

REVIEW ARTICLE

Efficacy and safety of icotrokinra (JNJ-2113) for moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Icotrokinra (JNJ-2113) is a first-in-class targeted oral peptide that selectively binds to the interleukin-23 (IL-23) receptor and blocks IL-23 signaling. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of Icotrokinra to assess its efficacy and safety versus control in moderate-to-severe plaque psoriasis. We performed a PRISMA-adherent systematic literature search across Scopus, PubMed, and Web of Science from their inception up to January 2026. Screening, data extraction, and risk of bias assessment were made by two independent authors. A meta-analysis was conducted in R with sensitivity and subgroup analyses. We included four studies comprising five RCTs. Oral icotrokinra significantly improved physician-assessed and psoriasis area and severity index (PASI) responses compared with control in RCTs. For Investigator's Global Assessment (IGA) 0/1, benefit was evident by week 2 (risk ratios (RR) = 3.24%, 95% confidence interval (CI) 1.01–10.46) and remained consistent through week 16 (RR = 7.35%, 95% CI 5.67–9.54), with an overall pooled effect RR = 7.31 (95% CI 6.25–8.55). Complete clearance (IGA 0) emerged from week 8 (RR = 23.65%, 95% CI 6.74–82.95), overall RR = 12.44 (95% CI 6.88–22.51). PASI 75 overall RR = 6.74 (95% CI 5.75–7.91); PASI 90 RR = 14.38; PASI 100 RR = 11.17. PSSD symptom 0 at week 16: 256/1226 vs 9/551 (RR=9.62%, 95% CI 5.14–18.01). Icotrokinra offers rapid and clinically significant improvements in plaque psoriasis, particularly on IGA and PASI, and these responses continue to improve over time; by week 8, complete clearance became significantly more frequent with icotrokinra. Safety outcomes were comparable between icotrokinra and placebo, and there was no meaningful increase in serious adverse events.

Keywords: Interleukin-23 receptor, icotrokinra, plaque psoriasis, psoriasis area and severity index.

Introduction

Plaque psoriasis is a chronic skin disease that involves immune-mediated inflammation. It affects 2%–3% of the world's population, and among them, up to one-third have moderate-to-severe disease, which can become debilitating and require systemic therapy [1,2]. Psoriasis involves more than skin and is associated with reduced health-related quality of life (HRQoL), reduced work productivity, worsened psychosocial well-being, and an increased risk of comorbid cardiometabolic (i.e., heart disease) and inflammatory conditions [3–5]. The current treatment goals have shifted to achieving complete or

near-complete skin clearance with a rapid, durable onset. Requirements for defining skin clearance are strict, with the skin clearer (or nearly clear) than with a composite

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score of psoriasis area and severity index (PASI) 90/100 and an Investigator's Global Assessment (IGA) score of 0/1, in addition to marked alleviation of associated symptoms [6,7].

In the past few decades, biologic therapies for the management of psoriasis, such as those targeting tumor necrosis factor- α , as well as those targeting interleukin (IL)-17 and interleukin (IL)-23, have been developed and proven to be effective [8,9]. Unfortunately, due to the need for immunomodulation, parenteral administration, and a specific health care system, they may not be readily accepted or even accessible [10,11]. While alternatives, such as oral small molecules (methotrexate, apremilast, and JAK or TYK2 inhibitors), do exist, they tend to be associated with lower efficacy and may require more complex (or more frequent) laboratory monitoring [12,13]. Because of this, the need for oral therapies with similar efficacy to biologics, which are well-tolerated and have fewer side effects, remains.

Psoriasis is driven mainly by the IL-23/Th17 pathway, characterized by aberrant keratinocyte proliferation and severe inflammation mediated by IL-17A, IL-17F, and other related cytokines [14,15]. Most current biologics either neutralize IL-23 cytokines or downstream IL-17. In contrast, the direct antagonism of the IL-23 receptor (IL-23R) is a different mechanism and offers promise for selective pathway blockage [16]. Icotrokinra (JNJ-2113/JNJ-77242113) is the first targeted oral peptide and is the first of its kind, as it targets the IL-23 receptor and, therefore, does not cause generalized immunosuppression and also inhibits IL-23 receptor-mediated signaling [17].

Several recent randomized controlled trials (RCTs) have assessed icotrokinra for the treatment of moderate-to-severe plaque psoriasis and have shown a rapid onset of action, with positive PASI and IGA responses across multiple doses and patient populations [18]. In response to evolving expectations for treatment, they also implemented rigorous endpoints for treatment and patient response and reported deviations from them. As a result of the different studies, which focus on different designs and follow-up lengths, they do not have the power to detect adverse events. This study aims to present, for the first time, the efficacy and safety of icotrokinra compared with the control in patients with moderate-to-severe plaque psoriasis, as measured by physician-reported clearance, patient-reported PASI, and adverse effects over a clinically significant period.

Methods

Protocol and registration

The protocol for this study was developed and registered prospectively with PROSPERO (CRD420261309159). The study was conducted following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement guidelines [19,20]. A completed PRISMA checklist is provided in *Table S1* of the Supplementary materials.

Eligibility criteria

Inclusion criteria

We included studies following the subsequent PICO criteria: (i) population: Adults (≥ 18 years) and/or adolescents (≥ 12 years) with chronic plaque psoriasis (≥ 6 months) and moderate-to-severe disease; (ii) intervention: Oral icotrokinra (JNJ-77242113/JNJ-2113); (iii) comparator: Placebo; (iv) outcomes: The primary outcome was physician-assessed response: proportion achieving IGA 0/1 (clear/almost clear) at prespecified follow-up time points (weeks 2, 4, 8, 12, and 16) and clinical efficacy response: proportion achieving PASI 75 at prespecified time points (weeks 2, 4, 8, 12, and 16). Secondary outcomes included proportion achieving IGA 0, proportions achieving PASI 90 and PASI 100 and proportion achieving PSSD symptom score = 0. Safety outcomes included any reported adverse events (risk of adverse events leading to discontinuation, headache, overall infections, upper respiratory tract infection, nasopharyngitis, gastrointestinal adverse events, serious adverse events, serious infections, and malignancy) and (v) study designs: RCTs.

Exclusion criteria

Exclusion criteria for studies included non-randomized studies (e.g., observational studies, single-arm studies, case series, and case reports), and studies that were reviews, editorials, letters, or conference abstracts that did not contain adequate extractable data. We further excluded studies that did not include chronic moderate-to-severe plaque psoriasis (focusing on trials primarily on mild or non-plaque subtypes such as guttate, erythrodermic, or pustular psoriasis), did not assess oral icotrokinra, or had an ineligible comparator in the randomized phase. In addition, studies were excluded for not meeting the specified efficacy endpoint (IGA 0/1 or PASI 75) or for insufficient data to enable calculation of effect estimates.

Data sources and search strategy

We performed an extensive literature search across PubMed, Scopus, and Web of Science from their inception to January 2026 using the following search strategy (psoriasis OR psoriatic OR "plaque psoriasis") AND (icotrokinra OR "JNJ-77242113" OR "JNJ-2113" OR "PN-21235"), modified according to each database, with no other restrictions or limitations. Additionally, we reviewed the reference lists of all included studies and relevant reviews manually to identify any studies that might have been overlooked by the electronic search. The detailed search strategy for each database is provided in *Table S2* in the supplementary materials.

