Summary Table of Study Protocol

Title	Indirect treatment comparison of pegloticase in combination with methotrexate versus nanoencapsulated sirolimus plus pegadricase for the treatment of uncontrolled gout
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Research Question and Objectives	**Research question**: What is the relative efficacy and safety of pegloticase in combination with methotrexate (MTX) compared with nanoencapsulated sirolimus plus pegadricase (NASP) in individuals with uncontrolled gout? **Objectives**: • To estimate the relative treatment effect on treatment response, defined as serum uric acid (sUA) <6 mg/dL for ≥80% of the assessment period (primary endpoint) CCI [redacted]
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STUDY GLOSSARY

Term	Definition
Bias	Systematic error.
Cohort	Group of individuals characterized by a common experience (e.g., occurrence of a specified disease; exposure to a given medication).
Confounder	An extraneous factor that accounts for a difference in disease frequency between the exposure groups. Factors associated with these extraneous causal factors that can serve as surrogates for these factors also are commonly called confounders.
Effect-measure modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier.
Evidence synthesis (ES)	Techniques comprising the combining and analysis of data from different studies (e.g., meta-analysis, network/meta-analysis). The studies from which data is combined can differ in relation to their design types, outcome measures, study interventions, study parameters, or patient population.
Exposure	Variable whose effect is of interest and is being studied.
Meta-analysis	Statistical method allowing for the combination of outcome data from more than one individual studies, while also accounting for uncertainties resulting from the combination of data from varying sources.
Network meta-analysis (NMA)	An extension of meta-analysis that enables the comparison of the relative effects of multiple treatments within a connected evidence network, even when some treatments have not been directly compared in head-to-head trials. NMA methods synthesize both direct and indirect evidence while accounting for uncertainty arising from multiple data sources.
Outcome	Event (such as disease occurrence or death) that is studied in relation to an exposure.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis data model
AE	Adverse event
AgD	Aggregate data
ANCOVA	Analysis of covariance
ASD	Absolute standardized difference
BFGS	Broyden-Fletcher-Goldfard-Shanno
BMI	Body mass index
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CrI	Credible interval
CSR	Clinical study report
DIC	Deviance information criterion
Dres	Residual deviance
DSU	Decision Support Unit
eGFR	Estimated glomerular filtration rate
ESS	Effective sample size
FDA	US Food and Drug Administration
ICMJE	International Committee of Medical Journal Editors
IR	Infusion reaction
IPD	Individual participant data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
JCA	Joint clinical assessment
LOCF	Last observation carried forward
LS	Least squares
MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
MD	Mean difference
MMRM	Mixed models for repeated measures
MTX	Methotrexate
NASP	Nanoencapsulated sirolimus plus pegadricase
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio

PC	Product complaint
PSRF	Potential scale reduction factor
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RCT	Randomized controlled trial
RPMM	Regression and predictive mean matching
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
sUA	Serum uric acid
TEAE	Treatment-emergent adverse event
TSD	Technical support document
ULT	Urate-lowering therapy
US	United States
XOI	Xanthine oxidase inhibitor

2. ABSTRACT

Study Title

Indirect treatment comparison of pegloticase in combination with methotrexate versus nanoencapsulated sirolimus plus pegadricase for the treatment of uncontrolled gout.

Relevant Systematic Literature Review (SLR)

This evidence synthesis is informed by an Amgen-sponsored SLR that identified randomized controlled trials (RCT) evaluating pegloticase-based regimens and relevant comparators for uncontrolled gout. The SLR, initially completed in 2024 and updated in 2026, identified four eligible RCTs: C405/C406, MIRROR RCT, COMPARE, and DISSOLVE I/II. These trials form the evidence base for the indirect treatment comparison (ITC).

Research Question

What is the relative efficacy and safety of pegloticase in combination with methotrexate (MTX) versus nanoencapsulated sirolimus plus pegadricase (NASP) in adults with uncontrolled gout?

Background and Rationale

Uncontrolled gout is a severe, refractory condition characterized by persistent hyperuricemia, frequent flares, and the presence of tophi in individuals who have not responded to standard urate-lowering therapy. Pegloticase, a pegylated recombinant uricase, is an approved treatment in this setting but is limited by immunogenicity leading to loss of response. The MIRROR RCT recently demonstrated that co-administration of MTX with pegloticase significantly improves sustained urate-lowering response and reduces infusion reactions compared with pegloticase alone.

NASP is an investigational uricase-based therapy designed to minimize immunogenicity and has shown promising efficacy in Phase 2 and 3 trials. In the absence of head-to-head trials comparing pegloticase + MTX and NASP, an ITC is warranted to assess the relative efficacy and safety of these two regimens.

Feasibility

A feasibility assessment confirmed the viability of conducting an ITC using evidence from the identified RCTs. These trials form a connected evidence network through shared comparator arms, enabling anchored indirect comparisons. Among the identified

studies, MIRROR RCT and COMPARE provide the most relevant and comparable evidence for evaluating pegloticase + MTX versus NASP.

