)	71 (5.5%)
Arthralgia	7 (1.2%)	19 (1.5%)
Back pain	4 (0.7%)	16 (1.2%)
Metabolism and nutrition disorders	21 (3.7%)	41 (3.2%)
Hypertriglyceridaemia	7 (1.2%)	10 (0.8%)
Respiratory, thoracic and mediastinal disorders	11 (1.9%)	37 (2.9%)
Cough	1 (0.2%)	15 (1.2%)
General disorders and administration site conditions	10 (1.8%)	34 (2.6%)
Fatigue	3 (0.5%)	15 (1.2%)
Vascular disorders	10 (1.8%)	28 (2.2%)
Hypertension	7 (1.2%)	22 (1.7%)

[a] Confidence interval based on-study-size adjusted Wald statistics.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.0.

For the 24-weeks **active-controlled** period, 65% of the patients in the deucravacitinib versus 58% of the patients in the icotrokinra group reported at least 1 TEAE. On SOC-level, most common TEAEs were Infections and infestations (40% *versus* 30%), Musculoskeletal and connective tissue disorders (7.6% *versus* 9.8%), Skin and subcutaneous disorders (13% *versus* 8.9%), and Gastro-intestinal disorders (13% *versus* 8.7%). TEAEs numerically more (a difference of at least 0.5%) frequent in icotrokinra compared to deucravacitinib were: Myalgia (1.4% *versus* 0.5%), Psoriasis (1.4% *versus* 0.8%), Headache (4.4% *versus* 3.2%), Fatigue (2.2% *versus* 1.6%).

For the **uncontrolled** safety dataset through data cut-off, 62% of the patients had 1 or more AEs with an AEIR of 172.4/100 PY. The most frequent AEs were in the SOCs Infections and infestations (38%)

with an AEIR of 77.2, Investigations (9.4%) with an AEIR of 15.3, Musculoskeletal and connective tissue disorders (8.7%) with an AEIR of 13.9, Gastro-intestinal disorders (8.4%) with an AEIR of 13.6, and Skin and subcutaneous disorders (8.0%) with an AEIR of 12.8. By PT, most common (2.5% or more) were Nasopharyngitis (14%), Upper respiratory tract infection (9.1%), Headache (4%), Arthralgia (2.7%), Hypertension (2.5%), and COVID-19 (2.5%). The incidence rates for exposure to icotrokinra were smaller as compared with the corresponding EAIR's in the placebo-controlled period.

Adolescents

In the pooled 16-weeks **placebo-controlled** period, 18/25 (72%) of the patients in the placebo group versus 22/47 (47%) in the icotrokinra group had 1 or more AEs. Most common TEAE per SOC were Infections and infestations (32% *versus* 30%), Investigations (20% *versus* 13%), Gastrointestinal disorders (4.0% *versus* 4.3%), and Skin and connective tissue disorders (12% *versus* 4.3%). TEAEs on PT-level that were numerically more common in icotrokinra compared to placebo (difference with placebo of 2.5% or more) were gastroenteritis (0 *versus* 4.3%), hyperuricaemia (0 *versus* 4.3%), headache (0 *versus* 4.3%), sinus bradycardia (0 *versus* 4.5%).

In the **uncontrolled** safety data of study PSO3001 through data cut-off, 70% of the adolescents had 1 or more AEs. The most frequent AEs were in the SOCs of Infections and infestations (47%), Investigations (24%), Metabolism and nutrition disorders (14%), Skin and subcutaneous disorders (12%), Gastro-intestinal disorders (7.6%), Musculoskeletal and connective tissue disorders (7.6%). By PT, most common were Upper respiratory tract infection (18%), Nasopharyngitis (18%), blood CPK increased (6.1%), blood uric acid increased (6.1%). Most other TEAEs occurred in 1-2 cases. The AEIRs of the most common AEs at SOC and PT level were generally lower in the data collected up to safety cut-off, as compared to the 16-week placebo-controlled period, with few exceptions (blood CPK increased, acne).

5.4.3.1. Adverse drug reactions

At submission of the dossier, the applicant proposed no ADRs for inclusion in section 4.8 of the SmPC given that, no ADRs were identified for icotrokinra during the controlled periods, and through the last safety data cut-off date no additional ADRs were identified. TEAEs for icotrokinra would have been identified as ADRs if a causal relationship between icotrokinra and the AE was a reasonable possibility.

For AE analysis and groupings, MedDRA version 27.0 was used. ADR determination was performed in 3 distinct periods (placebo-controlled, active-comparator, and long-term), each using a 2-step process: 1) application of a predefined statistical threshold, followed by 2) a more in-depth review of the AEs that satisfied the first step. The placebo-controlled period was the main period for analysing ADRs. In addition, all SAEs, abnormal laboratory findings, and vital signs underwent separate medical review of all MedDRA PTs (without threshold cut-off) as a screen for potential ADRs. Imbalances were assessed through medical review to identify potential ADRs.

For the **placebo-controlled** period, the prespecified statistical threshold was a TEAE, PT, or PT grouping with an incidence of at least 1%, based on the aggregate sample size (N=1864 study participants) to differentiate between the icotrokinra and placebo groups. The specified rules were:

Step 1

1. If there was an increased incidence in the icotrokinra group relative to the placebo group and the 95% CIs of the RR excluded 1, then the AE would be added to the ADR list.

2. If RR was ≥2 but the 95% CIs included 1, the AE underwent further analysis in Step 2.

3. If RR was 1<RR<2 and the 95% CIs included 1, the AE was not further considered, unless there was a specific medical reason to further evaluate the AE in Step 2.

4. If RR was <1 (i.e., the incidence was lower in the icotrokinra group than in the placebo group), the AE was not further considered.

Step 2 AEs identified in Step 1 underwent medical evaluation by the applicant, including assessment of biologic plausibility, challenge-rechallenge occurrence, frequency of reporting, time to onset plausible, extent of dose-response, and whether the event is known to be caused by related drugs.

In the **active-controlled** period of 24-weeks comparing icotrokinra and deucravacitinib (PSO3002 and 3004), the ADR analysis was also performed in two steps.

Step 1
1. If an AE is labelled as ADR for deucravacitinib *and* the incidence for icotrokinra was similar to or higher than the incidence for deucravacitinib (ie, the frequency as indicated in the deucravacitinib product information), the AE was added to the ADR list, if not already identified.
2. For AEs not listed for deucravacitinib, the rules for the placebo-controlled period were applied.

Step 2 This step was performed similarly as for the placebo-controlled period.

In the long-term **uncontrolled** period (cumulative safety data through the safety data cut-off date; N=2367) there was no comparator. ADR determination was performed based on medical judgement using the guidelines described above and by comparison of the EAIRs in the long-term period with the placebo-controlled EAIRs.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest

The adverse events of special interest for the 4 'phase 3' icotrokinra studies as defined by the applicant, are malignancy, possible Hy's Law, and active TB (Table 37). Based on the ADRs for approved anti-IL23 products, there are additional events of interest, including: infections, MACE, hypersensitivity, suicidal behaviour (see Table 38 further below).

Table 37. Overall Summary of Subjects With 1 or More Treatment-emergent Adverse Events of Special Interest per Hundred Subject-years of Follow-up Through the Safety Data Cut-off Date; Safety Analysis Set (Pooled PSO3001, 3002, 3003, and 3004)

	Through Week 16		Through Week 24[a]		Through Safety Data Cut-off Date[b]
	Placebo	JNJ-77242113	JNJ-77242113	Deucravacitinib	JNJ-77242113
Analysis set: Safety analysis set	568	1296	632	634	2367
Average duration of follow-up (weeks)	15.63	15.92	23.54	23.28	35.57

Total subject-years of follow-up	170.1	395.3	285.2	282.8	1613.7
Subjects with events per 100 subject-years					
Malignancy	0.59 (1/169.8)	1.52 (6/394.6)	1.05 (3/284.6)	0.71 (2/282.5)	0.62 (10/1612.3)
Nonmelanoma skin cancer	0.00 (0/170.1)	0.25 (1/395.1)	0.35 (1/285.0)	0.00 (0/282.8)	0.12 (2/1613.3)
Malignancy other than nonmelanoma skin cancer	0.59 (1/169.8)	1.27 (5/394.8)	0.70 (2/284.8)	0.71 (2/282.5)	0.50 (8/1612.8)
Possible Hy's Law	0.00 (0/170.1)	0.51 (2/395.1)	0.00 (0/285.2)	0.35 (1/282.5)	0.12 (2/1612.3)
Active TB events	0.00 (0/170.1)	0.00 (0/395.3)	0.00 (0/285.2)	0.00 (0/282.8)	0.00 (0/1613.7)
Positively adjudicated active TB events	0.00 (0/170.1)	0.00 (0/395.3)	0.00 (0/285.2)	0.00 (0/282.8)	0.00 (0/1613.7)

[a] Includes only 77242113PSO3002 and 77242113PSO3004 studies.

[b] Includes data for subjects randomised to JNJ-77242113, data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113, and data after Week 24 for deucravacitinib subjects who crossed over to receive JNJ-77242113.

Note: For 77242113PSO3001, data that occurred during the withdrawal period (on or after Week 28 and before retreatment) were excluded for subjects who were rerandomised to placebo at Week 24.

Note: "Malignancy", "Possible Hy's Law", and "Active TB" events were identified in the eCRF through investigator assessment.

Note: Positively adjudicated active TB events were determined by infectious disease adjudication committee.

Note: Adverse events are coded using MedDRA Version 27.0.

Note: Crude pooling method was used to calculate the rates. Crude rates are calculated as (number of subjects with adverse events/total subject-years at risk)*100.

Malignancy

Through week 16 (pooled studies PSO3001, 3002, 3003, and 3004), malignancies were reported in 6 (0.5%) participants treated with icotrokinra and 1 (0.2%) participant in the placebo group (PT: invasive ductal breast carcinoma). In the 6 participants treated with icotrokinra with malignancy through week 16, 2 participants had a history of the same type of malignancy prior to study enrollment (malignant melanoma in 1 participant and keratoacanthoma in 1 participant), and in the remaining 4 participants, the malignancies were all reported soon after initiating icotrokinra treatment (day 14 to day 60). Through week 24 (pooled PSO3002 and 3004), malignancies were reported in 3 (0.5%) icotrokinra-treated participants (all reported prior to week 16 and mentioned above) and 2 (0.3%) deucravacitinib-treated participants.

Through the safety data cut-off date, malignancies were reported in 4 additional participants treated with icotrokinra, with PTs: squamous cell carcinoma of lung (fatal event); B cell small lymphocytic lymphoma; squamous cell carcinoma of skin; chronic lymphocytic leukaemia. In total 10 (0.4%) were reported in the icotrokinra groups. The corresponding EAIR for malignancies in icotrokinra-treated

participants was 0.64 per 100 subject-years through the safety data cut-off date. When compared with an EAIR of 1.52 per 100 subject-years through week 16, this indicates that malignancy risk did not increase with increased exposure to icotrokinra. Compared with the expected incidence in the general US population using the National Institutes of Health SEER database (excluding cervical cancers in situ and nonmelanoma skin cancers), the SIR in the total icotrokinra group was 1.07 (95% CI: 0.46, 2.10) based on an expected number of events of 7.51 and an observed number of events of 8.

Drug-induced liver toxicity (Hy's law)

Through week 16, 2 events of possible Hy's Law were reported in participants treated with icotrokinra and none in the placebo group. Neither case was confirmed as Hy's Law as the ALP criteria (>2x ULN) was not met and confounding factors were present. One participant had cholestasis and an AE of post-viral hepatitis, and the other participant had cholestasis and concomitant isoniazid and alcohol use.

Through week 24, 1 event of possible Hy's Law was reported in a deucravacitinib-treated participant. Through the safety data cut-off date, no additional possible Hy's Law cases were identified in icotrokinra-treated participants.

Active TB and LTBI

Through the safety data cut-off date, there were no cases of investigator-reported active TB or other AEs with PTs that triggered active LTBI/TB adjudication in any treatment group.

Other AE of Interest

Table 38. Overall Summary of Treatment-emergent Other Adverse Events of Interest Through Week 16; Safety Analysis Set (Pooled PSO3001, 3002, 3003, and 3004)

	Placebo	JNJ-77242113
Analysis set: Safety analysis set	568	1296
Average duration of follow-up (weeks)	15.63	15.92
Subjects with 1 or more adverse events of:		
Positively adjudicated latent TB events	0	0
Positively adjudicated opportunistic infections (excluding TB)	0	1 (0.1%)
Serious infections	2 (0.4%)	2 (0.2%)
Positively adjudicated extended MACE	0	3 (0.2%)
Positively adjudicated MACE	0	3 (0.2%)
Positively adjudicated other cardiovascular events	1 (0.2%)	3 (0.2%)
Hepatic adverse events leading to discontinuation of study agent	1 (0.2%)	1 (0.1%)
Serious hepatic adverse events	0	2 (0.2%)
Hypersensitivity	7 (1.2%)	28 (2.2%)
Anaphylactic reaction	0	0
Suicidal Ideation and Behavior (SIB)	0	1 (0.1%)
Depression (excluding suicidal ideation and behavior)	1 (0.2%)	3 (0.2%)

	Placebo	JNJ-77242113

Note: Positively adjudicated latent TB events, and opportunistic infections were determined by infectious disease adjudication committee. "Serious infections" were defined as any adverse events which were coded to the MedDRA system organ class "Infections and infestations" and were considered to be serious by the investigator.
Note: Positively adjudicated MACE, extended MACE, and other cardiovascular events were determined by cardiac adjudication committee. MACE events include cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Extended MACE events include MACE events, hospitalization for unstable angina, and coronary revascularization.
Note: "Hepatic adverse events" identified by SMQ "Drug related hepatic disorders – comprehensive search" (narrow scope). "Serious hepatic adverse events" identified by SMQ "Drug related hepatic disorders – comprehensive search" (narrow scope) and were considered serious by the investigator.
Note: "Hypersensitivity" events identified by SMQ "Hypersensitivity" (narrow scope). "Anaphylactic reaction" events identified by SMQ "Anaphylactic reactions" (narrow scope).
Note: "Depression" events identified by SMQ "Depression excluding suicide and self-injury" (narrow scope). Suicidal Ideation and Behavior (SIB) events are based on the most severe postbaseline C-SSRS values (Suicidal ideation=1, 2, 3, 4, 5; Suicidal behavior=6, 7, 8, 9) and identified in the Adverse Event CRF through investigator assessment (Suicidal ideation, Suicidal behavior, Completed suicide [score 10]).
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.0.
Note: Crude pooling method was used to calculate the proportions.