Study selection

The database search results were imported into EndNote [21] to identify and remove duplicate records. The cleaned library was then transferred to the Rayyan platform [22] for independent screening. Using Rayyan with the blind mode enabled, two authors independently evaluated

the titles and abstracts. The full texts of the retrieved records were subsequently examined by two authors to determine their eligibility based on predefined criteria. Any disagreements were resolved through consensus, with a third author consulted if needed.

Data extraction

Two separate authors collected relevant data from each included study and entered it into a standardized, pre-tested Google Sheet after a calibration meeting. The data included key details of the studies, such as study name, publication year, country, population characteristics, intervention and control details, and follow-up duration. They also recorded baseline parameters of the enrolled patients, including sample size, age, sex, disease duration, and baseline PASI score.

Risk of bias assessment

Two authors evaluated the risk of bias in the included studies, resolving disagreements through discussion and, if necessary, a third author's input. The potential bias in each trial was assessed with the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [23]. Each domain was rated as "Low," "Some concerns," or "High" risk, with the overall risk assessment determined by these domain-level evaluations.

Statistical analysis and heterogeneity

Meta-analyses were performed in *R* [24] using the meta package. For each dichotomous efficacy and safety endpoint, pooled treatment effects were calculated as risk ratios (RRs) using the Mantel–Haenszel method. A random-effects model was applied, and between-study variance (τ^2) was estimated using the Paule–Mandel estimator. To account for sparse data and trials with zero events in one or both arms, a continuity correction of 0.5 was applied. Statistical heterogeneity was assessed using the I^2 statistic and τ^2 , with corresponding heterogeneity tests reported. Sensitivity analyses were conducted using leave-one-out procedures to evaluate the influence of individual studies on pooled estimates, and subgroup analyses were performed where applicable (by follow-up time point) to explore potential differences across strata. All analyses were two-sided, and statistical significance was set at $p < 0.05$.

Results

Study selection

The electronic search across PubMed, Scopus, and Web of Science identified 56 records. After removing 24 duplicates, 32 unique records were screened based on title and abstract, with 23 excluded as clearly irrelevant

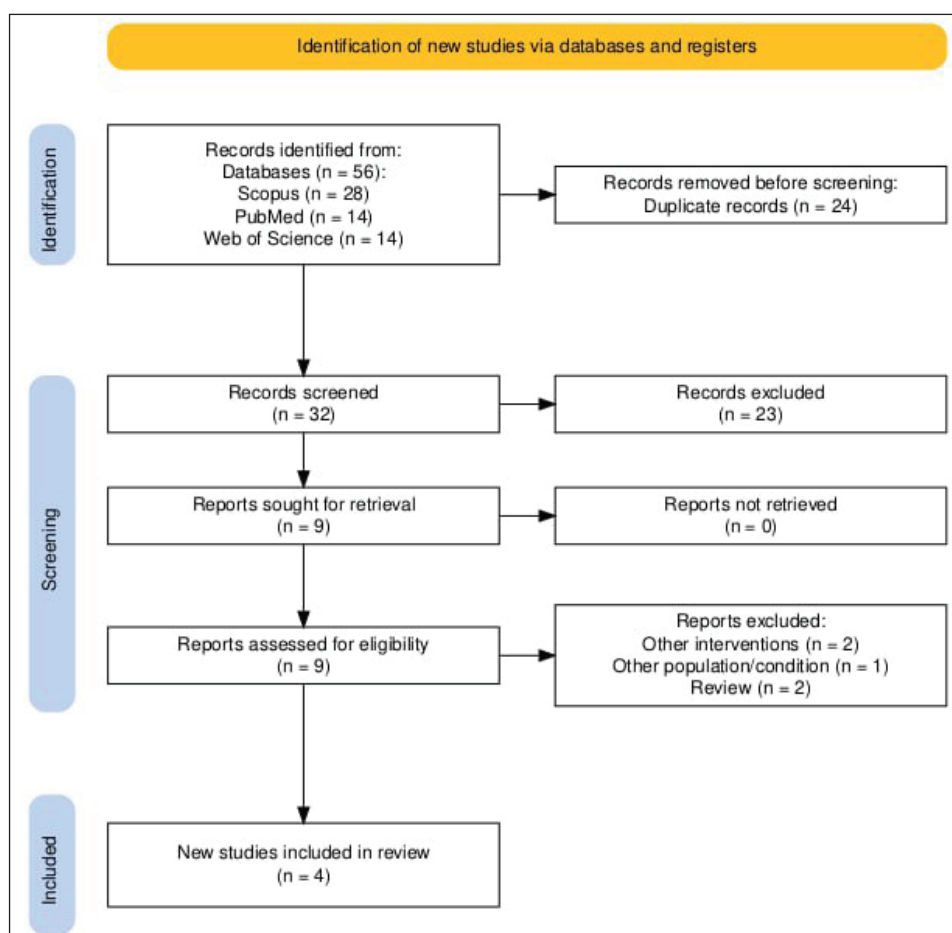


Figure 1. PRISMA flow diagram summarizing study identification, screening, eligibility assessment, and inclusion.

Table 1. Summary and baseline characteristics of included studies.

Study ID	Study design	Location	Population	Intervention	Control	Disease severity	Concomitant therapies	study period	Sample size		Age, mean ± SD		Sex, male, n (%)		Disease duration, y, mean ± SD		PASI, mean ± SD	
									I	C	I	C	I	C	I	C	I	C
Gold 2025 (ICONIC-ADVANCE-1)	RCT (NCT06143878)	Multicentric across 13 countries	Adults (aged ≥18 years) diagnosed with plaque psoriasis for at least 6 months	Once-daily oral icotrokinra (200 mg tablet)	G2: deucravacitinib (6 mg capsule), G3: Placebo	Moderate-to-severe plaque psoriasis	No concomitant topical therapies, phototherapies, or systemic medications	24 weeks	311	G2: 307, G3: 156	47.1 ± 13.19	G2: 46.3 ± 13.87, G3: 46.9 ± 12.78	223 (72)	G2: 200 (65), G3: 105 (67)	17.52 ± 11.1	G2: 16.81 ± 12.81, G3: 17.73 ± 12.75	18.93 ± 5.36	G2: 18.8 ± 6.25, G3: 17.73 ± 5.42
	RCT (NCT06220604)								322	G2: 327, G3: 82	45.9 ± 13.78	G2: 45.6 ± 13.22, G3: 48.4 ± 13.78	218 (68)	G2: 223 (68), G3: 55 (67)	17.43 ± 13.38	G2: 16.82 ± 12.03, G3: 21.21 ± 15.17	18.43 ± 5.29	G2: 18.06 ± 4.62, G3: 18.62 ± 7.02
Bissonnette 2024 (FRONTIER 1)	RCT (NCT05223868)	Multicentric at 60 sites across North America, Europe, and Asia	Adults with plaque psoriasis for at least 6 months	Oral icotrokinra (JNJ-77242113) 25 mg once daily, 25 mg twice daily, 50 mg once daily, 100 mg once daily, or 100 mg twice daily	Placebo	Moderate-to-severe plaque psoriasis	No concomitant treatments for psoriasis except for shampoos (salicylic acid and non-medicated topical moisturizers)	16 weeks	212	43	44.4 ± 12.24	43.9 ± 14.70	151 (71)	25 (58)	18.3 ± 12.48	17.9 ± 14.37	19.07 ± 5.94	18.99 ± 5.34
Bissonnette 2025 (ICONIC-LEAD)	RCT (NCT06095115)	Multicentric across 138 sites in North America, Europe, Argentina, and Asia	Adults and adolescents (> 12 years) with plaque psoriasis for at least 6 months	Oral icotrokinra at a dose of 200 mg once daily	Placebo	Moderate-to-severe plaque psoriasis	No concomitant treatments for psoriasis, except for therapy for latent TB in 20 participants	24 weeks	456	228	42.4 ± 16.3	43.2 ± 16.6	291 (64)	156 (68)	17.3 ± 13.9	16.6 ± 12.7	19.4 ± 7.1	20.8 ± 8.1
Gooderham 2025 (ICONIC-TOTAL)	RCT (NCT06095102)	Multicentric across 69 sites in North America, Europe, Argentina, and Asia	Adults and adolescents (≥12 years of age) with scalp, genital, and/or hand/foot psoriasis for at least 6 months	Oral icotrokinra at a dose of 200 mg once daily	Placebo	Moderate to severe plaque psoriasis	No concomitant treatments for psoriasis	16 weeks	208	103	45.3 ± 14.6	43.5 ± 13.8	137 (65.9)	63 (61.2)	16.8 ± 13.3	15.2 ± 10.5		