Treatment response demonstrated the strongest cross-trial comparability among the evaluated outcomes and was therefore selected as the primary endpoint for the ITC. Across studies, treatment response definitions (serum uric acid [sUA] <6 mg/dL for ≥80% of the assessment period) and assessment approaches were broadly aligned. In addition, the availability of individual patient data (IPD) for the pegloticase trials enables covariate adjustment to balance the key baseline characteristics between MIRROR RCT and COMPARE. In contrast, greater heterogeneity was identified for CCI [redacted] including differences in derivation methods, outcome definitions, and reporting practices. These outcomes were therefore considered more appropriate for exploratory analyses.

Objectives

The primary objective is to estimate the relative treatment effect of pegloticase + MTX versus NASP on treatment response (defined as maintaining sUA <6 mg/dL for ≥80% of the assessment period) during month 6 among adults with uncontrolled gout. Additional supportive analyses will evaluate treatment response during month 3 and months 3 & 6 combined. CCI [redacted]

CCI [redacted]

Statistical Outcomes

The primary efficacy outcome is treatment response during month 6, defined as maintaining sUA <6 mg/dL for ≥80% of the assessment period. Additional supportive analyses will evaluate treatment response during month 3 and months 3 & 6 combined.

CCI [redacted]

For binary outcomes, relative effects will be estimated as odds ratios (ORs). For the continuous outcome, relative effects will be estimated as mean differences (MDs). Treatment response outcomes will be analyzed using IPD from MIRROR RCT and aggregate data from the COMPARE trial. For exploratory outcomes, published aggregate treatment effect estimates will be used where available, supplemented by analyses of available IPD when required outcome data is not publicly reported.

Statistical Analysis Plan

For analyses of treatment response, MIRROR RCT and COMPARE will form the primary analysis set. Anchored matching-adjusted indirect comparison (MAICs) will be performed for treatment response during month 6, month 3, and months 3 & 6 combined, using IPD from MIRROR RCT (pegloticase + MTX vs pegloticase) and aggregate trial data from COMPARE (NASP vs pegloticase). Baseline characteristics, including age, body mass index, baseline sUA, and baseline tophi, will be matched so that the weighted MIRROR RCT population aligns with the COMPARE population. Adjusted ORs with 95% confidence interval (CI) will be estimated for pegloticase + MTX vs NASP.

For treatment response, sensitivity analyses will evaluate the robustness of findings to alternative covariate adjustment strategies, handling of missing baseline covariate data, and removal of population adjustment. An additional exploratory NMA analysis will be conducted for month 6 treatment response using an expanded evidence network that incorporates the lower NASP dose through inclusion of DISSOLVE I/II.

Standard NMAs will be performed for the[redacted] using relevant trials where feasible. Given the small number of studies (2-4 per network), fixed-effect models will be used as the primary approach, with random-effects models explored in sensitivity analyses where appropriate. All exploratory findings will be interpreted with additional caution due to greater indirectness, residual heterogeneity, and outcome-specific limitations.

3. AMENDMENTS AND UPDATES

None.

4. OBJECTIVES

4.1 Primary Objective(s)

The primary objective is to estimate the relative treatment effect of pegloticase in combination with methotrexate (pegloticase + MTX) versus nanoencapsulated sirolimus plus pegadricase (NASP) on treatment response during month 6, among adults with uncontrolled gout. Treatment response is defined as maintaining serum uric acid (sUA) <6 mg/dL for ≥80% of the assessment period. Additional supportive analyses will evaluate treatment response during month 3 and months 3 & 6 combined using the same response definition.

4.2 Exploratory Objective(s)

CCI [redacted]

5. OUTCOMES

The primary outcome is treatment response during month 6, defined as maintaining sUA <6 mg/dL for ≥80% of the assessment period. Additional supportive analyses will evaluate treatment response during month 3 and months 3 & 6 combined, using the same definition. CCI [redacted]

Relative treatment effects of pegloticase + MTX versus NASP will be estimated as odds ratios (ORs) for binary outcomes, including treatment response CCI [redacted]

6. BACKGROUND AND RATIONALE

6.1 Disease or Therapeutic Area

Uncontrolled gout is a severe and debilitating form of inflammatory arthritis characterized by persistent hyperuricemia (sUA ≥6.0 mg/dL), frequent and painful flares, and the development of tophaceous deposits [1]. It typically occurs in individuals whose disease remains inadequately controlled despite conventional oral urate-lowering therapies (e.g., allopurinol or febuxostat) due to inadequate response, intolerance, or contraindication. In a large claims-based study in United States (US), over 95,000 individuals were identified

as having uncontrolled gout based on prescription patterns and sUA levels, and those with persistently elevated sUA over time had higher healthcare utilization and poorer clinical outcomes [2].

For adults with uncontrolled gout who do not achieve adequate disease control with oral therapy, uricase-based treatments have emerged as an important therapeutic option. Pegloticase, a PEGylated recombinant uricase, lowers sUA by converting uric acid to allantoin, a more soluble metabolite that is excreted by the kidneys [3]. The pivotal C405/C406 phase 3 trials established the efficacy of pegloticase monotherapy in this population, with 42% of individuals receiving biweekly pegloticase achieving the primary urate-lowering response compared with 0% in the placebo arm; however, treatment was also associated with infusion reactions and loss of response related to immunogenicity [4]. Pegloticase was approved by the US Food and Drug Administration (FDA) in 2010 for the treatment of chronic gout in adults who are refractory to conventional therapy.