Infections

In the pooled **placebo-controlled** data up to week 16, the proportion of participants with 1 or more overall infections was similar in the icotrokinra and placebo groups. The most commonly reported infection PTs were nasopharyngitis (7.3% *versus* 6.9%) and upper respiratory tract infection (4.9% *versus* 5.0%), that were reported in a similar proportion of participants in the icotrokinra and placebo groups. The other infections that occurred in the placebo-controlled period (COVID-19, urinary tract infection, influenza, bronchitis, pharyngitis, sinusitis, gastroenteritis viral, oral herpes) all occurred in a similar or lower proportion in the icotrokinra group, as compared to placebo. There were 2 positively adjudicated opportunistic infections reported in 1 participant (both nonserious laryngitis fungal) in the icotrokinra group and there were no positively adjudicated opportunistic infections in the placebo group. Diverse **fungal infections** appeared almost exclusively in the icotrokinra treated group, not in placebo. The relative risk (RR) for fungal infections for icotrokinra vs placebo was 3.27 (95% CI=0.750, 14.263). All reported fungal infections were nonserious and were predominately cutaneous tinea or mucocutaneous candida infections.

In the pooled **active-controlled** data up to week 24, the proportion of participants with 1 or more overall infections was lower in the icotrokinra group compared with the deucravacitinib group.

In the pooled **uncontrolled** data through the safety data cut-off date, the proportion of participants in the total icotrokinra group with at least 1 infection overall was 38% with a corresponding EAIR of 77.20 per 100 subject-years, compared with an EAIR of 91.03 per 100 subject-years through week 16. In total, 12 (0.5%) patients had one or more **serious infections** while being exposed to icotrokinra, with a corresponding EAIR of 0.77 per 100 subject-years, compared with an EAIR of 0.51 per 100 subject-years through week 16. The serious infections were diverticulitis (n=4), bacterial gastroenterocolitis (n=1), pneumonia, (n=3), Eppstein-Barr virus infection (n=1), infective exacerbation of COPD (n=3, one with pneumonia). There were 9 participants who discontinued study intervention due to an AE of infection.

Cardiovascular events including MACE and VTE

In the pooled **placebo-controlled** data up to week 16, cardiovascular events were reported in 5 (0.4%) participants in the icotrokinra group and in 2 participants (0.2%) in the placebo group. Positively adjudicated **MACE** were reported in 0.2% (n=3) of participants in the icotrokinra group and no participants in the placebo group. There were 2 cases (0.2%) of **VTE** in the icotrokinra group and no cases in the placebo group.

In the pooled **active-controlled** data up to week 24, cardiovascular events were reported in 4 participants in the icotrokinra (0.6%) and in 6 participants in the deucravacitinib (0.9%) groups. Positively adjudicated MACE were reported in 0.3% (n=2) of participants in the icotrokinra group and 0.5% (n=3) of participants in the deucravacitinib group; the cases of MACE and of VTE in the icotrokinra group occurred before week 16 and are described above. In the deucravacitinib group, no cases of VTE occurred.

In the pooled **uncontrolled** data through the safety data cut-off date, the proportion of participants in the total icotrokinra group with a positively adjudicated cardiovascular event was 0.5% (11 participants) with a corresponding EAIR of 0.70 per 100 subject-years, compared with an EAIR of 1.27 per 100 subject-years through week 16. The proportion of participants in the total icotrokinra group with positively adjudicated MACE was 0.1% (3 participants) with a corresponding EAIR of 0.19 per 100 subject-years, compared with an EAIR of 0.76 per 100 subject-years through week 16. All 3 positively adjudicated MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) were reported through week 16, and there were no additional participants with MACE through the safety data cut-off date. Three of the positively adjudicated other cardiovascular events (VTE in 2 participants and arrhythmia requiring intervention in 1 participant) occurred prior to week 16, other cardiovascular events occurred in 6 additional participants after week 16 and through the safety data cut-off date Transient Ischaemic Attack (n=2), VTE (n=2), arrhythmia requiring intervention (n=1), severe/accelerated hypertension leading to hospitalisation (n=2).

Hypersensitivity

In the pooled **placebo-controlled** data up to week 16, the proportion of participants with 1 or more hypersensitivity reactions was numerically larger in the icotrokinra (2.2%) as compared to the placebo (1.2%) group (Table 39). **Drug hypersensitivity** occurred in a single case on icotrokinra. Most reported PTs were in the Skin and subcutaneous tissue disorder SOC (icotrokinra 1.4% and placebo 0.9%). In both groups, none of the hypersensitivity reactions were serious, none of the hypersensitivity reactions led to interruption of study intervention, and all hypersensitivity reactions were mild or moderate in severity. In single cases, hypersensitivity led to discontinuation of icotrokinra or placebo.

In the pooled **active-controlled** data up to week 24, the proportion of participants with 1 or more hypersensitivity reactions was numerically lower in the icotrokinra (2.8%) as compared to the deucravacitinib (4.1%) group.

In the pooled **uncontrolled** data through the safety data cut-off date, the proportion of participants in the total icotrokinra group with at least 1 hypersensitivity reaction through the safety data cut-off date was 2.9% with a corresponding EAIR of 4.49 per 100 subject-years, compared with an EAIR of 7.16 per 100 subject-years through week 16. PTs reported in >2 participants were urticaria in 12 (0.5%) participants, eczema in 11 (0.5%) participants, dermatitis contact in 8 (0.3%) participants, rhinitis allergic in 7 (0.3%) participants, dermatitis allergic in 5 (0.2%) participants, dermatitis in 4 (0.2%) participants, and dermatitis acneiform and dermatitis atopic each in 3 (0.1%) participants. There were no treatment-emergent anaphylactic reactions reported through the safety data cut-off date.

Suicidal Ideation and Behaviour

In the pooled **placebo-controlled** data up to week 16, suicidal ideation was reported in 0.1% (n=1) of participants in the icotrokinra group and no participants in the placebo group.

In the pooled **active-controlled** data up to week 24, Suicidal ideation was reported in 0.2% (n=1) of participants in the icotrokinra group (same case as above) and 0.2% (n=1) of participants in the deucravacitinib group.

In the pooled **uncontrolled** data through the safety data cut-off date, one of the suicidal ideation events was reported through week 16 (see above) and 1 additional participant reported suicidal ideation events after week 24 through the safety data cut-off date. There had been no icotrokinra-treated participants with suicidal behaviour.

Serious adverse events

The proportion of participants with 1 or more SAEs was similar for the icotrokinra (1.6%) and placebo (2.1%) groups through week 16 (pooled PSO3001, 3002, 3003, and 3004) and for the icotrokinra (2.8%) and deucravacitinib (3.2%) groups through week 24 (pooled PSO3002 and 3004).

In the pooled **placebo-controlled** period through week 16, no PT was reported as an SAE in >1 participant in the icotrokinra or placebo group (Table 39). The most frequently occurring SAEs fell within the SOC's of neoplasms, cardiac disorders, hepatobiliary disorders, respiratory disorders.

In the pooled **active-controlled** period through week 24, no PT was reported as an SAE in >1 participant in the icotrokinra or deucravacitinib group with the exception of infective exacerbation of chronic obstructive airways disease in 3 (0.5%) icotrokinra-treated participants, 1 of whom also had serious pneumonia.

In the **uncontrolled** data through the safety cut-off date, the proportion of participants in the total icotrokinra group with at least 1 SAE was 3.2% with a corresponding EAIR of 4.92 per 100 subject-years, compared with a numerically larger EAIR of 5.35 per 100 subject years through week 16. PTs reported in >1 participant were diverticulitis and **pneumonia** in 4 (0.2%) participants, **infective exacerbation of chronic obstructive airway disease** in 3 (0.1%) participants, and atrial fibrillation, craniofacial fracture, syncope, intervertebral disc protrusion, and meniscus injury each reported in 2 (0.1%) participants.

Adolescents

In adolescents exposed to icotrokinra, 2 SAEs (arthralgia, pancreatitis) occurred in the **placebo controlled** period and another 3 SAEs (syncope (n=2), lumbal vertebral fracture) in the **uncontrolled** data set up to data cut-off.

Table 39. Number of Subjects With 1 or More Treatment-emergent Serious Adverse Events Through Week 16 by System Organ Class, Preferred Term; Safety Analysis Set (Pooled PSO3001, 3002, 3003, and 3004).

	Placebo	JNJ-77242113
Analysis set: Safety analysis set	568	1296
Average duration of follow-up (weeks)	15.63	15.92
Subjects with 1 or more serious adverse events (crude)	12 (2.1%)	21 (1.6%)
Subjects with 1 or more serious adverse events (adjusted)	12 (1.9%)	21 (1.6%)
95% CI[a]	(0.9%, 3.0%)	(0.9%, 2.2%)
Risk difference (95% CI)[a]		-0.4% (-1.6%, 0.9%)
System organ class Preferred term		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2%)	6 (0.5%)
Adenocarcinoma of colon	0	1 (0.1%)
Benign neoplasm of bladder	0	1 (0.1%)
Breast cancer	0	1 (0.1%)
Keratoacanthoma	0	1 (0.1%)
Pancreatic carcinoma	0	1 (0.1%)
Prostate cancer	0	1 (0.1%)
Invasive ductal breast carcinoma	1 (0.2%)	0
Cardiac disorders	0	3 (0.2%)
Acute myocardial infarction	0	1 (0.1%)
Coronary artery disease	0	1 (0.1%)
Myocardial infarction	0	1 (0.1%)
Hepatobiliary disorders	1 (0.2%)	3 (0.2%)
Biliary dilatation	0	1 (0.1%)
Hepatitis	0	1 (0.1%)
Hypertransaminasaemia	0	1 (0.1%)
Cholecystitis acute	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	3 (0.2%)
Chronic obstructive pulmonary disease	0	1 (0.1%)
Pulmonary embolism	0	1 (0.1%)
Sleep apnoea syndrome	0	1 (0.1%)
Acute respiratory failure	1 (0.2%)	0
Gastrointestinal disorders	0	2 (0.2%)
Haematemesis	0	1 (0.1%)
Pancreatitis	0	1 (0.1%)
Infections and infestations	2 (0.4%)	2 (0.2%)
Gastroenteritis bacterial	0	1 (0.1%)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.1%)
Arthritis bacterial	1 (0.2%)	0
COVID-19 pneumonia	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Nervous system disorders	1 (0.2%)	2 (0.2%)
Subarachnoid haemorrhage	0	1 (0.1%)
Tremor	0	1 (0.1%)
Sciatica	1 (0.2%)	0
Injury, poisoning and procedural complications	4 (0.7%)	1 (0.1%)
Limb injury	0	1 (0.1%)
Concussion	1 (0.2%)	0
Craniofacial fracture	1 (0.2%)	0
Pelvic fracture	1 (0.2%)	0
Tendon rupture	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	1 (0.2%)	1 (0.1%)
Arthralgia	0	1 (0.1%)
Neck pain	1 (0.2%)	0
Skin and subcutaneous tissue disorders	1 (0.2%)	1 (0.1%)
Diabetic foot	0	1 (0.1%)
Psoriasis	1 (0.2%)	0
Vascular disorders	2 (0.4%)	0
Hypertensive urgency	1 (0.2%)	0
Phlebitis superficial	1 (0.2%)	0

[a] Confidence interval based on study-size adjusted Wald statistics.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.0.
Note: Adjusted proportions are proportions adjusted by the total sample size from the combined placebo and JNJ-77242113 treatment groups in a study.
Note: Crude pooling method was used to calculate the proportions for system organ class and preferred terms.

Diverticulitis

In the **uncontrolled** safety data up to data cut-off, four participants treated with icotrokinra had SAEs of diverticulitis. All 4 participants were overweight (≥29.9 kg/m^2; 3 weighing >90 kg) and had a history of smoking, both are risk factors for diverticulitis or for complicated diverticulitis (Strate 2019). In addition, 2 participants had concomitant use of an NSAID (i.e., ibuprofen and etoricoxib) which is also a risk factor for diverticulitis and 1 participant had a prior history of diverticulum intestinal. Two of these 4 participants were rechallenged with icotrokinra with no further events and 1 participant had resolution while continuing on icotrokinra. In addition, nonserious AEs of diverticulitis were reported in 2 icotrokinra participants through the safety data cut-off date. An additional SAE of diverticulitis was reported in an obese (BMI 36.2 kg/m^2) male participant with a history of ibuprofen use in PSO2002. This event was reported as resolved, with treatment interruption while hospitalised and resuming treatment without further events reported.

The diverticulitis incidence rate in icotrokinra-treated participants in the pooled **uncontrolled** data through the safety data cut-off date was 0.38 per 100 subject-years, showing no increase with increased exposure to icotrokinra compared to an EAIR of 0.51 per 100-subject years through week 16; EAIR for diverticulitis with icotrokinra use was also similar to that reported for psoriasis patients (0.661 per 100 subject-years) as well as controls (0.538 per 100 subject-years) (Lee 2019).

Gastro-intestinal disorders

Besides diverticulitis, gastrointestinal SAEs including ulceration, inflammation, and haemorrhage were comprehensively reviewed in icotrokinra-treated participants. Two participants had fatal GI bleeding (discussed below), both of whom had several risk factors for gastrointestinal bleeding, including concomitant medication use, underlying medical conditions, and/or lifestyle risk factors. One participant had a perforated acute gastric ulcer with peritonitis, and one participant had anal fistula, both of whom had underlying risk factors.

Deaths

Through **the safety cut-off date**, in pooled PSO3001, 3002, 3003, and 3004, there were 5 deaths in participants treated with icotrokinra, of which 2 were in the placebo-controlled period through week 16 and the remaining 3 were through the safety data cut-off date. There were no deaths in the placebo and deucravacitinib groups.

Through week 16, there were 2 deaths in participants treated with icotrokinra:

- A male participant with a BMI of 37.1 kg/m^2 and a medical history including parkinsonism, bipolar disorder, ECG Q wave abnormal, and hypertension. At the time of study entry, the concomitant medications included losartan, benserazide hydrochloride/levodopa, lithium carbonate, aripiprazole, and primidone. On day 3, the participant started to experience worsening of generalized mobility, involuntary movements and progressive intense tremors. Study intervention was stopped on day 12. On day 17, he experienced 3 episodes of haematemesis, a seizure, and 2 cardiorespiratory arrests, resulting in death on the same day. The first dark-coloured emetic episode occurred after an afternoon snack followed by 2 more episodes of dark-coloured emesis. According to the participant's guardian, the participant was conscious and oriented when he was taken to the medication room. However, after the infusion of an unspecified medication he had a seizure and was promptly sent to the "red room". The fatal event as reported by the investigator was **haematemesis** and was considered related to the study intervention by the investigator. The event was adjudicated as a noncardiovascular death, with cause of haemorrhage neither cardiovascular or stroke related.