I, intervention; C, control; RCT, randomized controlled trial; NCT, ClinicalTrials.gov identifier; G, group; mg, milligram; y, years; PASI, Psoriasis Area and Severity Index; SD, standard deviation; TB, tuberculosis.

to the review question. Full texts of nine articles were then obtained and assessed for eligibility. During this process, five articles were excluded, leaving four studies [18,25–27] that met the inclusion criteria. These four studies were incorporated into qualitative synthesis and meta-analysis (Figure 1).

Characteristics of included studies

Five multicenter RCTs were included (ICONIC-ADVANCE-1/-2, FRONTIER 1, ICONIC-LEAD, and ICONIC-TOTAL) that enrolled adults (and, in two of the trials, adolescents ≥12 years) with plaque psoriasis for at least 6 months and of moderate-to-severe intensity. Studies were undertaken in North America, Europe, Asia, and other regions (spanning 60–138 sites and 1–13 countries) with randomized treatment durations of 16 or 24 weeks. In four trials, Icotrokinra was administered orally at 200 mg once daily, while FRONTIER 1 investigated several dose levels (25–100 mg once or twice daily). In all trials, placebo was the principal control, and in two studies, an active comparator (deucravacitinib 6 mg daily) was also included. Overall, psoriasis therapies were largely prohibited, with a few exceptions (e.g., topical treatments such as shampoo/moisturizers; a small subset was allowed to receive TB therapy). Of the 2,755 participants randomized, the average age was 42–47 years, 64%–72% were males, the average duration of disease was 16–18 years, and the baseline PASI was 18–21. Table 1 shows a summary and patients’ baseline characteristics of the included studies.

Risk of bias and quality assessment

Among the included four studies incorporating five RCTs, four RCTs showed low risk of bias, while one trial [ICONIC-TOTAL (Gooderham 2025)] showed some concerns, with no studies deemed as high risk of bias. Figure 2 illustrates risk of bias graphs.

Efficacy outcomes

Across the included trials, oral icotrokinra was associated with significantly higher rates of physician-assessed clearance compared with control. For achievement of IGA 0/1, the pooled effect favored icotrokinra at all prespecified time points, reaching statistical significance as early as week 2 (RR = 3.24%, 95% CI: 1.01–10.46; I^2 = 27.7%) and remaining robust through weeks 4, 8, 12, and 16 (week 4: RR = 6.31%, 95% CI: 3.83–10.39; I^2 = 0%; week 8: RR = 8.25%, 95% CI: 5.86–11.63; I^2 = 0%; week 12: RR = 7.61%, 95% CI: 5.73–10.11; I^2 = 0%; week 16: RR = 7.35%, 95% CI: 5.67–9.54; I^2 = 0%). The overall pooled analysis similarly demonstrated a marked benefit (RR = 7.31%, 95% CI: 6.25–8.55; I^2 = 0%), with no evidence of subgroup differences across follow-up time points (test for subgroup differences p = 0.604) (Figure 3). Leave-one-out sensitivity analyses did not change the direction of effect for IGA 0/1 at any time point, and pooled estimates remained statistically significant from week 2 onward (Figure S1–4).

For the more stringent endpoint of IGA 0, early time points (weeks 2 and 4) did not demonstrate a statistically significant difference (week 2: RR = 0.50%, 95% CI: 0.09–2.89; week 4: RR = 2.41%, 95% CI: 0.57–10.14); however, clear superiority of icotrokinra emerged by week 8 and persisted thereafter (week 8: RR = 23.65%, 95% CI: 6.74–82.95; week 12: RR = 21.31%, 95% CI: 8.83–51.42; week 16: RR = 25.89%, 95% CI: 12.66–52.96). The overall pooled analysis showed significantly higher IGA 0 response with icotrokinra versus control (RR = 12.44%, 95% CI: 6.88–22.51) with low-to-moderate heterogeneity (I^2 = 19.1%) and significant differences across time-point subgroups (p < 0.0001), consistent with increasing treatment effect over time (Figure 4). Leave-one-out sensitivity analyses yielded comparable pooled estimates across omissions at each time point (Figure S5–8).