Because the efficacy of pegloticase monotherapy can be limited by anti-drug antibody formation, immunomodulation strategies have been evaluated to improve treatment durability. In the MIRROR RCT, co-administration of MTX with pegloticase resulted in significantly higher response rates than pegloticase plus placebo at both 6 months (71.0% vs. 38.5%) and 12 months (60.0% vs. 30.8%), together with a markedly lower infusion reaction rate (4.2% vs. 30.6%) [5, 6]. These findings support pegloticase + MTX as the clinically relevant pegloticase-based regimen in current practice. Consistent with these data, the pegloticase FDA label was expanded in 2022 to include coadministration with MTX, and current prescribing materials describe MTX as the recommended co-therapy regimen.

An alternative uricase-based approach under investigation is NASP (formerly SEL-212). NASP combines pegadricase with nanoencapsulated sirolimus (ImmTOR) in an effort to mitigate immunogenicity while maintaining urate-lowering efficacy [7]. NASP has been evaluated in phase 2 and phase 3 clinical trials in adults with uncontrolled gout. These include the phase 2 COMPARE trial, which directly compared NASP (0.15 mg/kg ImmTOR) with pegloticase monotherapy [8], and the phase 3 DISSOLVE I and II trials, which evaluated two NASP regimens (0.15 mg/kg ImmTOR and 0.10 mg/kg ImmTOR) versus placebo [9]. The 0.15 mg/kg regimen was evaluated consistently across both COMPARE and DISSOLVE I/II, whereas the 0.10 mg/kg regimen was evaluated only in DISSOLVE I/II.

Although both pegloticase + MTX and NASP have been evaluated in clinical trials in adults with uncontrolled gout, NASP has only been compared directly with pegloticase monotherapy and has not been compared with pegloticase + MTX. This evidence gap supports the need for an ITC to evaluate the relative efficacy and safety of pegloticase + MTX versus NASP.

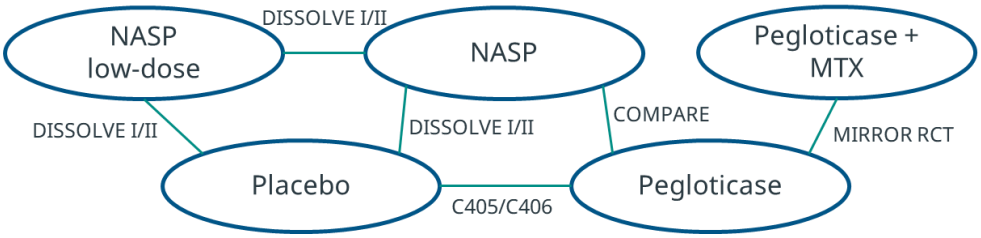
6.2 Rationale and Feasibility

No randomized controlled trial (RCT) has directly compared pegloticase + MTX with NASP in adults with uncontrolled gout. To address this evidence gap, an ITC is warranted based on the available randomized evidence from MIRROR RCT, C405/C406, COMPARE, and DISSOLVE I/II. These studies provide a connected evidence base through shared comparator arms involving pegloticase monotherapy and placebo (Figure 1).

The feasibility assessment indicated that the included studies were broadly comparable with respect to the target population, as all enrolled adults with uncontrolled gout despite prior xanthine oxidase inhibitor (XOI) therapy. However, several differences were identified that may contribute to heterogeneity, including variations in study period, geographic setting, study designs, and protocol-defined stopping rules. Notable differences include the open-label design of COMPARE, the earlier conduct of C405/C406 relative to the other studies, and variation in the application and definition of stopping rules across trials. These and other differences in study design and characteristics are discussed in detail in Section 8.1 and should be considered when interpreting ITC results.

Among the outcomes evaluated in the feasibility assessment, treatment response demonstrated the strongest cross-trial comparability and was therefore identified as the most suitable endpoint for comparative analyses. Treatment response was consistently defined across studies and supported an anchored population-adjusted comparison between MIRROR RCT and COMPARE. CCI [redacted] comparisons were limited by outcome-specific differences, including endpoint derivation, analytic methods, missing-data handling, treatment-discontinuation rules, and availability of reported data. CCI [redacted] Other outcomes, such as tophus response and gout flares, were not considered suitable for inclusion because of substantial differences in how they were defined, assessed, or reported across studies.

Figure 1. Network plot for anchored ITC



Abbreviations: MTX, methotrexate; NASP, nanoencapsulated sirolimus plus pegadricase

Note: NASP corresponds to ImmTOR 0.15 mg/kg + pegadricase 0.2 mg/kg, NASP low-dose corresponds to ImmTOR 0.1 mg/kg + pegadricase 0.2 mg/kg, Pegloticase represents pegloticase monotherapy (8 mg infusion every 2 weeks) in C405/C406 and COMPARE, and pegloticase (8 mg infusion every 2 weeks) + placebo in MIRROR RCT

6.3 Scope for Analysis

The objective of this ITC is to estimate the relative efficacy and safety of pegloticase + MTX versus NASP in adults with uncontrolled gout using evidence from RCTs.