- A male participant with a history of hyperlipidaemia, hypertension, right bundle branch block, concomitant amlodipine besilate/perindopril arginine use, and a BMI of 31.5 kg/m^2 who on day 34 experienced chest pain during physical work, lost consciousness, had ventricular fibrillation, was cardioverted and transported to a hospital where 2 cardiac angiograms showed no large vessel occlusion or significant stenosis. On day 35, during the second cardiac angiogram, he experienced ventricular fibrillation twice, bradycardia, hypotension, and asystole resulting in death. The fatal event of **myocardial infarction** was considered by the investigator to be not related to study intervention. The event was adjudicated as a cardiovascular death.

Through the safety data cut-off date, there were 3 additional deaths in icotrokinra-treated participants:

- A male participant, with a history of ischemic heart disease, hyperlipidaemia, hypertension, Type 2 diabetes, obesity, deep vein thrombosis, abnormal chest x-ray finding in the left lower lung prior to study enrollment that was not considered significant by the investigator, former alcohol use, and a former smoking history (5 pack-years), was initially randomised to placebo and crossed over to icotrokinra on day 113. On day 368, the participant experienced abdominal pain, chest pain, cough and a deterioration in health requiring hospitalisation and an SAE of squamous cell carcinoma of lung was reported. On day 373, a CT scan of chest and abdomen revealed a 31×26×38 mm nodule in segment 9 of the right lung, 11 mm and 10 mm metastatic nodules in segment 6, and numerous hypodense liver lesions (up to 12 mm in size) with peripheral contrast enhancement, consistent with metastases. On day 412, the participant died due to **squamous cell carcinoma of the lung**. This fatal event was considered by the investigator to be not related to study intervention. The event was adjudicated as a noncardiovascular death due to malignancy.
- A male participant, with a history of hypertension, varicose veins, former smoking (7 packs every week for 23 years) and current alcohol use (1 can of beer per week and 50 mL of distilled spirits per week), was randomized to icotrokinra. Concomitant use of acetylsalicylic acid (75 mg daily since March 2021) was reported. On day 385, the participant was found dead at home with cause of death listed as **gastrointestinal haemorrhage**. It was reported that the participant had nausea for 2 days followed by vomiting since the previous night, including episodes of black vomit. This fatal event was considered by the investigator to be not related to study intervention. The event was adjudicated as a non-cardiovascular death due to gastrointestinal bleeding.
- A male participant, with history of gastroesophageal reflux disease, hypertension, obesity Class III (BMI 42.6 kg/m2), PsA, and anemia, was initially randomized to placebo and crossed over to icotrokinra on day 113. On day 252, he was found deceased at home with cause of death listed as toxicity to various agents. The fatal event of **toxicity to various agents** (verbatim term: cocaine toxicity induced hypertensive cardiovascular disease) was considered by the investigator to be not related to study intervention. Autopsy findings included cardiomegaly (560 g), coronary and aortic atherosclerosis, pulmonary congestion, cerebral swelling, cystitis with diverticula, and chronic kidney changes. The adjudication process was ongoing at the time of database lock.

5.4.5. Discontinuation due to adverse events

The proportion of participants with 1 or more AEs leading to discontinuation of study intervention was similar in the icotrokinra (2.0%) and placebo (3.0%) groups through week 16 (pooled PSO3001-3002, 3003, 3004) and for the icotrokinra (2.5%) and deucravacitinib (3.0%) groups through week 24 (pooled PSO3002 and 3004). Through the safety cut-off date, the proportion of participants in the total

icotrokinra group with at least 1 AE leading to discontinuation of study intervention through the safety data cut-off date was 2.0% with a corresponding EAIR of 3.08 per 100 subject-years, compared with an EAIR of 6.63 per 100 subject-years through week 16. In the pooled data through the safety data cut-off date, PTs that led to discontinuation of study intervention in >1 participant were psoriasis and psoriatic arthropathy each in 3 (0.1%) participants and diarrhoea, nausea, pneumonia, and headache each in 2 (0.1%) participants.

For all 4 studies (PSO3001, PSO3002, PSO3003, and PSO3004) there was no allowance for dose reductions, thus there are no discontinuations concerning dose reductions.

The proportion of participants with 1 or more AEs leading to interruption of study intervention was similar in the icotrokinra (3.9%) and placebo (4.2%) groups. The majority of AEs were of mild or moderate severity. The proportions of participants in both groups who had 1 or more SAEs leading to interruption of study intervention were 0.5% for the icotrokinra group and 0.7% for the placebo group. The proportion of participants with 1 or more AEs leading to interruption of study intervention who eventually discontinued study intervention was low in both the icotrokinra (0.2%) and placebo (0.9%) groups.

5.4.6. Safety in special populations

Age

For the elderly, the age group >65 years of age was not further partitioned into age ranges (Table 40).

Table 40. Summary of Key Safety Events Through Week 16 by Age Group; Safety Analysis Set (77242113PSO3001, 77242113PSO3002, 77242113PSO3003, and 77242113PSO3004)

	≥65 to <75 years		≥75 to <85 years		≥85 years	
	Placebo (N=51) n (%)	JNJ-77242113 (N=103) n (%)	Placebo (N=6) n (%)	JNJ-77242113 (N=21) n (%)	Placebo (N=1) n (%)	JNJ-77242113 (N=1) n (%)
Average duration of follow-up (weeks)	15.72	16.04	13.86	16.04	16.14	16.14
Subjects with 1 or more adverse events	22 (43.1%)	53 (51.5%)	2 (33.3%)	9 (42.9%)	0	0
Subjects with 1 or more serious adverse events	1 (2.0%)	2 (1.9%)	1 (16.7%)	2 (9.5%)	0	0
Fatal	0	0	0	0	0	0
Hospitalization/prolong existing hospitalization	1 (2.0%)	2 (1.9%)	1 (16.7%)	2 (9.5%)	0	0
Life-threatening	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0
Other (medically important)	0	0	0	0	0	0
Subjects who discontinued study agent	0	4 (3.9%)	1 (16.7%)	1 (4.8%)	0	0
Psychiatric disorders[a]	0	1 (1.0%)	0	0	0	0
Nervous system disorders[a]	2 (3.9%)	3 (2.9%)	0	2 (9.5%)	0	0
Cardiac disorders[a]	1 (2.0%)	0	0	1 (4.8%)	0	0
Vascular disorders[a]	3 (5.9%)	3 (2.9%)	1 (16.7%)	0	0	0
Cerebrovascular disorders[b]	0	0	0	0	0	0
Infections and infestations[a]	5 (9.8%)	30 (29.1%)	2 (33.3%)	4 (19.0%)	0	0
Gastrointestinal disorders[a]	4 (7.8%)	12 (11.7%)	0	0	0	0
Skin and subcutaneous tissue disorders[a]	1 (2.0%)	6 (5.8%)	1 (16.7%)	2 (9.5%)	0	0

	≥65 to <75 years		≥75 to <85 years		≥85 years	
	Placebo (N=51) n (%)	JNJ-77242113 (N=103) n (%)	Placebo (N=6) n (%)	JNJ-77242113 (N=21) n (%)	Placebo (N=1) n (%)	JNJ-77242113 (N=1) n (%)

[a] MedDRA system organ class.
[b] Cerebrovascular disorders includes adverse events with a MedDRA HLGT of 'Central nervous system vascular disorders'.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 27.0.
Note: Crude pooling method was used to calculate the proportions.

In the **placebo-controlled** period, the occurrence of TEAEs, SAEs, infections, and study discontinuations due to AE was generally lower or similar in the icotrokinra group as compared to the placebo group, for adolescents and patient groups <65 year of age. In patients >65 years of age and comparing icotrokinra (n=125) to placebo (n=58), for icotrokinra there were higher proportions of patients with at least 1 TEAE (50% *versus* 41%) and patients with one or more infections (27% *versus* 21%) and discontinuations due to an AE (4.0% *versus* 1.7%).

In the **active-controlled** period, the occurrence of TEAEs, SAEs, infections, and study discontinuations due to AE was generally lower or similar in the icotrokinra group as compared to the deucravacitinib group, for patient groups 18<65 year of age (adolescents were not treated with deucravacitinib.) In patients >65 years of age and comparing icotrokinra (n=65) to deucravacitinib (n=65), for icotrokinra there were higher proportions of patients with at least 1 TEAE (68% *versus* 57%) and patients with one or more infections (37% *versus* 26%) and discontinuations due to an AE (7.7% *versus* 4.6%).

Psoriasis severity and Psoriasis of special areas

In the pooled placebo-controlled period, the occurrence of TEAEs, SAEs, infections, and study discontinuations due to AE was generally lower or similar in the icotrokinra group as compared to the placebo group, irrespective of psoriasis severity (PASI total score, IGA 3 or 4). Also, in patients with or without special area involvement (ss-IGA score≥3, sPGA-G score ≥3, hf-PGA score ≥3), the pattern of occurrence of TEAEs was similar.

Hepatic and renal impairment

A dedicated **renal** impairment PK study has been performed, and renal impairment was included in the PopPK study. An approximately 2-fold higher renal clearance and a lower metabolite/unchanged drug ratio in subjects with moderate or severe renal impairment indicate that a decrease in renal metabolism contributes to an increased exposure in renally impaired patients exposed to icotrokinra (see PK discussion).

No formal PK studies with icotrokinra were conducted in participants with **hepatic** impairment. Changes in hepatic function are considered unlikely to have any effect on the elimination of icotrokinra as it is not metabolised through hepatic pathways, hepatic enzyme levels had no effect in the PopPK model (see PK section).

According to the exclusion criteria of the pivotal studies, patients with a current diagnosis or signs or symptoms of severe, progressive, or uncontrolled renal or liver disease were not included. The SmPC section 4.2 provides information on use in both conditions:

Renal impairment

No dose adjustment is recommended for patients with mild, moderate or severe renal impairment. Icotyde has not been studied in patients with end-stage renal disease and should only be used in these patients if the benefit outweighs the possible risk (see section 5.2).

Hepatic impairment

No dose adjustment is recommended in patients with mild, moderate, or severe hepatic impairment (see section 5.2).

5.4.7. Immunological events

In the icotrokinra 'phase 3' studies, the overall incidence of antibodies to icotrokinra through week 52 was 9.6% (199/2083 participants). Of the participants who were ADA positive, 60% (119/199) of the participants had the lowest measurable titre of 1:50 and 3% (6/199) had a peak titre of ≥1,000. Among the participants who were positive for antibodies to icotrokinra, none were positive for NAb. Population PK analysis using pooled data up to week 52 showed that C_{max} and AUC increased by 1.2- and 1.3-fold, respectively, compared with participants who did not develop ADA. There was no clinically relevant effect of ADA on safety (hypersensitivity reactions) of icotrokinra over the treatment duration of 52 weeks (see also Clinical pharmacology section).

5.4.8. Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies with icotrokinra have been performed. Based on *in vitro* studies and given that it is a peptide, icotrokinra is not a CYP enzyme substrate, inhibitor, or inducer. icotrokinra is not a substrate or inhibitor of P-gp or other major drug transporters at clinically relevant concentrations. Therefore, no clinically relevant drug interactions have been identified (see also Clinical pharmacology section).

5.4.9. Vital signs and laboratory findings

Haematology

Haematology toxicity profiles were generally mild and comparable between icotrokinra and placebo, and icotrokinra and deucravacitinib, and there was no clear increase over time in frequencies. There were very few Grade 3, and no Grade 4 events.

Chemistry

CPK increased was the most common observation with Grade > 0. Frequencies were comparable between icotrokira and placebo (both about 15%) and deucravacitinib (both about 22%), and up to 25% of the patients had CPK increased through the data cut-off date. Most cases concerned Grades 1 and 2 and about 1% had Grade 3 or 4 toxicity.

Imbalances were seen for Grade 2 Hyperkalaemia for icotrokinra versus placebo and its active control: Grade 2 toxicities were reported in 1.9% versus 0.4% in placebo and 2.9% versus 1.6% in deucravacitinib. Grade 3 Hyperkalaemia was also more common in icotrokinra versus deucravacitinib. At week 52, 8.1% had Grade > 0; 0.8% and 0.1% had Grade 3 and Grade 4 hyperkalaemia, respectively. Absolute numbers were low, there were no associated SAEs, and other factors, especially diuretics could not be excluded.

Liver function tests and Hy's law

No notable imbalances (in frequencies or shifts compared to placebo or active control group) were observed in ALT or AST toxicity Grade ≥ 2 or up to week 52, nor were there specific imbalances seen for ALT ≥3xULN, AST ≥3xULN, or total bilirubin ≥2xULN. Through week 52, 11 patients had ALT > 5x ULN, 2 had ALT > 10x ULN, and 2 had > 20x ULN; for AST these numbers were 7, 5, and 1. The

majority of ALT ≥5xULN and/or AST ≥5xULN was transient and not associated with hepatic AEs leading to discontinuation of study intervention or serious hepatic AEs. No patient fulfilled Hy's law criteria. The patients with *possible* Hy's law had confounding factors which could explain the liver function test findings (i.e., isoniazid use, infection).

ECG measurements

Numerical imbalances were seen for 1st degree AV-block at week 16 in icotrokinra (3.4%) versus placebo (1.1%), and icotrokinra (4.9%) versus deucravacitinib (2.1%); 3.0% had 1st degree AV-block at week 52. This difference is not of clinical relevance as the overall percentage of patients with ECG abnormalities was comparable between icotrokinra and placebo (11.9% versus 11.6%, respectively), and no other differences in heart conduction were observed between both groups. Furthermore, there is no reported association between IL23 inhibition and AV-block in literature (while inflammation in psoriasis is), analyses of congruent ECGs (i.e., 3 of 3 ECG readings with 1st degree AV block at Week 16) demonstrated similar results for both the icotrokinra and placebo groups, 1st degree AV blocks have a prevalence of about 4% in the general population (*Nicolaidou et al., 2016*) and the observed rates fit within this picture, there is no evidence for ECG / cardiovascular safety issues in non-clinical PD and repeat-dose studies, and finally the block is usually considered of no clinical concern.