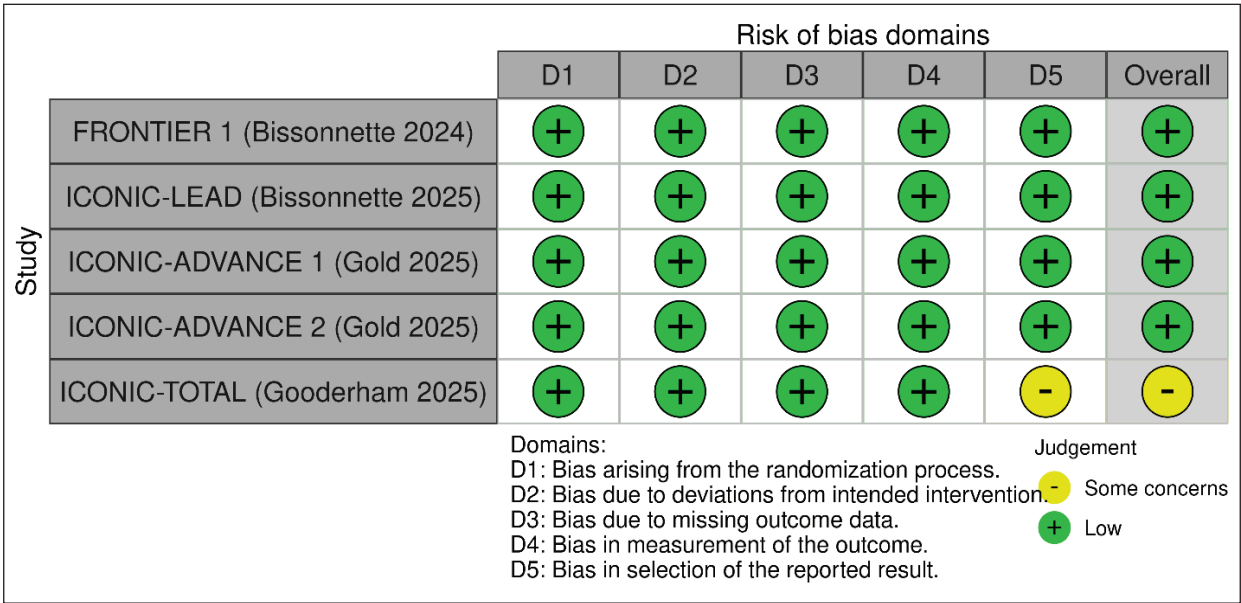


Figure 2. Risk of bias summary for included randomized controlled trials using the RoB 2 tool.



Figure 3. Forest plot of pooled risk ratios (RRs) for IGA 0/1 with icotrokinra versus control across follow-up time points.

Clinical response based on PASI thresholds was also consistently improved with icotrokinra. For PASI 75, treatment effects favored icotrokinra from week 4 onward (week 4: RR = 5.10%, 95% CI: 2.95–8.82; week 8: RR = 8.70%, 95% CI: 5.94–12.74; week 12: RR = 6.80%, 95% CI: 5.12–9.02; week 16: RR = 6.47%, 95% CI: 5.04–8.31), while the week-2 estimate did not reach statistical significance (RR = 3.89%, 95% CI: 0.95–15.96) (Figure 5). The overall pooled effect indicated substantially

higher PASI 75 response with icotrokinra (RR = 6.74%, 95% CI: 5.75–7.91; $I^2 = 0\%$) and no evidence of subgroup differences by time point ($p = 0.493$), with sensitivity analyses showing minimal change in pooled estimates (Figure S9–12).

For higher thresholds of clearance, icotrokinra showed increasing difference from control over time. PASI 90 was not statistically different at week 2 (RR = 0.50, 95% CI: 0.07–3.56) but became significant from week 4 onward

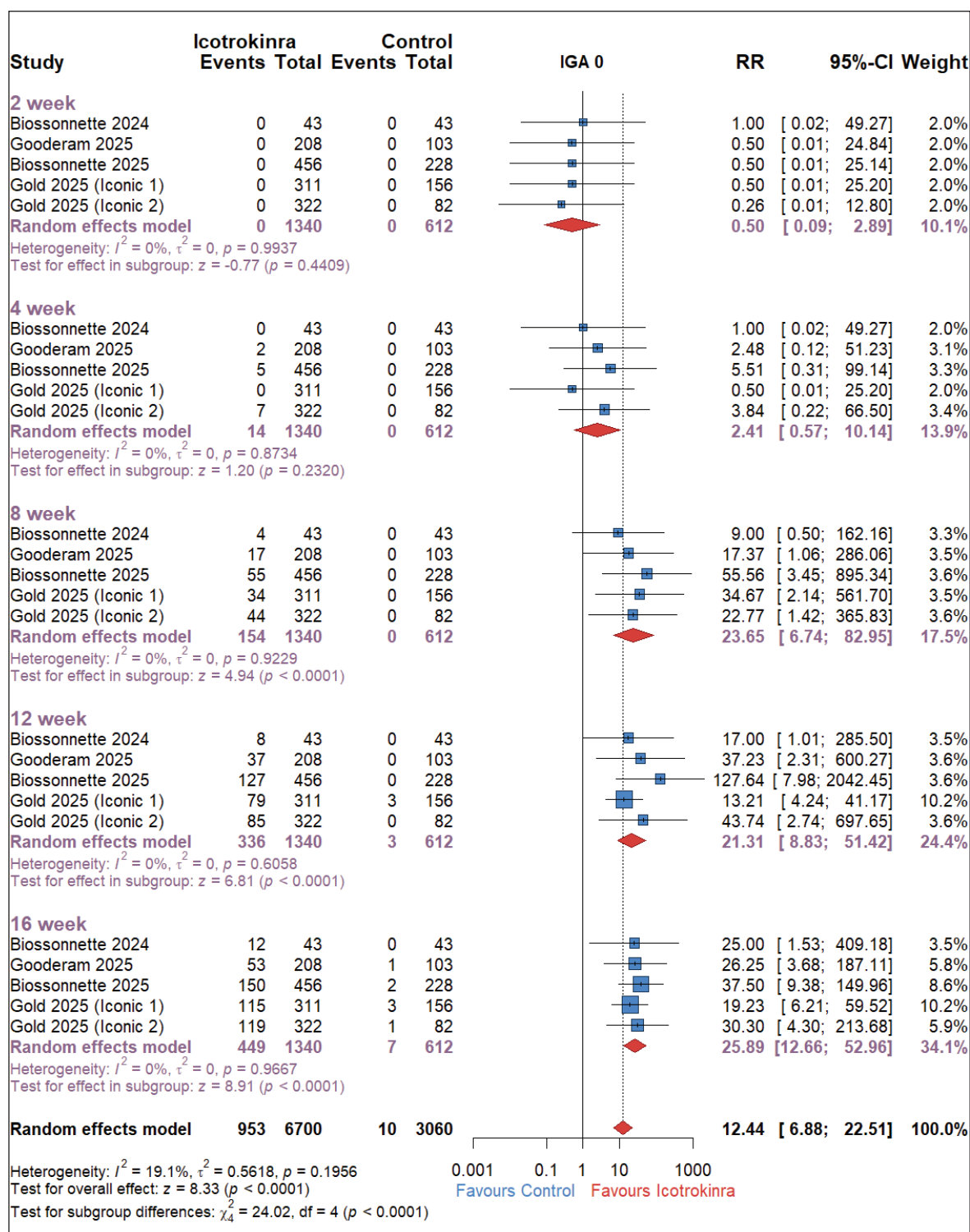


Figure 4. Forest plot of pooled RRs for IGA 0 with icotrokinra versus control across follow-up time points.