Based on the findings of the feasibility assessment, treatment response was identified as the primary outcome for comparative evaluation. The primary analyses will evaluate treatment response during month 6 (primary timepoint), with additional supportive analyses conducted for month 3, and months 3 & 6 combined, using anchored MAICs comparing MIRROR RCT and COMPARE. Anchored MAIC was selected as the primary analytical approach because the primary analysis involves a pairwise anchored comparison between MIRROR RCT and COMPARE through the common comparator of pegloticase monotherapy. The availability of IPD from MIRROR RCT enables population adjustment to align key baseline characteristics with those reported in COMPARE and to account for potential treatment effect modifiers identified during the feasibility assessment.

Sensitivity analyses will evaluate the robustness of the treatment response findings to alternative covariate adjustment strategies, handling of missing baseline covariate data, and removal of population adjustment. An additional NMA exploratory analysis of month 6 treatment response will be conducted using an expanded evidence network incorporating DISSOLVE I/II. Given that the primary analysis focuses on the NASP regimen evaluated in COMPARE and no FDA-recommended NASP dosage has been established, this analysis is intended to provide exploratory comparisons with both high and low-dose NASP regimens evaluated in the NASP clinical development program.

CCI [redacted] These outcomes were considered exploratory because the available evidence does not support the same degree of cross-study alignment, data completeness, and analytic comparability as

treatment response. For these outcomes, NMA was selected as a pragmatic and transparent evidence synthesis approach for evaluating comparative trends across the available evidence. These analyses are intended to provide supportive contextual evidence regarding efficacy and safety, and will be conducted using outcome-specific NMA networks identified through the feasibility assessment.

7. METHODS FOR DATA COLLECTION

7.1 Study Eligibility

A systematic literature review (SLR) conducted by Amgen identified RCTs evaluating the efficacy and safety of pegloticase-based regimens and relevant comparators [10]. Four studies met the eligibility criteria and were included in the evidence base: C405/C406, MIRROR RCT, COMPARE, and DISSOLVE I/II.

The phase 3 C405/C406 trials evaluated pegloticase monotherapy, while the phase 4 MIRROR RCT evaluated pegloticase in combination with MTX. NASP was evaluated in the phase 2 COMPARE trial, which directly compared NASP (0.15 mg/kg ImmTOR + pegadricase 0.2 mg/kg) with pegloticase monotherapy, and the phase 3 DISSOLVE I and DISSOLVE II trials, which compared two NASP regimens with placebo: NASP (0.15 mg/kg ImmTOR + pegadricase 0.2 mg/kg) and NASP low-dose (0.10 mg/kg ImmTOR + pegadricase 0.2 mg/kg).

Together, these studies provide a connected evidence base through shared comparator arms involving pegloticase monotherapy and placebo, enabling indirect comparisons between pegloticase + MTX and NASP. Accordingly, all four studies were included in the feasibility assessment to evaluate network connectivity, study comparability, and the suitability of available outcomes for ITC.

Additional studies of pegloticase + MTX were identified but were not eligible for inclusion in the current ITC. AGILE (NCT04511702), MIRROR OL (NCT03635957), and FORWARD OL (NCT04762498) were non-randomized studies and therefore could not contribute to an anchored comparison. FORWARD II (NCT06229145) evaluated alternative pegloticase + MTX dosing regimens (8 mg pegloticase Q2W versus CCI mg pegloticase CCI dosing is not currently approved by FDA) but did not provide additional evidence to support the planned ITC with NASP. Accordingly, these studies were excluded from the ITC evidence base.

7.2 Patient-level Data

IPD are available for C405/C406 and MIRROR RCT, which were used to characterize baseline patient characteristics, derive relevant outcome measures, and support planned population-adjusted analyses involving pegloticase + MTX. IPD were obtained from Analysis Data Model (ADaM) datasets. Derived variables were cross-validated against the corresponding trial publications and Clinical Study Reports (CSRs), where available.

For COMPARE and DISSOLVE I/II, only aggregate data (AgD) are available; therefore, baseline characteristics and outcomes for NASP and the comparator arms were extracted from published and publicly available sources.

For NMA-based exploratory analyses, published aggregate outcome data will be used where available. Available IPD will be used to derive specific outcome inputs only when the required outcome data were not reported in public sources.

7.3 Data Management and Quality Control Procedures

Data management and statistical analyses will be conducted using R (version 4.6.1). The MAIC programming will follow the methods and example code provided in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 18 [11]. The Bayesian NMA will be implemented using R package multinma (version 0.9.1) [12].

A study-level data extraction and derivation log will be maintained for all inputs used in the ITC. This log will document the source document or dataset (e.g., publication, CSR, or IPD), analysis population, extracted and derived values, any assumptions or calculations applied, and the results of independent quality control checks.

All project deliverables will comply with industry standards and undergo rigorous internal quality control procedures. As part of this process, a replication audit of the primary ITC analyses will be conducted to confirm the reproducibility and validity of the results.

8. DATA SYNTHESIS AND STATISTICAL ANALYSIS

8.1 Summarize Individual Studies

8.1.1 Study Characteristics

All four trials included in the feasibility assessment (MIRROR RCT, C405/C406, COMPARE, and DISSOLVE I/II) were RCTs in adults with uncontrolled gout (Table 1). MIRROR RCT, C405/C406 and DISSOLVE I/II were conducted under double-blind,

placebo-controlled conditions, whereas COMPARE was an open-label trial, which may introduce potential performance and assessment bias.