Growth

Height, weight, and Tanner stage data in adolescents mainly originated from study 3001 (n = 66); study 3003 included 6 adolescents only. The 66 patients in study 3001 were further scattered as part of these were initially assigned to placebo and later switched to icotrokinra according to protocol. Week 52 data were available in a subset of patients. Height and weight increased over time; Tanner stages tend to be generally higher at week 52, but data are limited due to small numbers and variability in exposure. Overall, safety profile in adolescents is considered similar to the one in adults.

5.4.10. Post-marketing experience

Not available.

5.4.11. Patient selection for safety

LTBI testing at treatment start

The applicant considered that exposure to icotrokinra does not increase the risk of LTBI reactivation and thus no LTBI testing should be mandated due to treatment with icotrokinra. This section contains data relevant to considering mandatory LTBI screening prior to icotrokinra initiation.

Certain systemic treatments for psoriasis are associated with the risk of reactivation of LTBI. In particular, the risk of LTBI reactivation has been described for older immunosuppressants such as methotrexate, as well as for systemic therapies in the TNF-α inhibitor class. These findings have resulted in requirements for LTBI testing/treatment for patients with psoriasis prior to initiation of most systemic therapies.

The applicant presented a dedicated report for justifying their position, concerning 6 elements: 1) the effect of icotrokinra on biomarkers that are considered to protect against activation of LTBI, 2) *in vitro* cytokine and immune cell profiling, 3) clinical safety data of patients treated with icotrokinra with and without prophylactic treatment for LTBI activation, 4) a review of clinical and observational data on

LTBI activation in patients treated with anti-IL23 therapies and with anti-TNFα, 5) observational 'real world' data from the US, 6) decision analytic and Benefit-risk modelling.

Biomarkers

Serum biomarkers associated with protection from TB (i.e., TNFα, IL-6, IL-12, IFNγ, and CXCL13) were not/or minimally affected by icotrokinra at week 16. IFN signaling appears not to be impacted by icotrokinra. Whole blood RNA sequencing showed that expression levels of IFN-inducible genes, including MX1, IFIT1, and SIGLEC1, remained similar to healthy controls in the icotrokinra cohort.

Non-clinical data

In vitro cytokine and immune cell profiling have been performed. Accordingly, icotrokinra did not seem to attenuate purified protein derivative induced intracellular IFN-γ production or T cell proliferation in an *in vitro* model developed to evaluate the impact of icotrokinra on TB antigen-specific immune responses. The experiments also showed that apremilast, deucravacitinib, and adalimumab do inhibit PPD stimulated memory CD4+ T cell responses, but icotrokinra does not.

Clinical safety data

Among the N=2498 participants randomised and treated with any study intervention in the pooled phase 3 studies, 173 (6.9%) were determined to have LTBI at or prior to baseline. Of the 173 participants, 50 (29%) completed LTBI treatment prior to screening, 92 (53%) received concomitant LTBI treatment, and 31 (18%) received no LTBI treatment.

Of the 92 participants who received concomitant LTBI treatment during the study, approximately 80% of participants received an INH-containing therapy: approximately 50% received INH monotherapy and another 30% received a rifamycin-based therapy containing INH.

Overall, treatment with icotrokinra was not associated with an increased risk of infection compared to placebo through week 16, or when compared with deucravacitinib through week 24. Of the 2498 participants randomised and treated with any intervention, 173 had LTBI at or prior to baseline (31 with *untreated* LTBI), and no cases of reactivated or de novo active TB occurred during the studies through the safety data cut-off date. Concomitant LTBI treatment was associated with an increase in the occurrence of both hepatic AEs and laboratory abnormalities compared with participants who did not receive LTBI treatment (Table 41).

Table 41. Number of Subjects With 1 or More Treatment-emergent Hepatic Adverse Events Through Week 16 by Baseline Latent Tuberculosis Infection (LTBI) Treatment Status; Safety Analysis Set (Pooled PSO3001, 3002, 3003, and 3004)

	Concomitant LTBI Treatment		No Concomitant LTBI Treatment	
	Placebo	JNJ-77242113	Placebo	JNJ-77242113
Analysis set: Safety analysis set	16	46	552	1250
Average duration of follow-up (weeks)	14.76	16.25	15.65	15.90
Subjects with 1 or more hepatic adverse events	2 (12.5%)	5 (10.9%)	13 (2.4%)	21 (1.7%)
System organ class Preferred term				
Investigations	1 (6.3%)	3 (6.5%)	11 (2.0%)	17 (1.4%)
Aspartate aminotransferase increased	1 (6.3%)	2 (4.3%)	4 (0.7%)	9 (0.7%)
Alanine aminotransferase increased	1 (6.3%)	3 (6.5%)	3 (0.5%)	7 (0.6%)
Gamma-glutamyltransferase increased	0	1 (2.2%)	3 (0.5%)	6 (0.5%)
Hepatic enzyme increased	0	0	2 (0.4%)	1 (0.1%)
Liver function test increased	0	0	1 (0.2%)	1 (0.1%)
Transaminases increased	0	0	1 (0.2%)	1 (0.1%)
Blood bilirubin increased	0	0	1 (0.2%)	0
Hepatobiliary disorders	1 (6.3%)	3 (6.5%)	2 (0.4%)	3 (0.2%)
Hepatic steatosis	0	0	1 (0.2%)	2 (0.2%)
Hepatic function abnormal	0	0	0	1 (0.1%)
Drug-induced liver injury	0	1 (2.2%)	0	0
Hepatic fibrosis	0	1 (2.2%)	0	0
Hepatitis	0	1 (2.2%)	0	0
Hypertransaminasaemia	0	1 (2.2%)	1 (0.2%)	0
Liver injury	1 (6.3%)	0	0	0
Gastrointestinal disorders	0	0	0	1 (0.1%)
Varices oesophageal	0	0	0	1 (0.1%)

Note: Concomitant treatment is defined as LTBI treatment during study. In 77242113PSO3001 and 77242113PSO3003, the decision to treat LTBI or not was made by the investigator. In 77242113PSO3002 and 77242113PSO3004, subjects determined to have LTBI were required either to have completed or initiated LTBI treatment prior to first administration of study intervention.
Note: Hepatic adverse events are defined based on "Drug related hepatic disorders – comprehensive search" SMQ narrow scope.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.0.
Note: Crude pooling method was used to calculate the proportions.

Review of clinical and observational studies

The applicant performed a review of published literature to characterise LTBI reactivation risk with IL-23i, including: 1) clinical study literature, 2) observational study literature, 3) AEs related to LTBI treatment, and 4) TB de novo infections and LTBI reactivation incidence with approved IL-23i. In IL-23i plaque psoriasis programs (i.e., guselkumab, tildrakizumab, and risankizumab), there are low numbers of active TB cases among participants treated with these IL-23i therapies with either positive or negative LTBI results at baseline.

Clinical studies

In the clinical studies of approved **anti-IL23** products, screening for LTBI was applied and treatment was mandatory for guselkumab and tildrakizumab (Table 42). In the studies for risankizumab, LTBI treatment was not mandatory: 441 participants tested positive in LTBI screening and 334 were untreated. In the average follow-up time of 8.8 years, no cases of activated LTBI occurred in the

untreated patients. Over all three products, 2 cases of TB occurred, irrespective of screening and LTBI treatment (Table 42).

Table 42. LTBI in pivotal psoriasis studies of IL-23 inhibitors

IL-23 Inhibitor	Studies	Total Number of Participants	Positive LTBI Test at Screening	# Untreated for LTBI at Screening	Follow-Up Time	Number of Active TB cases including LTBI reactivations
Guselkumab (TREMFYA®) (Puig 2020)	Two Phase 3 Studies: VOYAGE 1 and VOYAGE 2	Across the 2 studies: • 1,829 participants randomized across the 2 studies to: 100 mg guselkumab or 80 mg→40 mg adalimumab	130 participants: guselkumab, 69; adalimumab, 36; and placebo, 25	All participants with LTBI at screening received LTBI treatment	Through Week 100	**0**
Tildrakizumab (ILUMETRI®) (Blauvelt 2018)	One Phase 2b Study: P05495 Two Phase 3 Studies: reSURFACE 1 and reSURFACE 2	Across the 3 studies: • 705 participants randomized to 100 mg tildrakizumab • 708 participants to 200 mg tildrakizumab	N/A	All participants with LTBI at screening received LTBI treatment	Through Week 52 for P05495 and reSURFACE 1 and through Week 64 for reSURFACE 2	**1** (One case of bone TB with a negative test at screening in a 58-year old male with occasional Asia travel who received tildrakizumab)
Risankizumab (SKYRIZI®) (Gordon 2024)	In total, 20 psoriasis studies (Phase 1 through 4)	Across the 20 studies, 3,658 participants with psoriasis randomized to risankizumab (any dose)	441 participants	334 participants	Average follow-up time of 8.8 years	**1** One case of LTBI in a participant with psoriasis during screening, received prophylaxis, and developed active TB 4 years later

In addition to the guselkumab studies described above, pooled data from 11 plaque psoriasis and psoriatic arthritis trials (~4.400 participants; 10.787 PY of guselkumab exposure; up to 5 years follow-up) reported no cases of active TB (Strober 2024). Patients with LTBI were treated prior to or simultaneously with the first administration of study agent.

In clinical studies of **JAK and TNF-α inhibitors** in inflammatory diseases, the risks of TB appear to be higher. A comprehensive review of the risk of opportunistic infections in tofacitinib (a JAK inhibitor) studies showed that among the 5671 participants 26 cases of active TB were reported in participants treated with tofacitinib; of those, 24 cases were negative for LTBI at screening with a median of 64 weeks between tofacitinib start and TB diagnosis (Winthrop 2016). A review of 29 clinical studies with a total of 11.879 participants with inflammatory diseases (including psoriasis, PsA, RA, AS, CD, GvHD, and UC) reported a total of 45 TB cases among 7912 participants treated with TNF-α inhibitors, compared to 3 cases among the 3,967 patients in the control group (OR 1.94 [95%CI: 1.10, 3.44], p=0.02) (Zhang 2017).

Observational studies

A review of the literature was conducted to identify literature reviews and observational studies for reactivation of LTBI in patients treated with IL-23i. Four observational studies were found. Three of them concern relatively small samples of in total 52 patients with psoriasis and positive LTBI screening starting IL23i, without TB reactivation in the next 12-24 months (Ibba 2023; Manzanares 2024; Raimondo 2025). The other study was a retrospective cohort study using TriNetX data to assess the risk of infectious complications in patients with psoriasis managed by IL-23i (n=5272) and IL-17i with propensity-score matched TNF-α inhibitors (n=5272) as a comparator (Kridin 2023). According to the results, the risk of TB was 0.2% in IL-23i (n=10) vs 0.4% in TNF-α inhibitor (n=20), resulting in a hazard ratio (95%CI) of 0.42 (0.14 - 1.30). This study does not differentiate between LTBI reactivation and de novo TB infection or comment on LTBI therapy.

In a meta-analysis of 20 observational studies (Zhu 2024), including 4 studies of anti-IL23 with 324 patients, TNF-α inhibitors had a higher reactivation rate of LTBI compared with IL-17 inhibitors and IL-

23 inhibitors, which had a lower or zero risk of triggering LTBI reactivation. Accordingly, no effect of using LTBI prophylaxis (yes or no) could be found.

In a systematic review of in total 15 studies on psoriatic patients with LTBI who were treated with IL inhibitors (Li 2025), including 581 LTBI patients initiating IL-23i (guselkumab, risankizumab, tildrakizumab) without chemoprophylaxis, 1 case of TB reactivation occurred leading to a rate of TB reactivation of 0.17%.

Observational 'real world' data

The applicant analysed additional RWD from a variety of sources which captured the use of several IL-23i approved for treatment of plaque psoriasis. Two approaches were executed internally by the applicant using licensed RWD sources. The databases that were used were Merative MarketScan CCAE Database, IQVIA Adjudicated Health Plan Claims Data (IQVIA Pharmetrics Plus), Optum De-identified Clinformatics Data Mart Database –Date of Death (DoD), JMDC, and Optum EHR. With the exception of the JMDC database, the databases represented patients from the United States. Three of the databases had more than a million participants with the treatment indication of psoriasis or psoriatic arthritis.

The first approach was a retrospective **observational before-after period** analysis, in which identified participants initiating IL-23i were followed from enrollment to disenrollment in the insurance claims database. The period before and after initiation of the treatment of interest was compared using a conditional Poisson regression with time-varying covariates. According to the results, prior to compared with following initiation of IL-23i therapy, the incidence rate from the meta-analysis of the 4 data sources produced an incidence rate ratio IRR (95%CI) of 0.47 (0.21, 1.03).

The second approach was a retrospective **comparative cohort** analysis of patients initiating an IL-23i, an anti-TNF, or apremilast. Cox proportional hazards regression models with treatment as the only explanatory variable in propensity score matched samples were used to model time to the first TB outcome for participants initiating an IL-23i comparing to participants initiating an anti-TNF or apremilast (modelled separately). According to the results, the HR (95%CI) for TB comparing IL-23i to TNFα inhibitor from the meta-analysis was 0.76 (0.28 - 2.04). For the comparison with apremilast, the resulting HR (95%CI) from the meta-analysis comparing IL-23i to apremilast was 0.93 (0.29 - 2.94).

Decision analytic and Benefit-risk modelling

To evaluate the impact of LTBI testing and treatment in countries with low TB burden, the applicant developed a combined decision analytic/benefit-risk model to evaluate different strategies for LTBI testing and treatment in participants with moderate to severe plaque psoriasis treated with icotrokinra.

The model considers 3 distinct strategies:

1) LTBI testing required; if positive, LTBI treatment required.
2) LTBI testing required; if positive, consider LTBI treatment.
3) No specific LTBI testing or treatment requirement in the context of icotrokinra administration. It assumes that treating providers follow good clinical practice and local regulations for LTBI testing.

For each strategy, the model assessed a benefit-risk score based on the number of clinically apparent treatment-induced hepatitis cases, the number of reactivated TB cases, and the clinical impact (weight) of these cases. The goal is to find a treatment strategy that minimises burden. To inform the model parameters, a combination of clinical study data, literature, and expert assessments were employed. Sensitivity analyses showed the impact of uncertainties in a wide variety of parameters underlying the model.