(week 4: RR = 9.36%, 95% CI: 2.24–39.11; week 8: RR = 20.86%, 95% CI: 8.64–50.36; week 12: RR = 17.26%, 95% CI: 9.58–31.11; week 16: RR = 14.65%, 95% CI: 9.15–23.46), with a strong overall pooled effect (RR = 14.38%, 95% CI: 10.39–19.92; $I^2 = 0\%$) and evidence of differences across time-point subgroups ($p = 0.0129$) (Figure 6). Similarly, PASI 100 did not reach statistical significance at weeks 2 and 4 (week 2: RR = 0.50%, 95% CI: 0.07–3.56; week 4: RR = 2.03%, 95% CI: 0.39–

10.63) but demonstrated significant benefit from week 8 onward (week 8: RR = 17.88%, 95% CI: 4.33–73.86; week 12: RR = 38.81%, 95% CI: 9.61–156.75; week 16: RR = 26.41%, 95% CI: 11.44–60.99). The overall pooled analysis favored icotrokinra for PASI 100 (RR = 11.17%, 95% CI: 5.40–23.10) with low heterogeneity ($I^2 = 23.7\%$) and significant subgroup differences across follow-up time points ($p = 0.0004$) (Figure 7). Leave-one-out sensitivity analyses yielded comparable pooled

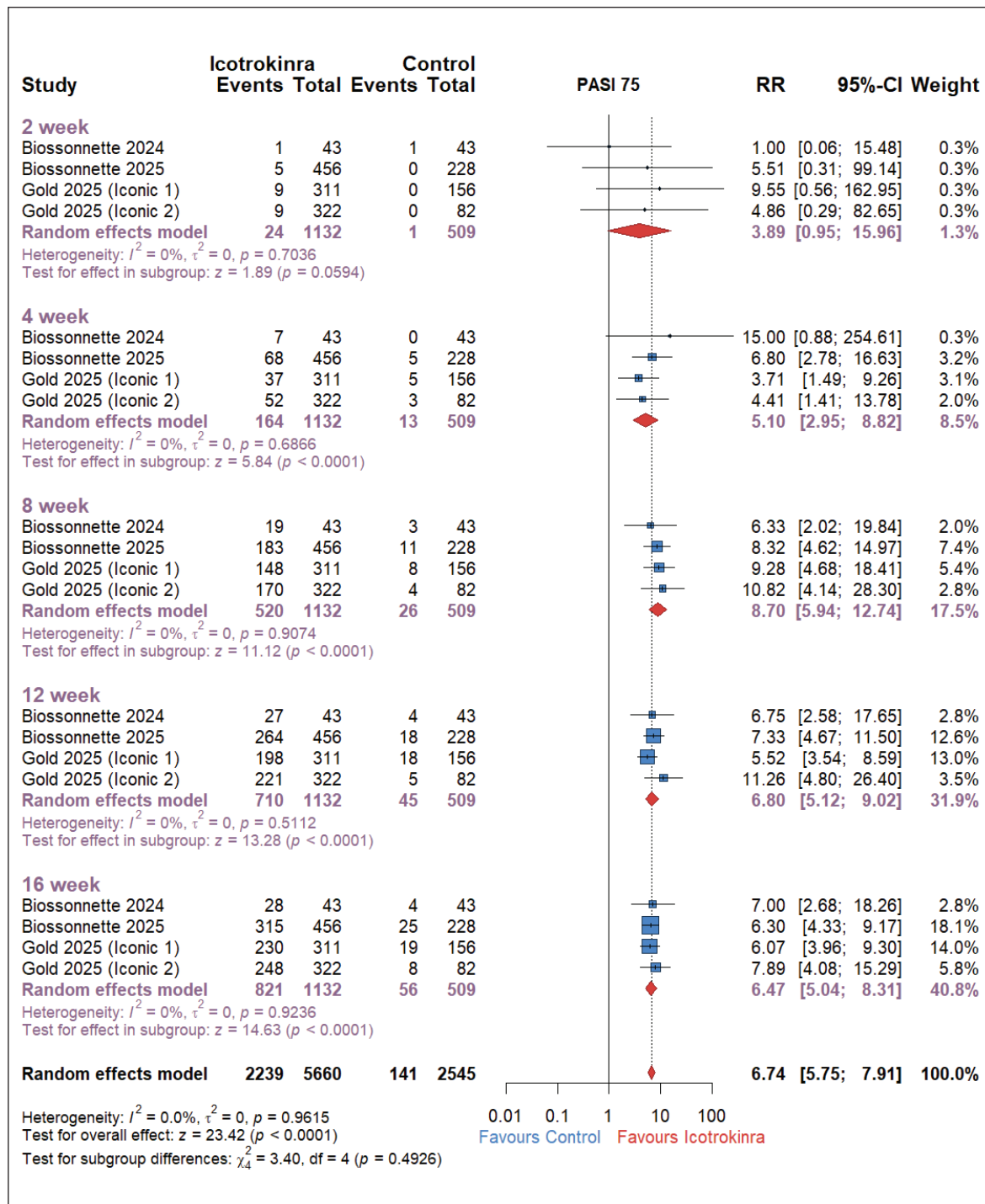


Figure 5. Forest plot of pooled RRs for PASI 75 with icotrekinra versus control across follow-up time points.

estimates across omissions at each time point in both outcomes (Figure S13–16 and S17–20, respectively).

For patient-reported symptom clearance, achieving a PSSD symptom score of 0 at week 16 was significantly more frequent with icotrekinra than with control (256/1226 vs 9/551; RR = 9.62%, 95% CI: 5.14–18.01; $P = 0\%$) (Figure 8). Leave-one-out sensitivity analysis demonstrated that statistical significance was preserved after sequential exclusion of each study (pooled RR range 7.93–12.95, with I^2 ranging from 0% to 19%) (Figure S21).

Safety outcomes

Across pooled safety endpoints, oral icotrekinra demonstrated a safety profile broadly comparable to control, with no statistically significant increases in overall or specific adverse events. Adverse events leading to discontinuation were not significantly different between groups (RR = 0.64%, 95% CI: 0.27–1.52; $P = 30.8\%$) (Figure S22). Headaches occurred at similar rates between arms (RR = 1.14%, 95% CI: 0.44–2.92; $P = 50.1\%$) (Figure S23). Infectious outcomes were comparable, including overall infections (RR = 1.11%,