Trial phase and timing differed across studies: C405/C406 was a phase 3 program conducted in 2006-2007, substantially earlier than the other trials, potentially introducing temporal heterogeneity in gout management practices and outcome assessment. In contrast, MIRROR RCT (phase 4, 2019–2022), COMPARE (phase 2, 2019–2020), and DISSOLVE I/II (phase 3, 2020–2023) were conducted over contemporaneous overlapping time periods. Most trials were conducted in North America; however, DISSOLVE II also included sites in Eastern Europe (Russia, Ukraine, Georgia, and Serbia), which may contribute to variability in patient characteristics and clinical practice patterns.

Each study evaluated at least one uricase-based therapy and included common comparator arms, forming a connected evidence network. In particular, pegloticase 8 mg intravenous (IV) biweekly (Q2W) monotherapy arm was evaluated in MIRROR RCT, C405/C406, and COMPARE, and placebo arms were included in C405/C406 and DISSOLVE I/II (Table 1), providing the anchors for the ITC. NASP and NASP low-dose were evaluated in DISSOLVE I/II, and two pegloticase dosing schedules (Q2W and Q4W) were studied in C405/C406. To align with the approved pegloticase regimen, the pegloticase Q4W arm in C405/C406 was excluded from this assessment. Throughout this document, “NASP” refers to ImmTOR 0.15 mg/kg + pegadricase 0.2 mg/kg in COMPARE and DISSOLVE I/II; “NASP low-dose” refers to ImmTOR 0.1 mg/kg + pegadricase 0.2 mg/kg in DISSOLVE I/II; “pegloticase” refers to pegloticase monotherapy (8 mg IV Q2W) in C405/C406 and COMPARE, and to pegloticase (8 mg IV Q2W) + placebo in MIRROR RCT; “pegloticase + MTX” refers to pegloticase (8 mg IV Q2W) + oral MTX (15 mg/week) in MIRROR RCT.

Across trials, eligibility criteria were broadly aligned, supporting comparability of the target population (Table 2). All studies enrolled adults with uncontrolled gout despite prior XOI therapy, ensuring a consistent definition of treatment-refractory disease. COMPARE and DISSOLVE I/II restricted enrollment to females of non-childbearing potential, whereas MIRROR RCT and C405/C406 allowed women of childbearing potential with negative pregnancy tests; given the predominantly male populations across trials, the impact of this difference is expected to be limited. C405/C406 applied a higher baseline sUA threshold (≥8 mg/dL) than the other trials (≥7 mg/dL), which may reflect inclusion of individuals with more severe hyperuricemia. In addition, MIRROR

RCT required ≥2 gout flares within 12 months, whereas COMPARE, C405/C406, and DISSOLVE I/II used a criterion of ≥3 flares within 18 months; despite the differences, these criteria are expected to identify clinically similar patient populations.

MIRROR RCT, COMPARE, and DISSOLVE I/II implemented protocol-defined stopping rules based on sUA thresholds indicative of inadequate urate-lowering response, triggering treatment discontinuation when prespecified criteria were met. However, the specific criteria varied by trial and treatment type (Table 3). For pegloticase-containing arms in MIRROR RCT and COMPARE, the stopping rules were aligned with the FDA label, where treatment is recommended to be discontinued when two consecutive sUA measurements exceed 6 mg/dL [13]. For the NASP arm in COMPARE, the stopping criteria were more stringent during early treatment, with discontinuation triggered by sUA >1 mg/dL at day 21 of treatment period 1, or >6 mg/dL at day 21 of treatment periods 2-5. In contrast, DISSOLVE I/II applied a more targeted two-stage stopping framework, requiring both: 1) demonstration of an early pharmacodynamic response (treatment period 1, 1-hour post-infusion sUA <2 mg/dL), and 2) subsequent indication of loss of response (sUA >1 mg/dL on day 21 of treatment period 1 or sUA >6 mg/dL on day 21 of treatment periods 2-5). C405/C406 did not include protocol-mandated stopping criteria based on sUA, allowing individuals to remain on therapy for the 6 months irrespective of changes in urate levels. Because treatment response requires sustained urate-lowering below the sUA threshold, individuals with an adequate and maintained response would not meet these stopping criteria. Differences in stopping-rule implementation are therefore relevant primarily for individuals with inadequate response or loss of response across studies, and should be considered when assessing the comparability of treatment-response outcomes.

Overall, the four trials enrolled broadly comparable populations of adults with uncontrolled gout and evaluated uricase-based regimens within connected comparator arms, supporting the feasibility of an anchored ITC. Nevertheless, several design and contextual differences were identified, including the open-label design of COMPARE, the earlier conduct of C405/C406, the broader geographic scope of DISSOLVE II, and variation in eligibility criteria and protocol-defined stopping rules. These differences represent potential sources of heterogeneity that cannot be fully addressed through population adjustment and should be considered when interpreting the ITC results.