Main model parameters (range) were: a prevalence of **LTBI** in the population of 7.5% (5% - 10%), a prevalence of LTBI in persons with risk factors of 31% (26% - 35%), a sensitivity of LTBI testing of 85.5% (81% - 90%), false positive LTBI tests of 3% (1% - 5%), an annual probability of **LTBI reactivation** of 0.25% (0.167% - 0.25%), a probability of LTBI reactivation while receiving prophylactic (INH) treatment of 0.0625% (0.0167% - 0.1%), and a relative risk of icotrokinra to **cause LTBI** of 1 (1 – 2) versus placebo, and a proportion of INH-induced **hepatitis** of 1.75% (0.5% - 3.0%), a probability of LTBI positive tested patients to receive no prophylaxis (if not mandatory) of 48% (48% - 56%). As weights for the health states of active TB and of clinical apparent hepatitis, published health state utility values were used. The used health state utility (range) for clinically apparent treatment-induced hepatitis was 0.735 (0.62 - 0.85), the utility for active TB was 0.66 (0.61 - 0.71) (Porco 2006; Guo 2008). Utility values reflect an individuals' health state on a normalised scale, where 1.0 is perfect health and 0 is death.

For strategies 1 and 3, the basic models are shown below.

Figure 26. LTBI Testing Required; If Positive, LTBI Treatment Required

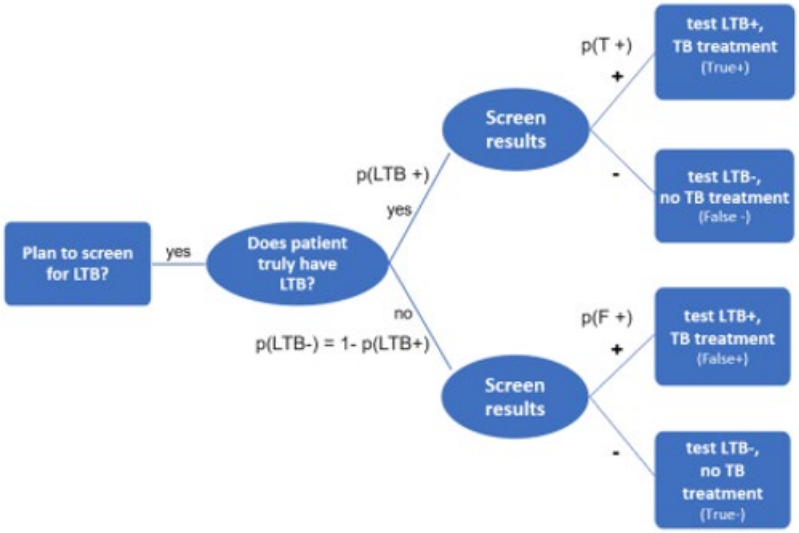
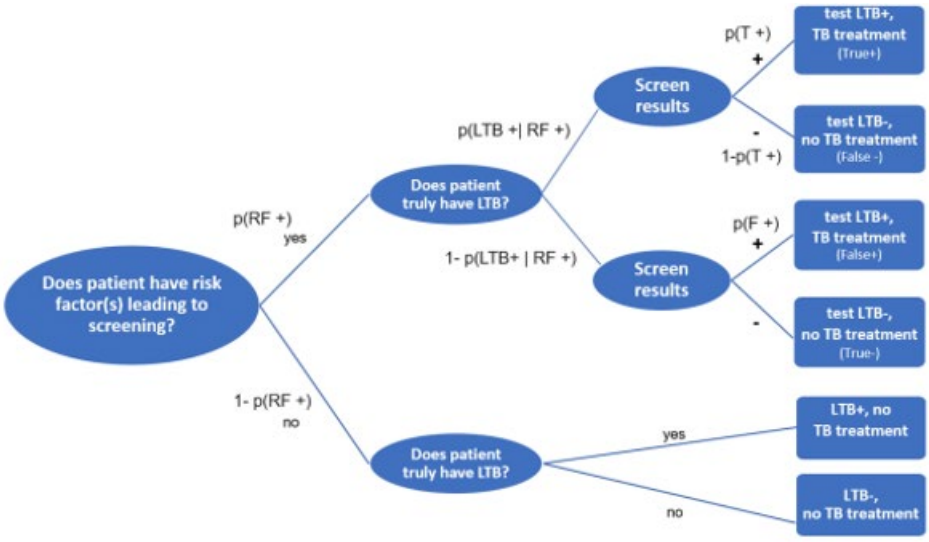


Figure 27. No Specific LTBI Testing or Treatment Requirement in the Context of icotrokinra Administration. Follow Good Clinical Practice and Local Regulations for LTBI Testing



According to the results using the prevalences, probabilities and strategies as denoted above, in a low TB burden region, the base case analysis indicates that Strategies 2 and 3 are projected to result in the highest incidence of TB cases and Strategy 1 the lowest (Table 43). Strategy 1 (mandatory LTBI screening and treatment) is estimated to lead to 0.7/10.000 reactivated TB cases per year and to 16.1/10.000 cases of hepatitis per year. **Strategy 3** (risk factor-based screening and treatment) is estimated to lead to 1.2/10.000 reactivated TB cases per year and to 7.0/10.000 cases of hepatitis per year. Strategy 2 has values in between the other strategies, numerically more close to Strategy 3. When attaching the (1-utility) weights to the occurrences of reactivated TB and hepatitis, Strategy 3 has the lowest burden, as compared to Strategy 1 and 2 (Table 43).

Table 43. Reactivated TB cases, treatment-induced hepatitis cases and clinical burden for three screening strategies over 1 year.

Strategy	Reactivated TB Cases/10,000 Individuals	INH-induced Hepatitis Cases / 10,000 Individuals	Clinical Burden (Units of Equivalent TB Cases / 10,000 Individuals)
1. LTBI testing required; if positive, LTBI treatment required	0.7	16.1	13.2
2. LTBI testing required; if positive, consider LTBI treatment	1.2	8.4	7.8
3. Follow good clinical practice for LTBI testing. No specific LTBI testing or treatment requirement in the context of icotrokinra administration	1.2	7.0	6.6

These results were stable to sensitivity analysis for all model parameters. Accordingly, the clinical impact of INH-induced hepatitis would have to be at least 10-fold worse than that of reactivated TB before Strategy 3 is no longer the least burdensome strategy. The probability of LTBI prophylactic treatment inducing hepatitis must be above 0.15% for Strategy 3 to remain the least burdensome option. If this probability is less than 0.15%, other strategies could be more favourable. While information is limited, the probability of hepatitis when using 3HP as treatment is approximately 0.4% (Sterling 2011).

Limitations of the model include the heterogenous expression of LTBI treatment-related clinically-apparent hepatitis and TB; assessment over a one-year period without consideration of age-related variations in susceptibility and reactivation rates; the design for a low TB burden region only; and that, separate from psoriasis management, public health considerations are important for TB care that could potentially be considered as well.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

The pooled safety data set for icotrokinra is quite large and includes a comparison of icotrokinra with placebo of 16 weeks and with deucravacitinib of 24 weeks and includes also follow-up data of 52 weeks. The main points of discussion during the assessment were: the applicant's conclusion that **no ADRs were identified** and proposal to not include a warning for mandatory **LTBI testing** at treatment start.

Exposure

The main safety data came from the four phase 3 trials PSO3001, 3002, 3003, and 3004, in which 2367 patients were (at least once) exposed to icotrokinra with 200 mg QD; 648 patients (≈50%) were exposed for 1 year. These included patients aligned with the proposed indication and the claimed posology of 200 mg QD. The four studies are similar in design which justifies pooling for safety. The collection of safety data is considered adequate regarding size, length of follow-up, timing / frequency and comprehensiveness. Safety data are available from 72 adolescent patients weighing at least 40 kg; 52 weeks data were available from 46 of them at the time of submission. The acceptability of the safety profile of icotrokinra to treat PSO in adolescents is supported by data in adults. More long-term data (up to week 52 and beyond) will become available. Overall, the size of the data base and the amount of exposure is acceptable in support of a Marketing Authorisation, according to the ICH E1 guideline, save for specific safety concerns.

Adverse Drug Reactions

Following the natural role of IL-23 and of IL23R expressing cells, infections can be expected as ADR. In humans, IL-23 is especially important in driving an early response to pathogens by directly influencing IL-17 production (McKenzie 2006), mainly for protection against bacterial and fungal infections (Schinocca 2021). In line with that, IL23R carrying cells are mainly located in lung, skin and the gastrointestinal tract (McKenzie 2006; Camard 2025). It has been reported that IL23R-deficient patients are susceptible to *mycobacterial* infections (Philippot 2023). However, it also is hypothesised that the rapid IL23-IL17 pathway is less important for the IL-12 mediated long term protective responses (McKenzie 2006), including response against *mycobacteria* (Chakerian 2006).

The main source of data to analyse potential ADRs was the 16-week placebo-controlled period, supplemented by the active controlled period with deucravacitinib, and the long-term follow-up data. Based on the available data, the applicant did not propose ADRs for icotrokinra. To compare, the other approved anti-IL23 products for psoriasis (risankizumab, tildrakizumab, and guselkumab, also ustekinumab as anti-IL-12/23 inhibitor) do have infections/ upper respiratory tract infections, headache, fatigue, injection site reactions and gastrointestinal disturbances (e.g. diarrhoea/nausea/vomiting), pruritis, back pain and fatigue, among the ADRs with frequencies of (very) common. For icotrokinra one would *a priori* expect similar ADRs, due to the similarity of the mechanism of action (see below for more detail).

An absence of outstanding differences in TEAEs between icotrokinra and placebo is remarkable, given that the product was shown to be effective in the placebo-controlled period. According to the applicant, the combination of low drug bioavailability, higher tissue penetration and increased expression of IL-23R in plaque psoriasis (compared to non-lesional skin and other tissues) is expected to result in a more targeted (tissue-specific) immunomodulatory effect of icotrokinra in psoriasis compared to modulation by IL-23 or IL-17 biologics. At least, it is not considered that the safety profile of icotrokinra is a biased product of selective inclusion and restricted safety assessments. Because exclusion criteria were similar for all 4 pivotal trials and can be considered standard. Illustratively, the pattern and occurrence of TEAEs in the 16-week placebo-controlled phase of the icotrokinra pivotal studies was quite similar as in the pivotal studies of deucravacitinib versus placebo (deucravacitinib EPAR). Also, there was no sparse collection of safety data. Safety data were collected during all study visits, and at early termination (if applicable) and all AEs, regardless of seriousness, severity, or presumed relationship to study intervention, were to be recorded in the CRF.

When analysing the overall safety profile and the common TEAEs of icotrokinra in the pooled safety databases, the product is safe. The occurrence of common TEAEs was similar between icotrokinra and placebo and basically similar for icotrokinra and deucravacitinib, on SOC and on PT-level. The EAIRs of the pooled data through data cut-off, were lower as compared to the EAIRs during the placebo-

controlled period. The pattern of safety data in adolescents does not differ from adults. More specifically: In the 16-weeks placebo-controlled period, 52% of the patients in the placebo group versus 49% in the icotrokinra group had 1 or more AEs and there were no SOC's or PT's with notably higher proportions of AEs for icotrokinra. The most common TEAEs per SOC (placebo *versus* icotrokinra) were Infections and infestations (26% *versus* 24%), Investigations (6.5% *versus* 6.8%), GI disorders (6.2% *versus* 6.6%), and Skin and connective tissue disorders (7.6% *versus* 6.2%). On PT-level, TEAEs numerically more common in icotrokinra, with a difference with placebo of 0.5% or more, were Nausea (0.5% *versus* 1.2%), Headache (3.3% *versus* 3.9%), Cough (0.2% *versus* 1.2%), Fatigue (0.5% *versus* 1.2%), and Hypertension (1.2% *versus* 1.7%); all these differences were <1% which is considered small and not pointing to causality. The comparison of the 24-week data of icotrokinra as compared to deucravacitinib provide support for these observations.

Overall, **SAEs** were not more frequent in the icotrokinra treated group, as compared to placebo and deucravacitinib. There was no tendency that occurrence of SAEs increased with more follow-up data. The most notable SAEs in icotrokinra treated patients were diverticulitis (n=4), pneumonia (n=4) and infective exacerbation of chronic obstructive airway disease (n=4) and GI bleeding (n=2). The probability that these conditions are ADRs is discussed further below.

Through the safety cut-off date, there were 5 **deaths** in participants treated with icotrokinra, there were no deaths in the placebo and deucravacitinib groups. Observation time for icotrokinra was considerably larger than observation time for the comparators, which in case of rare events may contribute to this skewness. Further, the 5 death causes are considered to be unrelated to icotrokinra. The death causes were listed as: haematemesis, myocardial infarction, squamous cell lung carcinoma, GI haemorrhage, intoxication. In all cases there were predisposing factors that were more likely than icotrokinra mediated events, leading to death.

In **adolescents**, the overall occurrence of TEAEs was lower in the icotrokinra group (47%) as compared to the placebo group (72%). At SOC- and PT-level, there were no remarkable differences in occurrence of TEAEs between icotrokinra and placebo. The sample size of adolescents is relatively low (N=72), meaning that numerical differences should be interpreted with care.

There are several AEs that deserve special attention, as these are ADRs or Important Potential Risks of approved anti-IL23 products, and may have an impact on Benefit-risk. These include infections, malignancy, MACE and VTE. Hypersensitivity and diverticulitis were more frequent in the icotrokinra treated group and therefore also deserve attention.

Although the occurrence of **hypersensitivity** reactions was relatively low (<3%), hypersensitivity reactions were more frequent in the icotrokinra-treated patients (2.2%) as compared to placebo (1.2%). These were mostly eczema, urticaria, and several forms of dermatitis, eye disorders or allergic rhinitis. Drug hypersensitivity occurred in a single case and there were no anaphylactic reactions. The numerical imbalance observed within the hypersensitivity reaction grouping was not reflected in the overall incidence of the individual preferred terms (eczema, dermatitis, rash, pruritis), when assessed irrespective of hypersensitivity. Based on the currently available safety data, inclusion of hypersensitivity as an ADR is not considered warranted.