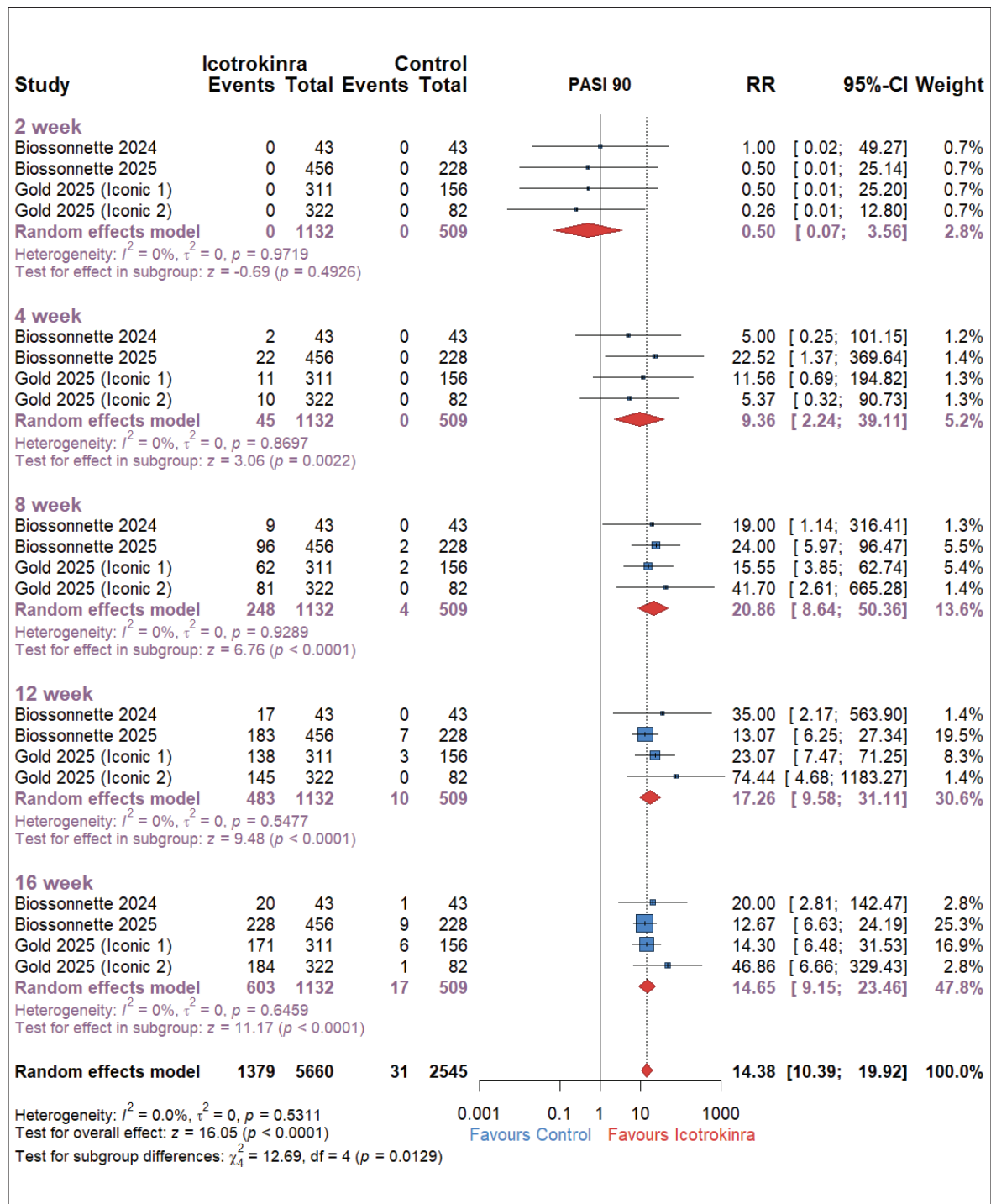


Figure 6. Forest plot of pooled RRs for PASI 90 with icetrokinra versus control across follow-up time points.

95% CI: 0.88–1.39; $I^2 = 0\%$) (Figure S24), upper respiratory tract infection (RR = 1.00%, 95% CI: 0.66–1.53; $I^2 = 0\%$) (Figure S25), and nasopharyngitis (RR = 1.07%, 95% CI: 0.75–1.52; $I^2 = 0\%$) (Figure S26). Gastrointestinal adverse events were similar between groups (RR = 1.04%, 95% CI: 0.73–1.49; $I^2 = 0\%$) (Figure S27). Serious outcomes were uncommon and did not differ significantly, including serious adverse events (RR = 0.61%, 95% CI: 0.29–1.29; $I^2 = 0\%$) and serious infections (RR = 0.48%, 95% CI: 0.11–2.10; $I^2 = 0\%$) (Figure S28 and S29, respectively). Finally, malignancy events were rare and not statistically different between

groups (RR = 1.18%, 95% CI: 0.27–5.28; $I^2 = 0\%$) (Figure S30).

Leave-one-out sensitivity analyses showed that the pooled safety findings were generally robust: excluding any single study did not change the overall conclusions for gastrointestinal adverse events (Figure S31), nasopharyngitis (Figure S32), upper respiratory tract infection (Figure S33), overall infections (Figure S34), malignancy (Figure S35), serious adverse events (Figure S36), or serious infections (Figure S37). Headache results also remained non-significant after omitting individual

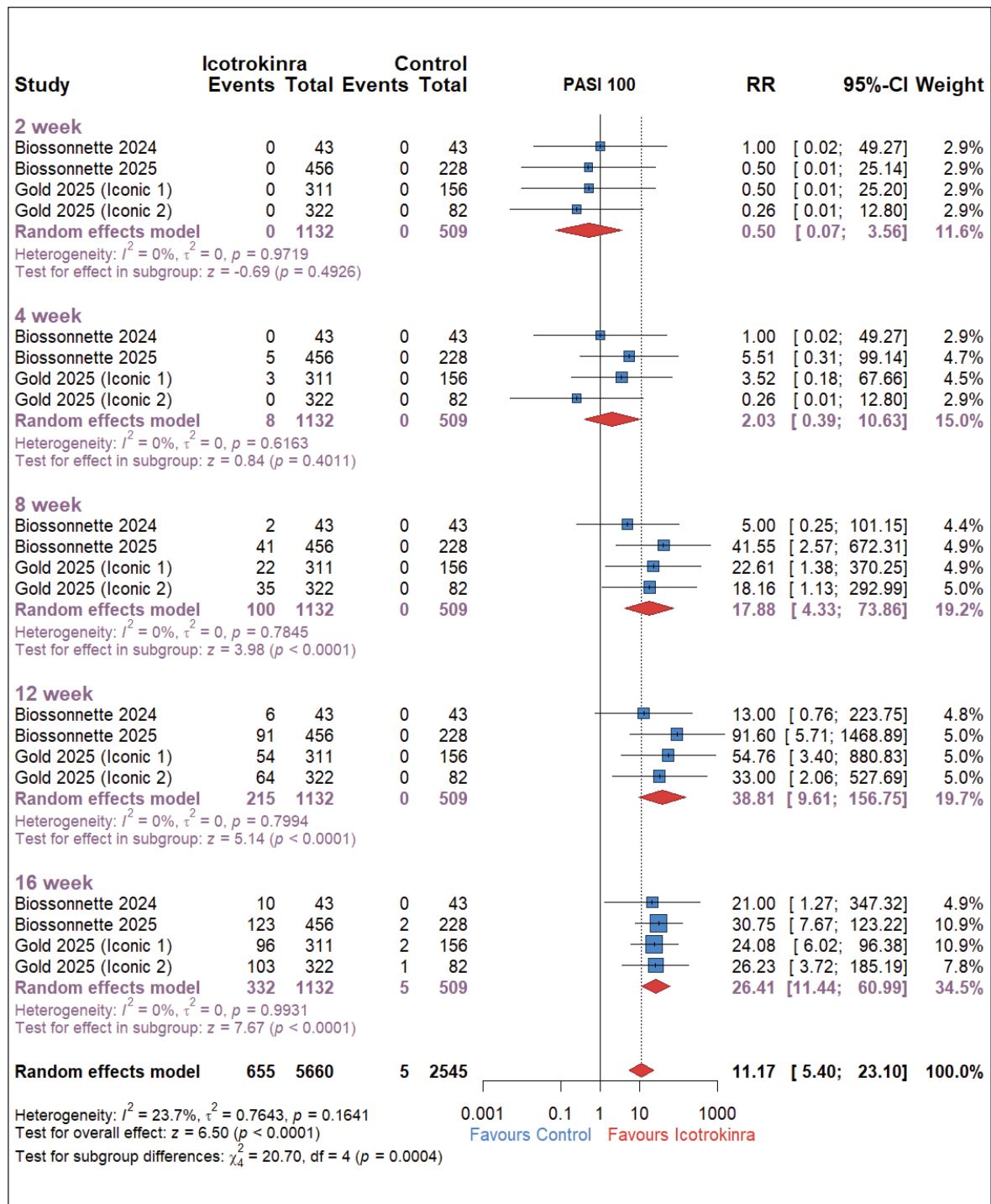


Figure 7. Forest plot of pooled RRs for PASI 100 with icetrokinra versus control across follow-up time points.

trials, although the magnitude and heterogeneity varied, suggesting some between-study variability (Figure S38). In contrast, adverse events leading to discontinuation showed the greatest sensitivity to Biossonnette 2025 removal (Figure S39).