Table 1. Study characteristics of MIRROR RCT, C405/C406, COMPARE, and DISSOLVE I/II

	MIRROR RCT	C405/C406	COMPARE	DISSOLVE I/II
Trial registry	NCT03994731	NCT00325195 (Two replicate trials)	NCT03905512	NCT04513366; NCT04596540 (Two replicate trials)
Phase	**Phase 4**	**Phase 3**	**Phase 2**	**Phase 3**
Publications	Botson et al., 2022 (6-month) Botson et al., 2023 (12-month)	Sundy et al., 2011	Baraf et al., 2023	No peer-reviewed publications Data available from conference abstracts and ClinicalTrials.gov
Study design	Randomized Double-blind Placebo-controlled	Randomized Double-blind Placebo-controlled	Randomized **Open-label**	Randomized Double-blind Placebo-controlled
Treatment regimens	**Pegloticase + MTX**: Pegloticase 8 mg IV Q2W (26 infusions from day 1 to week 50) + Oral MTX 15 mg/week **Pegloticase**: Pegloticase 8 mg IV Q2W (26 infusions from day 1 to week 50) + Oral placebo weekly (This study also included a 2-week MTX tolerability period and a 4-week MTX/placebo run-in period)	**Pegloticase**: Pegloticase 8 mg IV Q2W (12 infusions) **Placebo**: Placebo IV Q2W (12 infusions)	**Pegloticase**: Pegloticase 8 mg IV Q2W (12 infusions) **NASP**: ImmTOR 0.15 mg/kg + pegadricase 0.2 mg/kg IV Q4W (6 infusions)	**NASP**: ImmTOR 0.15 mg/kg + pegadricase 0.2 mg/kg IV Q4W (6 infusions) **NASP low-dose**: ImmTOR 0.1 mg/kg + pegadricase 0.2 mg/kg IV Q4W (6 infusions) **Placebo**: Placebo IV Q4W (6 infusions)
Regions	United States	United States, Canada, Mexico	United States	DISSOLVE I: United States DISSOLVE II: United States, **Russia, Ukraine, Georgia, Serbia**
Study timeframe*	Jun 2019 – Apr 2022	**Jun 2006 – Dec 2007**	May 2019 – Aug 2020	Aug 2020 – Jan 2023

Abbreviations: IV, intravenous; MTX, methotrexate; NASP, nanoencapsulated sirolimus plus pegadricase; Q2W, every 2 weeks; Q4W, every 4 weeks
*Study timeframes represent study start dates and completion dates as reported at ClinicalTrials.gov

Table 2. Selected key study inclusion criteria of MIRROR RCT, C405/C406, COMPARE, and DISSOLVE I/II

Inclusion criteria	MIRROR RCT	C405/C406	COMPARE	DISSOLVE I/II
Age	≥18 years	≥18 years	21 - 80 years	19 - 80 years
Sex	Male or female (negative pregnancy tests for women of childbearing potential)	Male or female (negative pregnancy tests for women of childbearing potential)	Male or female only of non-childbearing potential (hysterectomy or postmenopausal)	Male or female only of non-childbearing potential (hysterectomy or postmenopausal)
Hyperuricemia at screening	sUA ≥ 7 mg/dL	**sUA ≥ 8 mg/dL**	sUA ≥ 7 mg/dL	sUA ≥ 7 mg/dL
Uncontrolled disease	Failure to maintain normalization of sUA with XOI at the maximum medically appropriate dose (or XOI contraindicated)	Failure to normalize sUA after ≥3 months allopurinol at the maximum labeled dose or a lower dose based on dose-limiting toxicity or comorbidity (or contraindication)	Failure to normalize sUA and whose signs and symptoms are inadequately controlled with XOI at the medically appropriate dose (or XOI contraindicated)	Failure to normalize sUA and whose signs and symptoms are inadequately controlled with XOI at the medically appropriate dose (or XOI contraindicated)
Symptoms of gout	Defined as: • **≥ 2 gout flares within 12 months prior to screening**, OR • ≥ 1 tophus, OR • Gouty arthritis	Defined as: • ≥ 3 gout flares within 18 months prior to screening, OR • ≥ 1 tophus, OR • Gouty arthritis	Defined as: • ≥ 3 gout flares within 18 months prior to screening, OR • ≥ 1 tophus, OR • Gouty arthritis	Defined as: • ≥ 3 gout flares within 18 months prior to screening, OR • ≥ 1 tophus, OR • Gouty arthritis

Abbreviations: sUA, serum uric acid; XOI, xanthine oxidase inhibitor

Table 3. Comparison of stopping rules across trials

Study	Study treatments	Stopping rule	Action
MIRROR RCT	Pegloticase + MTX Pegloticase	• sUA > 6 mg/dL at 2 consecutive study visits (from ≥ Week 2; pre-dose)	Discontinue treatment
C405/C406	Pegloticase Placebo	• None	**No stopping rule**
COMPARE*	Pegloticase NASP	NASP arm: • sUA > 1.0 mg/dL (TP1 Day 21) or > 6.0 mg/dL (TP2-5 Day 21) Pegloticase arm: • sUA > 6.0 mg/dL at 2 consecutive pre-dose measurements	Discontinue treatment
DISSOLVE I/II*	NASP NASP low-dose Placebo	Criteria (both required): • sUA < 2.0 mg/dL (TP 1, 1-hour post-infusion), AND • sUA > 1.0 mg/dL (TP 1 Day 21) or > 6.0 mg/dL (TP 2-5, Day 21)	Discontinue treatment