Based on the data in the *overall* population, there is no indication that overall **infections** or serious infections are ADRs of icotrokinra, and there were no cases of TB. Infections were more frequent in icotrokinra treated patients >65 years of age as compared to placebo, which however is mainly attributed to a lower-than-expected occurrence of infections in the placebo group. A trend of more occurrence of infections was not apparent in patients >75 years, although the groups were small. Besides small clusters of pneumonia (n=3) and infective exacerbation of COPD (n=3), there are no other indications of an increased occurrence of upper and lower respiratory tract infections due to icotrokinra, while the numbers of occasions of pneumonia and infective exacerbation of COPD were low

and did not increase over time. In general, inhibitors of IL-23 can increase the risk of opportunistic **fungal infections**, with candidiasis being the most common. Fungal infections were occurring in single cases in the icotrokinra group, not in placebo (e.g., rates of fungal infections through Week 24 were similar in icotrokinra (1.9%) vs deucravacitinib (2.2%). The relative risk (95%CI) for fungal infections for icotrokinra vs placebo was 3.3 (0.75 - 14.3). Therefore, fungal infections are included as ADR with frequency 'common' (SmPC section 4.8). Importantly, IL-23 has a role in host defence, notably in the acute response against exogenous or endogenous danger signals in gut, skin and lungs (McKenzie 2006; Schinocca 2021). Based on the mechanism of action of icotrokinra, respiratory tract infections could be expected. From the mechanistic perspective, it is not clear how safe it is to use icotrokinra in patients with (serious) infections. No clinical data are available, patients with a history of chronic or recurrent infectious disease, history of invasive opportunistic infections (e.g., active TB), serious infection were not included in the pivotal studies. Therefore, a contraindication to use icotrokinra in clinically important active infections (e.g. active tuberculosis, SmPC section 4.3) and a **warning** for use in clinically important infections is included in SmPC section 4.4, in line with approved anti-IL23 products (e.g. risankizumab, tildrakizumab). The warning recommends that treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Based on the currently available data, there is no indication that **malignancy** is an ADR of icotrokinra. From the non-clinical carcinogenicity studies, it can be concluded that there is no indication of carcinogenic potential for icotrokinra (see non-clinical discussion). In the 16-week placebo-controlled period, malignancies were somewhat more frequent in the icotrokinra group as compared to placebo (0.5% versus 0.2%). However, the period of up to 16 weeks of treatment is relatively short for development of clinically overt malignancy and causality is therefore unlikely. Also, there was no difference in malignancies in the 24 weeks comparing icotrokinra with deucravacitinib. Through the safety data cut-off date, malignancies had occurred in 10 (0.4%) patients treated with icotrokinra, which does not seem to be increased in comparison with the background rate in the general US population with the SIR (95%CI) of 1.07 (0.46 - 2.1). Immunosuppressants in general are considered to have the potential to increase the risk of malignancy. However, the role of IL-23 in tumour response is not fully clear but it appears a safe option (Yan 2018; Macagno 2024). Also, there is evidence from long term observational studies that anti-IL23 in psoriasis patients may not lead to malignancy (Vangilbergen 2024).

Based on the overall safety data, the laboratory values and the vital signs, there is no indication that **MACE or VTE** would be an ADR of icotrokinra. Mechanistically, there is no obvious reason for anti-IL23 treatment to cause CVD. Also, the non-clinical data did not lead to a safety signal for cardiovascular events (see non-clinical discussion). There were few cases of MACE and VTE, occurring similarly in the icotrokinra and placebo and deucravacitinib treated groups. In icotrokinra treated patients, there was no tendency that the occurrence of cardiovascular events increased over time.

Diverticulitis is included as ADR with frequency 'uncommon' (SmPC section 4.8). All patients with diverticulitis had risk factors, but patients with psoriasis seem to only have a slightly (1.16) higher risk for developing diverticulitis (Lee 2019). During the controlled period, there were 2 nonserious cases of diverticulitis in icotrokinra compared to none in placebo or deucravacitinib. During the uncontrolled period through the safety cut off, there were 4 participants with SAE of diverticulitis on icotrokinra. Icotrokinra differs from other IL-23 inhibitors due to its oral route of administration. The (local) concentration of IL-23 inhibitor in the gastrointestinal (GI) tract is considerably higher compared to that of the monoclonal antibodies risankizumab and tildrakizumab. It is acknowledged that confounding factors were present and that patients either improved while on treatment or had negative rechallenge results. However, all patients received corrective treatment, and improvement while maintaining treatment is therefore expected.

Icotrokinra is an oral medication and IL-23 has a role in protecting the intestine, warranting attention to GI toxicity. However, the clinical data do not give rise to suspicion for more general **gastrointestinal toxicity**, despite the two cases of fatal bleeding (see discussion on Deaths).

Special populations

The safety profile of icotrokinra was similar for males and females, patients weighing up to 90 kg or more, adolescents and adults <65 years of age, patients with or without psoriasis of special areas. In patients >65 years of age the safety profile of icotrokinra is somewhat less favourable than placebo and deucravacitinib, with higher proportions of discontinuations due to an AE.

Laboratory findings

Haematology, chemistry, vital signs, ECG, and growth in adolescents, generally did not raise concerns, including CPK increased and Hyperkalaemia. A higher frequency of 1st degree AV-block was identified in the icotrokinra group at week 16 compared to placebo and deucravacitinib. However, as there were no other differences in ECG abnormalities, no other differences in heart conduction, absence of differences in PR-intervals between baseline and week 16, and the fact that a 1st degree AV-block is commonly not of clinical concern together with absence of nonclinical safety signs, this was not considered a safety issue.

Although groups size and follow-up length are limited, there were no concerns with regard to growth and Tanner stages in adolescents.

LTBI testing at treatment start

The applicant considered that exposure to icotrokinra does not increase the risk of LTBI reactivation and thus no LTBI testing should be mandated due to treatment with icotrokinra. Instead, patients should be screened for LTBI in presence of risk factors, in line with local guidance. In EMA **Scientific Advice** (EMA/SA/0000131317, June 2023) and during the MAA procedure, this different approach to TB testing and anti-TB treatment for LTBI, compared to other products with the same target, was considered subject to careful review.

It can be agreed that when initiating treatment with icotrokinra, no mandatory screening for LTBI using X-rays, skin test and IGRA, is needed in countries with a low occurrence of LTBI, including Europe. The totality of non-clinical, clinical and observational data does not point towards an increased risk of TB activation following treatment with icotrokinra. The regulatory history is, that mandatory screening for TB is included in the SmPC's of all immunosuppressive agents, like anti-TNFα. Indeed, TNFα is known to have a role in protecting from LTBI activation, and treatment with anti-TNFα did cause activation of LTBI. However, IL-23 has a dual role in the immune system and can be seen as an immune modulator. The main role of IL-23 appears to be the rapid response to bacterial and fungal infections in mucosal cells (McKenzie 2006), which may be particularly relevant during early infection or under conditions of impaired Th1 immunity. Current evidence from experimental models and human immunology indicates that IL-23 is not essential for the maintenance of LTBI, provided that IL-12/IFN-γ-mediated Th1 immunity is preserved.

It is not totally clear whether the different mechanism of action of icotrokinra, blocking the IL23-receptor that is upregulated in psoriatic tissue, makes it different regarding LTBI activation, as compared to approved antibodies against IL-23. However, it must also be considered that meanwhile, more clinical and observational data are available that can support absence of mandatory LTBI screening for inhibitors of IL-23.

Concerning icotrokinra, the available non-clinical and clinical and observational data show that the risk of TB is lower for treatment with anti-IL23 as compared to treatment with anti-TNFα. The non-clinical in vitro results do not suggest a modified immune response to TB antigen following inhibition of the IL-

23 pathway with icotrokinra (see Non-clinical discussion). Icotrokinra had no major impact on selected biomarkers important for an immune response against *M. tuberculosis* (see PD section). Safety data from clinical studies with icotrokinra do not indicate an increased risk of LTBI re-activation, no cases of TB occurred. Safety data from approved IL-23 inhibitors do not point to a substantial risk for activation of LTBI or TB. Safety data in patients who initiated anti-IL-23 while being LTBI positive without receiving prophylactic treatment are relatively scarce, but do not show cases of TB. Also, infections are not considered to be an ADR for icotrokinra, in contrast to approved inhibitors of the IL23 pathway (risankizumab, guselkumab, tildrakizumab, mirikizumab, and also ustekinumab). Applying no mandatory testing is in line with the risk-based screening approach of the WHO and the ECDC. Also, more in general, it is regarded that broad testing for LTBI should not be performed in countries with a low prevalence of LTBI (Allan 2025). Three strategies (mandatory screening + treatment, mandatory screening + consider treatment, at risk screening + consider treatment) have been modelled by the applicant in a decision analytic/benefit-risk model. Accordingly, there is a small advantage in 'at risk' screening as compared to 'mandatory screening + consider treatment', given that, both screening approaches led to a similar amount of cases of TB (1.2/10.000 annually for both), however, the 'at risk' screening led to fewer cases of hepatitis (7.0/10.000 *versus* 8.4/10.000 annually). Ultimately, there is a limited amount of clinical data in patients positive for LTBI initiating anti-IL23 without prophylactic treatment for LTBI. Moreover, IL-23 plays a role in host defence in the lungs. Therefore, as mentioned above, a contraindication in clinically important active infections and a warning to recommend that treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated, to also address any potential cases of TB, have been included in the PI. Additionally, serious infections will be included as a safety concern in the PSUR for further monitoring.

5.4.12.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs requested by the CHMP for inclusion in the SmPC are described below.

Table 44. ADRs proposed for inclusion in the SmPC

Infections and infestations	
Fungal infections[a]	'common'
Diverticulitis	'uncommon'
[a] Fungal infections include tinea pedis (n=4), tinea versicolor (n=2), oral candidiasis (n=2), onychomycosis (n=1), skin candida (n=1), urinary tract candidiasis (n=1), vulvovaginal candidiasis (n=1), fungal skin infection (n=1), genital infection fungal (n=1), ear infection fungal (n=1), and laryngitis fungal (n=1).	

Based on the available data, the applicant did not propose ADRs for icotrokinra. Although the safety data point to an overall safe profile, this is not totally agreed (see Safety discussion, excerpt below).

- Four participants treated with icotrokinra experienced SAEs of diverticulitis. All patients also had confounding factors. IL-23 does have a role in protecting the gut and a causative role of anti-IL23 taken orally is considered a reasonable possibility. Icotrokinra's oral administration, resulting in considerably higher local concentrations in the gastrointestinal (GI) tract compared to monoclonal antibodies like risankizumab and tildrakizumab, may contribute to the fact that GI disorders are not an ADR for these products. IL-23 remains crucial for sustained, amplified, and pathogenic type 17 responses (McGeachy et al., 2009; Ghoreschi et al., 2010; Buonocore et al., 2010; Sonnenberg et al., 2012), providing a biological rationale for potential GI effects.

- The rate of **fungal infections** in the icotrokinra group was 1.1% compared with the placebo group (0%). The RR (95%CI) in the occurrence of infections in the icotrokinra group compared with placebo for bacterial infection was 0.72 (0.498 - 1.028), viral infections 0.77 (0.580 - 1.014) and fungal infections 3.27 (0.750 - 14.263) provide clear evidence for an increased risk of fungal infections. As the primary target of icotrokinra is the skin, there is mechanistic plausibility for the predominance of cutaneous or mucocutaneous fungal infections.

5.4.12.2. Conclusions on clinical safety

Overall, the extent of exposure is acceptable in support of a Marketing Authorisation, according to the ICH E1 guideline and the targeted population requiring chronic treatment. When analysing the overall safety profile and the common TEAEs of icotrokinra in the pooled safety databases, the product is deemed safe. In adolescents, the safety profile was similar as in adults.

Fungal infections and diverticulitis are considered as ADR.

It can be agreed that when initiating treatment with icotrokinra, no mandatory screening for LTBI screening is needed in countries with a low occurrence of LTBI, including Europe. However, from the mechanism of action of icotrokinra and from the available data, it is not clear how safe it is to use icotrokinra in patients with (serious) infections. Therefore, a contraindication and a warning against use in clinically important active infections (including active TB) are included in the SmPC sections 4.3 and 4.4. This is in line with approved anti-IL17 and anti-IL23 products. Additionally, serious infections will be included as a safety concern in the PSUR for further monitoring.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 45. Summary of safety concerns in the proposed RMP, version 1.5

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy

6.1.2. Discussion on proposed safety specification

The applicant has not proposed to include other 'important potential risks' or any 'important identified risks' in the icotrokinra summary of safety concerns. This is agreed.

The applicant proposed to include **malignancy** as important potential risk. By its very nature, malignancy is serious enough to impact Benefit/Risk. However, risk for malignancy did not materialise in the current safety data, although follow-up and amount of exposure may not be long enough to fully exclude risks. On the other hand, based on the non-clinical data, it can be concluded that there is no indication of carcinogenic potential for icotrokinra. This was based on the absence of genotoxic potential, the absence of findings in the chronic studies in rats or monkeys indicative of pre-neoplastic potential or endocrine disruption and the absence of carcinogenic findings in the 2-year rat and the 6-month transgenic mouse study (see non-clinical discussion). Icotrokinra is highly specific for the IL23R,

so off-target effects are not expected. Also, when considering the IL23 pathway, there is no clear indication for a causative role of anti-IL23 and cancer. Consequently, malignancy has been removed as an important potential risk. The applicant will monitor reports of malignancy through routine pharmacovigilance.

The applicant proposed to include **serious infections** as important potential risk. However, these events are by their nature serious enough to impact Benefit/Risk and are also theoretically possible due to the mode of action of icotrokinra and the immune modulating function of the IL23 receptor. Serious infections occurred very infrequent in the safety data of icotrokinra, although there were some small clusters of pneumonia and infective exacerbation of COPD in icotrokinra patients (see Safety discussion and SmPC). Serious infections are not considered as ADR, it is agreed to retain serious infections as risk of icotrokinra in the PSUR for further monitoring through routine pharmacovigilance and through routine signal detection activities.

The applicant proposed to include **serious hypersensitivity reactions** as important potential risk in the list of safety concerns. however, serious hypersensitivity reactions are theoretically possible with any medication; in the clinical data, no cases of serious hypersensitivity reactions occurred, there was one case of drug hypersensitivity in an icotrokinra treated patient and there were no anaphylactic reactions. Any cases of serious hypersensitivity reactions that emerge from these studies will be captured in the PSURs and would also be managed through routine signal detection activities. Routine pharmacovigilance is therefore considered to be sufficient to characterise this risk and inclusion as an important potential risk is not warranted.

It is agreed not to include **embryofoetal toxicity** as an important potential risk in the RMP. Maintaining use during pregnancy as missing information is also agreed. The applicant removed 'use during breastfeeding' as missing information from the icotrokinra RMP and will include 'use during breastfeeding' as a safety concern in the PSUR. The applicant, inherently, committed to review available interval data from literature and post-marketing experience in the PSUR, which is accepted.

Long-term safety of icotrokinra is not agreed as missing information. Overall, the safety profile of icotrokinra does not lead to specific long term safety concerns. The safety data in adolescents and the non-clinical data did not give rise to concerns regarding growth and development, the population in the study (n=72) will be followed for up to 3 years and the data are expected. Therefore, growth and development in adolescents are not considered for inclusion as missing information in the RMP.