Discussion

The treatment of moderate-to-severe plaque psoriasis requires a complex systemic therapy that demands high levels of skin clearance and convenience. Targeted oral antagonism of the IL-23 receptor provides a mechanism

analogous to biologics without the need for injections. Among the pooled analyses of RCTs included in this systematic review and meta-analysis, icetrokinra (JNJ-2113/JNJ-77242113) consistently outperforms placebo in physician-assessed and patient-reported outcomes, while maintaining a safety profile of short-term adverse events comparable to that of the control group. IL-23 receptor oral peptide demonstrated robust, clinically significant change (IGA 0/1 separation by week 2) and deepening response over time. By weeks 8–16, significantly more participants achieved stringent clearance endpoints

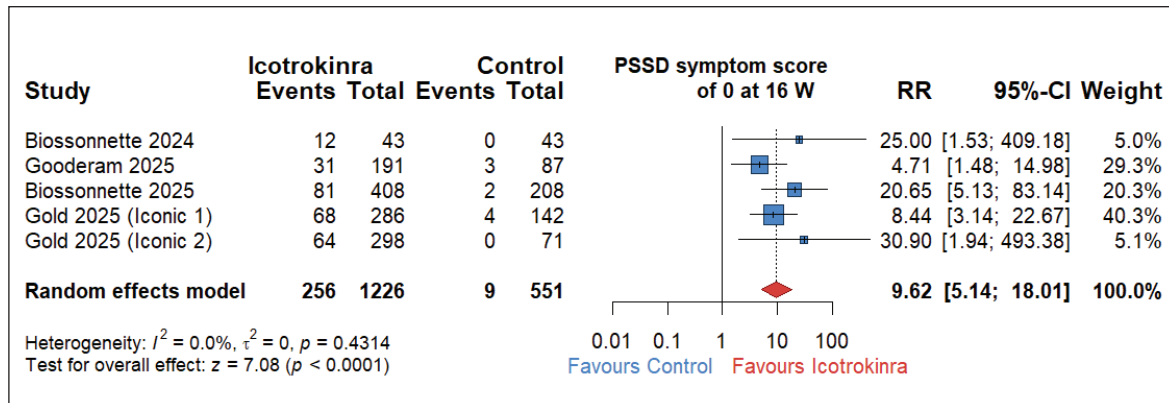


Figure 8. Forest plot of pooled RRs for PSSD symptom score = 0 at week 16 with icotrokinra versus control.

(IGA 0 and PASI 90/100). Improvement was documented as both significant and reliable, with response time of “almost clear” to “complete clearance”.

Across the included RCTs for icotrokinra, the large and very homogeneous improvement in IGA and PASI, and the obvious deepening of response between weeks 8 to 16, is mechanistically coherent with proximal blockade of the IL-23 receptor. This is a choke-point that fuels pathogenic Th17/Tc17 programs, which drive IL-17/IL-22-mediated hyperproliferation of keratinocytes and permanence of plaques (28). As a targeted oral peptide, icotrokinra acts on the extracellular IL-23R and inhibits IL-23 signaling at the receptor level, a mode of pathway interruption more in line with IL-23 biologics than with classic small-molecule oral agents [29]. This might explain why our synthesis shows early “near-clear” separation (IGA 0/1 significant by week 2), and subsequently, a time-dependent increase in stringent endpoints (e.g., IGA 0 and PASI 100 becoming significant from week 8 and beyond), which is suggestive of progressively terminating the IL-23-sustained inflammatory cycle, rather than simply lowering the activity of the inflammatory loop.

In comparison, apremilast (inhibition of PDE4) modulates intracellular cAMP and multiple cytokines but usually leads to less pronounced maximal clearance: In ESTEEM 1, PASI 75 at week 16 was 33.1% vs 5.3% with placebo (13), and in ESTEEM 2, sPGA 0/1 at week 16 was 20.4% vs 4.4% with placebo (30). Deucravacitinib (inhibition of allosteric TYK2) is mechanistically located closer to the IL-23/Th17 axis than apremilast, and the phase 3 efficacy reflects this: in POETIK PSO-1 at week 16, PASI 75 was 58.4% (vs 12.7% placebo; 35.1% apremilast), PASI 90 35.5% (vs 4.2%; 19.6%), PASI 100 14.2% (vs 0.6%; 3.0%), and sPGA 0/1 53.6% (vs 7.2%; 32.1%) (31). Therefore, the larger and increasingly “deep” effects that we saw with icotrokinra over time across PASI 90/100 and IGA 0 are biologically plausible: antagonism at the receptor level of IL-23R may provide a more complete functional shutdown of IL-23 signaling that sustains the psoriatic plaques, leading to the pronounced late emergence of complete/near-complete clearance in our pooled RRs [32].

IGA 0/1 is a practical endpoint determined by a physician that is consistent with “clear/almost clear” disease, a common minimum target for systemic therapy candidates. Separation from control for Icotrokinra occurred as early as week 2 (RR = 3.24), with a marked, stable, and large effect sustained through week 16 (overall RR = 7.31), and almost no heterogeneity at each of the many time points ($I^2 = 0\%$ from week 4 onward). This consistency supports the reproducibility of the treatment effect across trials. Clinically, the week 2 signal is important as early visible improvements support adherence, reduce the need for rescue medication, and bolster patient confidence during the high-burden induction period. Furthermore, the sustained effect is consistent with modern treat-to-target goals and supports targeting the IL-23 pathway as a rapid means to achieve significant reductions in plaque and erythema [33,34].

PASI 75 has been a standard benchmark against which meaningful clinical response and historical comparability across system-wide trials have been benchmarked. From week 4 and onward, Icotrokinra produced large and consistent improvement (week 4 RR = 5.10; week 8 RR = 8.70; week 16 RR = 6.47), with a highly stable overall effect (RR = 6.74) and, with no heterogeneity ($I^2 = 0\%$) detectable. Remarkable consistency like this is uncommon in psoriasis meta-analyses because of the variability often introduced at the trial level due to prior biologic exposures, baseline PASI, and the geography of trial enrollers. The absence of time-point subgroups with differences ($p = 0.493$) is strong evidence that the PASI 75 effect is strong and remains so throughout the induction period, once the differences have separated. This profile provides practical evidence that supports the expectation that many patients will reach PASI 75 within the mid-induction window and is strong evidence anchoring treat-to-target discussions that use PASI-based thresholds in combination with BSA and PGA/IGA (35).