Abbreviations: MTX, methotrexate; NASP, nanoencapsulated sirolimus plus pegadricase; Q4W, every 4 weeks; sUA, serum uric acid; TP, treatment period

* In COMPARE and DISSOLVE I/II, the schedule of assessments was defined by treatment period rather than calendar month. Each treatment period corresponded to 28 days and was therefore broadly comparable to one month

8.1.2 Baseline Characteristics

For the comparison of baseline characteristics, treatment arms within each trial were combined, as any potential planned ITC would be anchored and make use of all relevant arms within each study (Table 4). Comparisons focused on variables identified a priori as potential prognostic factors and/or effect modifiers. A previous ITC comparing pegloticase + MTX with placebo identified age, body weight, chronic kidney disease (CKD) status, baseline sUA, and presence of baseline tophi as key covariates that may act as both prognostic factors and effect modifiers. Additional variables, including sex, race, alcohol use, duration of disease, prior number of acute gout flares, and chronic synovitis or arthropathy, were considered potentially relevant but of lower importance.

The availability of baseline characteristics was more limited in COMPARE and DISSOLVE I/II: neither study reported alcohol use, the number of acute gout flares prior to enrollment, or chronic synovitis/arthropathy. Both studies reported BMI rather than body weight, and BMI was therefore used as a proxy. In addition, COMPARE did not report disease duration or CKD status.

Relative to MIRROR RCT, COMPARE and DISSOLVE I/II included lower proportions of females (4.1% and 3.8% vs 11.2%, respectively) and fewer individuals with baseline tophi (40.6% and 63.0% vs 75.7%). Mean BMI was higher in COMPARE than in MIRROR RCT (35.1 vs 32.7 kg/m²). Among characteristics reported for DISSOLVE I/II, individuals had a slightly shorter mean disease duration (11.8 vs 13.9 years) and a lower prevalence of CKD (23.0% vs 32.2%) than those enrolled in MIRROR RCT (Table 4).

Collectively, the patient characteristics were broadly comparable across studies, although clinically relevant imbalances were observed for several variables, most notably baseline tophi and BMI in COMPARE relative to MIRROR RCT. These differences support the use of population adjustment for the primary treatment response analyses and should be taken into account when interpreting the ITC results.

Table 4. Comparison of baseline patient characteristics: MIRROR RCT vs comparator trials

Variable	Measure	MIRROR RCT	C405/C406	ASD*	COMPARE	ASD*	DISSOLVE I/II	ASD*
Number of individuals (ITT)	N	152	128^		170		265	
Age	Mean (SD)	54.7 (12.6)	56.0 (14.5)	0.09	52.3 (10.9)	**0.20**	54.9 (10.5)	0.02
Sex - Female	n (%)	17 (11.2%)	24 (18.8%)	**0.21**	7 (4.1%)	**0.27**	10 (3.8%)	**0.28**
Race - White[#]	n (%)	105 (69.5%)	84 (65.6%)	0.08	131 (77.1%)	**0.17**	213 (81.9%)	**0.29**
BMI (kg/m^2)	Mean (SD)	32.7 (6.4)	32.7 (7.3)	0.00	35.1 (7.0)	**0.36**	33.1 (6.3)	0.06
Alcohol use	n (%)	92 (60.5%)	48 (37.5%)	**0.47**	*NR*	-	*NR*	-
Serum uric acid (mg/dL)[+]	Mean (SD)	8.9 (1.6)	10.1 (1.9)	**0.68**	8.9 (1.7)	0.00	8.6 (1.4)	**0.18**
Disease duration (year)	Mean (SD)	13.9 (10.7)	14.7 (11.3)	0.07	*NR*	-	11.8 (9.1)	**0.21**
Number of acute gout flares`	Mean (SD)	10.8 (14.2)	9.9 (12.7)	0.07	*NR*	-	*NR*	-
Chronic synovitis or arthropathy	n (%)	118 (77.6%)	76 (59.4%)	**0.40**	*NR*	-	*NR*	-
Baseline tophi	n (%)	115 (75.7%)	91 (71.1%)	**0.10**	69 (40.6%)	**0.76**	167 (63.0%)	**0.28**
Chronic kidney disease~	n (%)	49 (32.2%)	35 (27.3%)	**0.11**	*NR*	-	61 (23.0%)	**0.21**

Abbreviations: ASD, absolute standardized mean difference; BMI, body mass index; ITT, intention-to-treat; SD, standard deviation

* Absolute standardized differences (ASDs) were used to assess the imbalances in baseline characteristics between ITT population (with all arms combined within each trial) of MIRROR RCT and comparator studies

^ For C405/C406, the pegloticase q4wk arm was excluded, as it is not the approved dosage and is not included in the feasibility assessment

[#] For categorical variables, only the number of individuals with non-missing data were included in the denominator of the percentage calculation

[+] In DISSOLVE I/II, both screening and baseline serum uric acid values have been reported. Baseline values are presented here

` In C405/C406, number of acute flares in prior 18 months was reported; in MIRROR RCT, number of acute gout flares in prior year was reported

~ In C405/C406, chronic kidney disease was defined as a creatinine clearance of less than 60 mL/min calculated with the Cockcroft-Gault equation; in MIRROR RCT, stage 3 chronic kidney disease was defined as eGFR <60 ml/minute/1.73 m^2; in DISSOLVE I/II, chronic kidney disease refers to Stage 3a or 3b disease (eGFR < 60 mL/min/1.73 m^2)

8.1.3 Outcome definitions

8.1.3.1 Treatment response

Treatment response was the primary endpoint across all four included trials and was consistently defined as maintaining sUA <6 mg/dL for ≥80% of the assessment period. Month 6 response was reported in all four studies, whereas month 3 and months 3 & 6 response were reported in all studies except DISSOLVE I/II (Table 5).