It is useful to regard probable class effects and risks of approved anti-IL23 products for the Safety Specifications of icotrokinra. These additional issues include: serum sickness, MACE (guselkumab), MACE, SIB, IBD (tildrakizumab), MACE (risankizumab), CV events, VTE (ustekinumab). However, given the non-clinical and clinical data up to now, it is not considered that these important potential risks for other approved products should be included in the important potential risks of icotrokinra. Especially also the risk on MACE/CV events and thromboembolism can be followed through routine PhV in PSURs.

The applicant committed to the inclusion of **rebound** as important potential risk in the PSUR and continued monitoring through routine pharmacovigilance activities. In the randomised withdrawal phase of Study PSO3001, three cases (3/172 patients; 1.7%) fulfilling EMA-defined criteria for rebound were observed within 2 months following discontinuation of icotrokinra. These included one case of new-onset pustular psoriasis with widespread skin involvement after 29 days and two cases of worsening of psoriasis to 141% and 155% of baseline PASI occurring 41 and 60 days after treatment discontinuation, respectively. All three cases previously had good to excellent control of psoriasis at the time-point of treatment discontinuation (PASI 75, 90, PASI 100 response, respectively). It remains uncertain whether the extent of the worsening, the temporal relationship, and the clinical course in these cases are consistent with a gradual worsening of the underlying disease; consequently, a rebound effect cannot be excluded. Based on the limited data available, a causal relationship has not

been established. While no established biological mechanism for rebound following IL-23 inhibition has been demonstrated, icotrokinra differs from monoclonal antibodies as the first oral IL-23 receptor antagonist. Its shorter half-time and shorter time to loss of PASI90 after withdrawal indicate reduced pharmacodynamic persistence, thus absence of an established biological mechanism cannot be automatically extrapolated to icotrokinra. Therefore, as mentioned above, rebound will be included in the PSUR and will be monitored through routine pharmacovigilance activities.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The applicant proposed routine pharmacovigilance activities, e.g. adverse reactions reporting and signal detection.

Specific adverse reaction follow-up questionnaires:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

In addition, the applicant has proposed the following additional pharmacovigilance activities:

Table 46. Planned additional pharmacovigilance activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3: Required additional pharmacovigilance activities				
A Retrospective Cohort Study Using Administrative Health Insurance Claims Databases to Assess Adverse Pregnancy, Fetal, and Infant Outcomes in Women Who Were Exposed to icotrokinra for an Authorized Indication During Pregnancy Planned	To monitor pregnancy outcomes in women exposed to icotrokinra for an authorised indication during pregnancy and linked infant outcomes in infants up to 1 year of age	• Use during pregnancy	Protocol submission	30 Jun 2027
			Start of data collection	31 Dec 2030
			Interim reports	31 Dec 2031 31 Dec 2034
			End of data collection	31 Mar 2037
			Final study report submission	31 Mar 2038

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The applicant has removed the previously proposed focused cumulative reviews of pregnancy and breastfeeding in PSURs (which will be on a 6 monthly frequency following authorisation) to monitor pregnancy outcomes in women exposed to icotrokinra during pregnancy and the linked infant outcomes up to 1 year of age, as well as outcomes to 1 year for children whose mothers received icotrokinra while breastfeeding. Use in pregnancy is missing information in the RMP. In addition to proposed aPhV, this will therefore be routinely followed in PSURs (in accordance with relevant guidance including GVP P III). The use in breastfeeding is a safety concern for the purposes of the PSUR and will also be followed in the PSURs.

6.2.2.2. Additional pharmacovigilance activities

The applicant has proposed a retrospective cohort study using administrative health insurance claims databases to assess adverse Pregnancy, foetal, and infant outcomes in women who were exposed to icotrokinra for an authorised indication during pregnancy. In general, the applicant's proposal to include in the RMP additional pharmacovigilance in the form of a Category 3 PASS to further characterise safety in pregnancy is supported. However, the applicant is requested to address the following within a feasibility analysis to be submitted prior to the full protocol submission:

- The applicant is requested to consider the current treatment landscape and the relevance of including non-biological agents, including novel small molecules, in the comparator group.
- The applicant is requested to confirm what actions they will take if the threshold of 20 exposures is marginally satisfied (<30 cases) in terms of comparative analyses.
- The applicant should discuss feasibility of the inclusion of EU databases within the currently proposed study or as a separate supplementary study. A discussion on the feasibility of an alternative study thorough the use of electronic healthcare records which may offer benefits in terms of more granular detail on key confounding factors including disease severity. A discussion on the feasibility of additional or alternative data sources such as use of electronic healthcare records which may offer benefits in terms of more granular detail on key outcomes and confounding factors including disease severity and greater representativeness should also be provided.
- Further information about the length of follow-up for outcomes of interest including MCM should be provided.

6.3. Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies imposed for this product.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 47. Planned routine risk minimisation measures

Use during pregnancy
Routine risk communication • SmPC Section 4.6 • PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk** • A recommendation to avoid the use of Icotyde during pregnancy is included in SmPC Section 4.6. • A recommendation to avoid administration of live vaccines to newborns potentially exposed to icotrokinra during pregnancy within the first 3 days after birth is included in SmPC Section 4.6 and PL Section 2. • Advice for patients who are pregnant, think that they may be pregnant, or are planning to have a baby is included in PL Section 2. **Other routine risk minimisation activities beyond the Product Information** None

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation activities are proposed by the applicant. This is considered acceptable.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.5 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the international birth date (IBD) to determine the forthcoming Data Lock Points. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 17 March 2026.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

Section 4.1 is accepted. The claimed indication is adequately substantiated by the comprehensive clinical data package. Efficacy is substantiated by a comprehensive data package including four phase 3 studies PSO3001, PSO3002, PSO3003, and PSO3004 (all ongoing), and supported by a phase 2 dose-ranging study and its extension (PSO2001 and PSO2002).

The study populations are in line with the target population in the indication. The studies enrolled participants with a PASI ≥12, a total IGA ≥3, and a total BSA ≥10%, who were candidates for phototherapy or systemic therapy. PSO3001 and PSO3003 also included adolescents ≥12 years of age weighing ≥40 kg.

Therefore, the final agreed indication is *Icotyde is indicated for the treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy.*

8.1.2. SmPC section 4.2 justification

Section 4.2 is accepted. The recommended dose of 200 mg once daily is adequate, and in line with the dose used in the main clinical studies.

8.1.3. SmPC section 5.1 justification

The wording in section 5.1 is accepted. The relevant baseline population characteristics, disease severity criteria including body areas involved have been described for both adults and adolescents.

As usual, results were limited to main analyses that were clinically relevant and statistically compelling. Only data from the main analysis were presented for the key secondary endpoints. Health-related quality of life/Patient reported outcomes have also been included.

8.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Icotyde (icotrokinra hydrochloride) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Psoriasis is a relatively common chronic inflammatory skin disease, affecting approximately 1% to 4% of the adult population and up to 1% of children worldwide (Armstrong AW 2021; Parisi 2013, 2020). **Plaque psoriasis** is the most common clinical sub-form, and is characterised by the presence of well-demarcated, erythematous plaques with overlying silvery scales. These plaques may be asymptomatic, but pruritis is common. Patients with plaque psoriasis can have different degrees of severity and/or special site involvement (scalp, genitals, nails, hand/feet); the latter are considered difficult to treat (Armstrong 2022; Merola 2018). Patients with chronic plaque psoriasis, regardless of area of involvement or age, report significant debilitation in social, psychological, and health related quality of life.

The proposed **indication** for icotrokinra is:

Icotyde is indicated for the treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy.

The recommended **dose** is 200 mg once daily. icotrokinra should be taken upon waking on an empty stomach with water at least 30 min before eating food.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 3.1 of this document.

The treatment goal is to achieve a clear or almost clear skin status and improve quality of life (Nast 2023).

The major treatment options for patients with plaque psoriasis range from topical therapies (corticosteroids, vitamin D analogues, calcineurin inhibitors) for mild disease, through phototherapy and conventional systemic agents (cyclosporin, methotrexate, oral retinoids), to targeted small molecules (e.g., apremilast, deucravacitinib) and biologics (TNF-, IL-12/23-, IL-17- and IL-23-inhibitors) for moderate to severe disease. Despite these options, many patients experience incomplete or unstable responses, treatment-limiting toxicity or loss of efficacy over time, leading to persistent physical, psychological, and social burden. Consequently, there is a need for additional therapies that can provide sustained, high levels of skin clearance with an acceptable safety profile.

icotrokinra is a 'first in class', orally administered peptide that selectively binds to the IL-23 receptor to competitively antagonise the binding of IL-23. This results in inhibition of proximal IL-23R signalling and downstream effector functions (e.g., cytokine secretion). Targeting IL-23R provides a distinct mechanism to modulate the IL-23/IL-17 pathway compared to targeting the ligand IL-23 (like the

approved IL-23 inhibitors guselkumab, risankizumab, tildrakizumab). The product is for oral administration, different to the available products targeting IL-23, IL-12/IL-23 or IL-17.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 6.3.2 of this document. The Application is supported by four pivotal studies; studies PSO3001, PSO3002, PSO3003, and PSO3004.

Moderate to severe plaque psoriasis (PSO3001, PSO3002, PSO3004)

Studies **PSO3001, PSO3002, and PSO3004** were conducted in the same population. The design of these studies shares many similarities; the design of studies PSO3002 and PSO3004 is almost identical.

- **PSO3001** is an ongoing randomised, double-blind, parallel-group, placebo-controlled, interventional study with randomised withdrawal and retreatment of icotrokinra in participants ≥12 years of age with moderate to severe plaque psoriasis (n=684).
- **PSO3002** and **PSO3004** are two ongoing randomised double-blind, parallel-group, placebo-controlled, and active-comparator controlled, studies, of similar design, in adult participants with moderate to severe plaque psoriasis (n=1085).

The patient populations of these three studies consisted of adults (and adolescents ≥12 years and weighing ≥40 kg in PSO3001) with moderate to severe plaque psoriasis defined by a total PASI ≥12, a total IGA ≥3, and a total BSA ≥10%, who were candidates for phototherapy or systemic treatment.

In PSO3001, participants were randomised (2:1) to icotrokinra 200 mg or placebo once daily. The study consisted of a 16-week double-blind placebo-controlled period, and a randomised withdrawal and retreatment period from week 24 through week 52 in adult responders (PASI75 or IGA0/1).

In PSO3002, participants were randomised (2:2:1) and in PSO3004 (4:4:1) to icotrokinra 200 mg, deucravacitinib 6 mg, or placebo once daily. The study consisted of a 16-week double-blind placebo-controlled period and a 24-week double-blind active-controlled period (in parallel).

The co-primary efficacy endpoints in PSO3001, PSO3002, and PSO3004 were 1) the PASI90 response at Week 16 and 2) an IGA score of 0/1 with at least a 2-grade improvement from baseline at Week 16.

Plaque psoriasis with at least moderate special site involvement (PSO3003)

Study **PSO3003** is ongoing, randomised, double-blind, placebo-controlled, parallel group, study to evaluate the clinical efficacy and safety of icotrokinra treatment compared with placebo in adult and adolescent participants with plaque psoriasis involving special areas (scalp, genital, and/or hand/foot).

Adults, and adolescents (≥12 years and weighing ≥40 kg) with plaque psoriasis (total BSA ≥1% and IGA≥2) involving special areas (ss-IGA score ≥3, and/or sPGA-G ≥3, and/or hf-PGA score ≥3) who were candidates for phototherapy or systemic treatment and had failed to respond to ≥1 topical therapy for treatment of psoriasis.

Participants were randomised (2:1) to icotrokinra 200 mg or placebo, once daily. The study consisted of a 16-week double-blind placebo-controlled period.

The primary efficacy endpoint was an IGA (overall) score of 0/1 and a ≥2-grade improvement from baseline at Week 16. Key secondary endpoints at week 16 were the proportion of participants with: ss-IGA score 0/1, sPGA-G score of 0/1, hf-PGA score.

9.3. Favourable effects

Moderate to severe plaque psoriasis (PSO3001, PSO3002, PSO3004)

The primary objectives were met, as demonstrated by the co-primary endpoints PASI90 and IGA0/1 at week 16 in all three individual studies.

PASI 90: A proportion of 50%, 55%, and 58% of participant treated with icotrokinra compared to 4%, 4%, and 1% of those treated with placebo had a PASI90 response at week 16 in studies PSO3001, PSO3002, and PSO3004 respectively. This translated into a 45% (95%CI: 40, 50; p<0.001), 51% (95%CI: 45, 57; p<0.001) and 57% (95%CI: 49, 62; p<0.001) treatment difference from placebo.

IGA 0/1: A proportion of 65%, 68%, and 71% of participants treated with icotrokinra compared to 8%, 11%, and 9% of those treated with placebo had an IGA 0/1 IGA score of 0 or 1 with a ≥2-grade improvement from baseline at week 16 in Studies 3001, 3002, and 3004, respectively. This translated into a 56% (95%CI: 50, 62; p<0.001), 57% (95%CI: 50, 64; p<0.001), and 62% (95%CI: 53, 69; p<0.001) treatment difference from placebo.

In the pooled analysis a proportion of 53% participants treated with icotrokinra compared to 3.6% with placebo had a PASI90 response at week 16. A proportion of 67% treated with icotrokinra compared to 9.2% with placebo had an IGA score of 0 or 1 with a ≥2-grade improvement from baseline at week 16.

Results on key secondary endpoints were:

At week 16, PASI100 and IGA 0 response rates ranged from 27-32% and 33-37% with icotrokinra, respectively. In contrast, 0.4-2.0% participants in the placebo group had a PASI100 or IGA 0 response.

At week 52 (in PSO3001), among PASI90 responders (n=128) at week 24, the response was maintained in 84% treated with icotrokinra versus 21% in those re-randomised to placebo. The median time to loss of PASI90 response was 10 weeks. Similar results were found for IGA 0/1 responses.

Adolescents

In study PSO3001 a sub-group of adolescents (n=72) was included. Frequency of moderate and severe plaque psoriasis, median PASI and median affected BSA at baseline were comparable in both adolescents and adults. Short-term treatment results in adolescents (≥12 years of age weighing ≥40 kg) at week 16 were comparable to the results of the total population in PSO3001. Moreover, comparative week 52 across study data support similar long-term efficacy in adolescents and adults. Based on similarity of the disorder and similarity of the treatment response in both populations, extrapolation of findings regarding maintenance of effect, relapse of psoriasis and risk of rebound following discontinuation of treatment in adults to adolescents can be agreed to.