Modern management of psoriasis focuses more on the depth of response (PASI 90/100), as almost complete clearances are the best predictor of quality of life. In the current meta-analysis, PASI 90 at week 2 did not show any difference (RR = 0.50) but from week 4 PASI 90 had a large effect overall (RR = 14.38) and no heterogeneity

($P = 0\%$). PASI 100 was more time dependent, with no significance at weeks 2, 3, and 4, and then icotrokinra was strongly favored from weeks 8 to 16 (overall RR = 11.17; $P = 23.7\%$; Subgroup $p = 0.0004$), which reflected the stepwise increases in the complete clearance and suggested a progressive pathway shutdown instead of an early plateau. In counselling, the stringent endpoints have low early control event rates, meaning the absolute responder proportions are more important [36]. This was also the case when patients benched the assessment of disease (PSSD symptom score 0), which was far more common with icotrokinra at week 16 (RR = 9.62; $P = 0\%$), demonstrating symptom relief from the disease. When sensitivity analyses were performed by omitting a single study, significance was preserved, indicating that the effects were true and not random artefacts of a single study.

Icotrokinra did not show evidence of a statistically significant increase in the overall adverse events leading to discontinuation (RR = 0.64), infection (RR = 1.11), upper respiratory tract infection (RR = 1.00), nasopharyngitis (RR = 1.07), gastrointestinal AEs (RR = 1.04), serious AEs (RR = 0.61), serious infections (RR = 0.48), or malignancy (RR = 1.18), with low heterogeneity in most of the domains. This is in the same direction of the safe profile, which IL-23 pathway biologics exhibit and which have been the most important driver for long term usage in psoriasis care [37,38]. However, the current synthesis of evidence is mainly focused on short-term tolerability. Safety in more vulnerable populations (e.g. frequent infections, malignancy, and complex comorbidities), rare events, events with a long latency period, and such events in more vulnerable populations will require ongoing pharmacovigilance and post-marketing surveillance.

Strengths and limitations

This study has several strengths that increase confidence in the clinical signal for icotrokinra. First, the synthesis was limited to RCTs, reducing confounding and strengthening causal inference. Second, efficacy was assessed across a clinically relevant and patient-centered hierarchy of endpoints (IGA 0/1, IGA 0, PASI 75/90/100) and a patient-centered (PSSD symptom score 0), thereby allowing for triangulation of benefits from both the physician and the patient. Third, effects were evaluated at several prespecified time points, clarifying a plausible biological time course: early separation for “almost clear” outcomes, with subsequent and progressive deep/complete clearance. Fourth, for key outcomes, between-study inconsistency was generally low ($I^2 \approx 0\%$), suggesting reproducibility across studies. Fifth, robustness was demonstrated with leave-one-out sensitivity analyses that retained the direction and significance of most efficacy and safety outcomes. Lastly, safety was synthesized across several event domains (discontinuations, gastrointestinal events, and serious events), providing a balanced short-term benefit-risk profile, in addition to the efficacy assessed, instead of considering efficacy in isolation. This study has several strengths that increase confidence in the clinical signal for icotrokinra.

However, this study has several limitations that should be considered when interpreting and evaluating these findings. First, the number of available trials and total events for several safety outcomes was small, leading to wide CIs and limited power to detect rare or delayed adverse events (e.g., serious infections or malignancy). Second, all outcomes were assessed over short follow-up periods (16 weeks), which may not capture long-term efficacy durability or cumulative safety risks, particularly for uncommon events. Third, clinical and methodological differences across trials—such as variations in baseline disease severity, prior treatment exposure, age distribution (adult vs adolescent), dosing regimens, and definitions or reporting of adverse events—may limit direct comparability despite low statistical heterogeneity in many pooled analyses. Finally, publication bias cannot be excluded, particularly because the evidence base appears to be dominated by a limited number of study programs, with few studies per outcome, making formal assessment of small-study effects unreliable.

Implications for clinical practice and future research

The most recent research on psoriasis recommends a treat-to-target method and upward adjustments based on disease severity, QoL impact, comorbidities, and patient preference, generally shifting from standard systemic and/or phototherapy to targeted immunomodulators and biologics when control is insufficient [39–41]. From that standpoint, it seems icotrokinra would allow for further expansion of the “oral targeted” approach; Icotrokinra demonstrated rapid physician-assessed improvement (IGA 0/1 separation by week 2) and progressively deeper clearances during weeks 8–16 (IGA 0, PASI 90/100), and short-term tolerability of infections, gastrointestinal events, serious events, and discontinuation was comparable to control. Clinically, this tolerability profile could make icotrokinra a viable option for patients who are averse to injections, as well as for those seeking an effective targeted oral regimen, or as the next step after a prior failure or intolerance to conventional oral agents. Integration into guidelines will require further data to evaluate long-term durability and safety, head-to-head effectiveness, and data in key subpopulations (e.g., prior biologic failure, high cardiometabolic burden, and pregnancy planning).

Conclusion

Based on its performance across RCTs, Icotrokinra indicates the potential for truly targeted, receptor-level oral immunotherapy to reduce the historic efficacy gap between oral and injectable biologics for moderate-to-severe plaque psoriasis. The treatment effects fit an early improvement, progressive, and deep-clearance pattern, which, structurally, supports a treatment mechanism and may suit treat-to-target strategies along with patients’ preference for oral medications. While no significant differences in the assessed short-term safety outcomes were detected compared with control, firm conclusions will require longer follow-up, comparative effectiveness research, and monitoring of real-world safety in higher-risk populations.

Conflict of interest

The authors declare that they do not have any conflicts of interest regarding this study.

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Ethical approval

No ethical approval was required for this study, as it is a PRISMA-compliant systematic review and meta-analysis. The protocol of this study was prospectively registered with PROSPERO to maintain transparency.

List of abbreviations

AE	Adverse event
BSA	Body surface area
CI	Confidence interval
cAMP	Cyclic adenosine monophosphate
GI	Gastrointestinal
HRQoL	Health-related quality of life
I ²	I-squared statistic (heterogeneity)
IGA	Investigator's Global Assessment
IL	Interleukin
IL-17	Interleukin-17
IL-17A	Interleukin-17A
IL-17F	Interleukin-17F
IL-23	Interleukin-23
IL-23R	Interleukin-23 receptor
JAK	Janus kinase
MH	Mantel-Haenszel method
PASI	Psoriasis area and severity index
PDE4	Phosphodiesterase-4
PICOs	Population, Intervention, Comparator, Outcomes, study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PRO	Patient-reported outcome
PSSD	Psoriasis symptoms and signs diary
R	R statistical software/environment
RCT	Randomized controlled trial
RR	Risk ratio
RoB 2	Revised Cochrane risk-of-bias tool for randomized trials
SAE	Serious adverse event
sPGA	Static Physician's Global Assessment
TB	Tuberculosis
Tc17 subset)	IL-17-producing cytotoxic T cell (CD8+ T cell subset)
Th17	T helper 17 cell
TNF- α	Tumor necrosis factor alpha
τ^2	Between-study variance in random-effects meta-analysis
TYK2	Tyrosine kinase 2
URTI	Upper respiratory tract infection

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Supplementary content (If any) is available online.

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