Plaque psoriasis with at least moderate special site involvement (PSO3003)

The primary endpoint of study 3003 was met. A proportion of 57% of participants treated with icotrokinra compared to 5.8% of those treated with placebo had an IGA 0/1 with a ≥2-grade improvement from baseline at week 16.

Key secondary endpoints related to special site psoriasis were met for scalp psoriasis and genital area psoriasis, but not for hand-foot psoriasis.

At week 16, among those with moderate scalp, genital, and/or hand/foot psoriasis (scores≥3) at baseline:

- 66% of participants treated with icotrokinra compared to 11% with placebo had an ss-IGA score of 0 or 1. Resulting in a treatment difference (95% CI) of 56% (45, 64) p<0.001.

- 77% of participants treated with icotrokinra compared to 21% with placebo had an sPGA-G score of 0 or 1. Resulting in a treatment difference (95% CI) of 55% (39, 68) p<0.001.

- 42% of participants treated with icotrokinra compared to 26% with placebo had an hf-PGA score of 0 or 1. Resulting in a treatment difference (95% CI) of 17% (-6.2, 37) p=0.144.

9.3.1. Uncertainties and limitations about favourable effects

EMA-rebound criteria were met in 3/172 adults in study 3001 after withdrawal of icotrokinra. Though a causal relationship has not been established based on the limited data base, rebound cannot be excluded. The rebound effect will continue to be monitored post-authorisation and reported in PSURs.

9.4. Unfavourable effects

The main safety data came from the four phase 3 trials PSO3001, 3002, 3003, and 3004, in which 2367 patients were exposed to the proposed posology 200 mg QD; 648 patients were exposed for 1 year. Safety data are available from 72 adolescent patients weighing at least 40 kg; 52 weeks data are available for 46 of them.

During both the 16-weeks placebo-controlled period as well as the 24-weeks active-controlled period, the frequency of patients with **a**t least one TEAE in the icotrokinra group was comparable to, or slightly lower than, the frequencies in the placebo and deucravacitinib groups. In the 16-weeks placebo-controlled period, 52% of the patients in the placebo group versus 49% in the icotrokinra group had 1 or more AEs. In the 24-weeks active controlled period, 65% of the patients in the deucravacitinib group versus 58% in the icotrokinra group had 1 or more AEs. The proportions of patients with at least one severe AE or SAE, and with discontinuation due to an AE are low (≤3%) in icotrokinra and comparator groups, but lowest in the icotrokinra group. In the uncontrolled 'long-term' safety data, the overall safety profile was similar to the 16-week and 24-week controlled periods. There were 5 deaths in icotrokinra treated patients and none in the comparator groups, in all cases there were predisposing factors more likely to cause death than icotrokinra.

In the placebo-controlled period, most common TEAEs per SOC (placebo *versus* icotrokinra) were: Infections and infestations (26% *versus* 24%), Investigations (6.5% *versus* 6.8%), GI disorders (6.2% *versus* 6.6%), and Skin and connective tissue disorders (7.6% *versus* 6.2%). On **PT**-level, TEAEs numerically more common in icotrokinra (difference with placebo of 0.5% or more) were (placebo *versus* icotrokintra): Nausea (0.5% *versus* 1.2%), Headache (3.3% *versus* 3.9%), Cough (0.2% *versus* 1.2%), Fatigue (0.5% *versus* 1.2%), and Hypertension (1.2% *versus* 1.7%); all these differences were <1%.

In the pooled placebo-controlled data up to week 16, the proportions of participants with 1 or more overall infections and with serious infections were similar in the icotrokinra (24% and 0.2%) and placebo (26% and 0.4%) groups. The occurrence of fungal infections in the icotrokinra group was 1.1% compared with the placebo group (0%). There were no cases of active TB/activated LTBI, in neither treatment group. Across the clinical program through week 16, there were 0 SAEs of diverticulitis (icotrokinra n = 0, placebo n=0, deucravacitinib = 0); in the uncontrolled period through the safety cut-off, there were 4 participants with SAE of diverticulitis reported on icotrokinra. (icotrokinra n=4; placebo n=1; deucravacitinib n=1). Hypersensitivity reactions, including eczema, dermatitis, urticaria, were more frequent in the icotrokinra treated patients (2.2%) as compared to placebo (1.2%).

In the pooled placebo-controlled data up to week 16, cardiovascular events were reported in 4 (0.4%) participants in the icotrokinra group and in 2 participants (0.2%) in the placebo group. Positively adjudicated MACE was reported in 0.2% (n=3) of participants in the icotrokinra group and no participants in the placebo group. There were 2 cases (0.2%) of VTE in the icotrokinra group and no cases in the placebo group.

In adolescents, the overall occurrence of TEAEs was lower in the icotrokinra group (50%) as compared to the placebo group (73%). At SOC- and PT-level, there were no remarkable differences in occurrence of TEAEs between icotrokinra and placebo.

9.4.1. Uncertainties and limitations about unfavourable effects

Safety data are available from 72 adolescent patients weighing at least 40 kg; 52 weeks data are available from 46 of them. Although this is a limited dataset, extrapolation from the adult safety data supports the acceptability of icotrokinra's safety profile for treating plaque psoriasis in adolescents.

Based on the mechanism of action of icotrokinra, it is not clear that how safe its use in patients with (serious) infections is as no data are available in this population including patients with a history of chronic or recurrent infectious disease, history of invasive opportunistic infections (e.g., active TB) or serious infection who were not included in the pivotal studies. A contraindication and a warning against use in clinically important active infections have therefore been included in the SmPC, in line with approved anti-IL-23 products (e.g. tildrakizumab, risankizumab). The warning recommends avoiding treatment in patients with clinically active infections and considering discontinuation if such infections develop.

The applicant proposed not to include a warning for mandatory LTBI screening, which would deviate from the approach taken with the other approved anti-IL-23 products (risankizumab, tildrakizumab, guselkumab). This is supported by several lines of evidence: non-clinical and PD data show no signal for an increased risk for TB or LTBI reactivation; no cases of active TB occurred in the clinical development of icotrokinra; safety data from approved IL-23 inhibitors do not point to a substantial risk of LTBI reactivation or TB; and although safety data in patients who initiated anti-IL23 while LTBI-positive without prophylactic treatment remain relatively scarce, they show no cases of TB. In addition, unlike other approved IL-23 pathway inhibitors (risankizumab, guselkumab, tildrakizumab, mirikizumab, and also ustekinumab) infections are not considered an ADR for icotrokinra.

The residual uncertainty regarding TB screening is addressed by the SmPC wording of sections 4.3 and 4.4 on clinically important active infections (including TB) and by including serious infections as a safety concern for further monitoring in the PSURs.

9.5. Effects table

Table 48. Effects Table for icotrokinra, for the treatment of moderate to severe plaque psoriasis (data cut-off: 3 April 2025)

Effect (short description)	*icotrokinra*	*Placebo*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable Effects				
PASI90 (≥90% reduction on PASI score) at week 16 - n/N (%)	581/1089 (53)	17/466 (3.6)	**SoE:** robust results; statistically significant difference between icotrokinra and placebo, across three individual studies **Unc:** none	Pooled PSO 3001, 3002, 3004
IGA 0/1 (skin clear/almost clear) at week 16 - n/N (%)	735/1089 (67)	43/466 (9.2)	**SoE:** robust results; statistically significant difference between icotrokinra and placebo, across three individual studies **Unc:** none	
Unfavourable Effects				
At least 1 AE at week 16 - n/N (%)	636/1296 (49)	295/568 (52)	**SoE:** Large sample and consistent with comparison to deucravacitinib at week 24. No increase with longer follow-up. **Unc:** none	Pooled PSO 3001, 3002, 3003, 3004
At least 1 SAE at week 16 - n/N (%)	21/1296 (1.6)	12/568 (2.1)	**SoE:** Large sample and consistent with comparison to deucravacitinib at week 24. No increase with longer follow-up. **Unc:** none	
At least 1 infection at week 16 - n/N (%)	311/1296 (24)	148/568 (26)	**SoE:** Large sample and consistent with comparison to deucravacitinib at week 24. No increase with longer follow-up. **Unc:** Long term data on serious infections are lacking.	
LTBI activation up to end of follow-up - n	0	0	**SoE:** No cases occurred, in line with evidence from anti-IL23. **Unc:** LTBI has low occurrence in Western World, small (n=31) sample of LTBI+ patients treated without prophylaxis.	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; PASI: psoriasis area and severity index; IGA: investigator's global assessment; PE: primary endpoint; SE: secondary endpoint; OR: odds ratio.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Favourable effects

The short-term effects observed with icotrokinra compared to placebo are robust, statistically significant, and clinically relevant: At week 16, statistically significant treatment differences were observed in the proportion of PASI90 and IGA 0/1 responders (co-primary endpoint) with icotrokinra 200 mg once daily versus placebo. Key secondary endpoints complemented the observed treatment effect. The co-primary endpoints, which reflect clear or almost clear skin (e.g., IGA 0/1) and significant improvements in PASI scores (90% improvement), supported by key secondary endpoints (PASI100, IGA 0, ss-IGA, PROs), provide meaningful measures of treatment success. Results were consistent across three placebo-controlled pivotal studies, each including an adequate number of participants.

Efficacy of icotrokinra was generally maintained among patients who continued icotrokinra treatment up to week 52, whereas those re-randomised to placebo gradually lost their response. At week 52 (end of the withdrawal phase) a statistically significant larger proportion of patients treated with icotrokinra compared to placebo, maintained their PASI90 response. The median time to loss of PASI90 response in patients in whom icotrokinra treatment was withdrawn was 10 weeks. Rebound will be further monitored in the PSUR.

In the sub-group of adolescents in study PSO3001 frequency of moderate and severe plaque psoriasis, median PASI and median affected BSA at baseline was comparable to adults. Short-term treatment results at week 16 in adolescents were generally comparable to the results in the total population in PSO3001.

Statistically significant larger proportions of adolescents had a PASI90/100/75, IGA 0/1 and/or IGA 0 response at week 16 with icotrokinra versus placebo. In agreement with PIP, adolescents did not take part in the randomised withdrawal period and long-term effects were evaluated as secondary endpoints at week 52. Available open-label data support clinically relevant and sustained long-term efficacy in adolescents on clinician rated outcomes and PROs with continued exposure to icotrokinra through Week 52 (study 3001), albeit with a potential bias through an open-label design. Comparative week 52 across study data support similar long-term efficacy in adolescents and adults. Based on similarity in disease and similarity in treatment response, findings regarding maintenance of effect, relapse of psoriasis and risk of rebound following discontinuation of treatment in adults can be extrapolated to adolescents.

A statistically significant and clinically relevant treatment difference was observed with icotrokinra versus placebo in PSO3003, in subgroups with at least moderate scalp (e.g., ss-IGA) and/or genital psoriasis (e.g., sPGA-G), but not with at least moderate hand/foot psoriasis (hf-PGA), where the difference was numerical.

The clinical development program for icotrokinra is adequate to support the indication. It is consistent with the guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr) and provided scientific advice (EMA/SA/0000131317). The study populations are in line with the target population in the indication. The studies enrolled participants with moderate-to-severe psoriasis defined as PASI ≥12, a total IGA ≥3, and a total BSA ≥10%, who were candidates for phototherapy or systemic therapy.

Unfavourable effects

The overall safety profile of icotrokinra is favourable. Given the similarity in targeting the IL-23 pathway, ADRs similar to those of risankizumab, tildrakizumab, and guselkumab would be expected a priori. However, SAEs were overall not more frequent in the icotrokinra treated group, as compared to placebo and deucravacitinib. There was no tendency that occurrence of SAEs increased with prolonged follow-up up to 52 weeks.

The safety profile of icotrokinra was similar for males and females, patients weighing up to 90 kg or more, adolescents and adults <65 years of age, and patients with or without psoriasis of special areas. This is important, as it points to a benign safety profile throughout main subpopulations of the intended target population.

Although the safety data indicate an overall favourable safety profile, the applicant's initial claim that icotrokinra has no ADRs is not agreed. Even though the anticipated risk for (serious) infections was low, respiratory infections or infections overall did not appear to be ADRs for icotrokinra, fungal infections were more frequent in the treated subjects compared to placebo. They were usually mild and mostly cutaneous. In patients >65 years of age on icotrokinra, the risk for infections was not higher than for the younger age groups. However, given its mechanism of action and the general role of IL-23, it remains unclear how safe icotrokinra will be in future patients with (serious) infections. Therefore, a contraindication and a warning have been included, in line with approved anti-IL23 products.

There is no consistency across approved biologicals or small molecules that are targeting the immune system in their warnings for screening for LTBI and initiating prophylactic treatment. For icotrokinra, it is considered acceptable that LTBI screening should not be mandatory but pertain to risk groups in line with the WHO and ECDC recommendations to only screen at-risk groups. This is considered sufficiently safe based on several factors: the role of IL-23 primarily in the rapid early response to new infections, the low prevalence of LTBI in Europe, the lower propensity for LTBI activation for anti-IL23 as compared to anti-TNFα agents, and the contraindication and a warning for clinically active infections (including TB) included in the product information. Serious infections will be followed in the PSURs, which is considered sufficient given low risk of serious infections observed to date.

Diverticulitis, and fungal infections are considered as ADRs and included in the product information; however, these events do not outweigh the observed benefits and the overall positive benefit-risk balance of icotrokinra.

9.6.2. Balance of benefits and risks

The overall B/R balance for icotrokinra is positive, with benefits outweighing the identified risks.

Icotrokinra 200 mg once daily demonstrated statistically significant and clinically relevant improvement over placebo in the treatment of moderate to severe psoriasis in adults, and adolescents (≥12 years of age weighing ≥40 kg), who were candidates for systemic therapy. Efficacy was consistently shown across studies, analyses, subgroups, and over time.

Icotrokinra appears to be safe, also for patients >65 years of age and adolescents. Although the presence of certain ADRs of icotrokinra cannot be excluded yet, the nature, frequency, and severity of these are not anticipated to outweigh the benefits. The safety concerns are manageable through appropriate labelling, warnings, monitoring and pharmacovigilance.

9.7. Benefit-risk conclusions

The benefit risk balance for icotrokinra is positive for the treatment of moderate to severe plaque psoriasis in adults, and adolescents 12 years of age and older and weighing at least 40 kg, who are candidates for systemic therapy.