The feasibility assessment identified several ITC-related considerations for treatment response analyses. C405/C406 could not be incorporated into an anchored indirect comparison because the placebo arm reported a 0% response rate for month 6 and months 3 & 6 (Table 5), rendering the corresponding relative effects inestimable. Although continuity corrections could be applied, such approaches would be expected to yield unstable estimates with substantial uncertainty and were therefore not considered appropriate for the primary analysis.

As a result of the exclusion of C405/C406, DISSOLVE I/II would only contribute primarily to comparisons involving NASP low-dose through a multi-step indirect pathway (i.e., pegloticase + MTX → pegloticase → NASP → NASP low-dose), increasing indirectness and uncertainty. DISSOLVE I/II also differed methodologically in how treatment response was derived: response status was estimated using multiple imputation when it could not be determined from available sUA assessments, whereas MIRROR RCT and COMPARE derived treatment response from observed and, where applicable, imputed sUA measurements collected during the assessment period (Table 6). Furthermore, because DISSOLVE I/II response rates were based on multiple imputation, no corresponding observed responder counts are available, and approximate event counts would need to be back-calculated from the reported response proportions and study-arm sample sizes (Table 6). Such reconstructed values may not fully preserve the uncertainty of the underlying model-based estimates, introducing further uncertainty into the expanded evidence network.

The primary analysis will focus on MIRROR RCT and COMPARE, with month 6 as the primary timepoint, consistent with the primary endpoint timing in MIRROR RCT, and month 3 and month 3 & 6 combined evaluated as additional timepoints. Although the two studies differed somewhat in their handling of missing sUA data and response derivation, these differences are expected to have a limited impact on comparability. Conceptually, individuals with evaluable sUA measurements throughout the assessment period would have response determined from observed data in both studies, while

individuals who discontinued treatment early or met protocol-defined stopping criteria would generally be classified as non-responders. Minor differences may occur for a small subset of individuals with missing sUA measurements who neither discontinued treatment nor met stopping criteria; however, these differences are unlikely to materially affect overall response estimates.

Taken together, these findings support the use of covariate-adjusted MAICs based on MIRROR RCT and COMPARE for treatment response during month 6 (primary timepoint), month 3, and months 3 & 6 combined. Given the increased indirectness and additional methodological heterogeneity associated with DISSOLVE I/II, these studies will be incorporated only in an exploratory NMA of month 6 treatment response to evaluate both NASP dose regimens within the expanded evidence network.

Table 5. Treatment response (sUA <6 mg/dL for ≥80% of the assessment period) across trials

	MIRROR RCT		C405/C406		COMPARE		DISSOLVE I/II*		
	Pegloticase + MTX	Pegloticase	Pegloticase	Placebo	NASP	Pegloticase	NASP	NASP low-dose^	Placebo
N	100	52	85	43	83	87	87	88	90
Month 3	79 (79.0%)	21 (40.4%)	44 (51.8%)	2 (4.7%)	58 (69.9%)	47 (54.0%)	*NR*	*NR*	*NR*
Month 6	71 (71.0%)	20 (38.5%)	37 (43.5%)	0 (0.0%)	45 (54.2%)	41 (47.1%)	51%	43%	8%
Months 3 & 6	70 (70.0%)	20 (38.5%)	36 (42.4%)	0 (0.0%)	44 (53.0%)	40 (46.0%)	*NR*	*NR*	*NR*

Abbreviations: MTX, methotrexate; NASP, nanoencapsulated sirolimus plus pegadricase; NR, not reported

* DISSOLVE I/II results are derived from multiple imputation; therefore, counts are not directly observable and only estimated percentages are presented

^ NASP corresponds to ImmTOR 0.15 mg/kg + pegadricase 0.2 mg/kg, NASP low-dose corresponds to ImmTOR 0.1 mg/kg + pegadricase 0.2 mg/kg

Table 6. Cross-trial comparability of treatment response (sUA <6 mg/dL for ≥80% of the assessment period)

Study	Assessment period*	Missing data handling (sUA)	Interpolation/response construction	Non-responder imputation
MIRROR RCT	Month 3 Month 6 Months 3 & 6	No imputation for sUA values[+]	The proportion of the assessment period with sUA below 6 mg/dL was estimated from available month 3, month 6, or months 3 & 6 assessments (including unscheduled visits) using interpolation between observations; ≥2 assessments from different visits required for responder classification.	Non-responder classification assigned if insufficient assessments (<2 assessments from different visits during the assessment period) or stopping rule met
C405/C406	Month 3 Month 6 Months 3 & 6	Selected missing plasma UA values imputed using baseline values[^]	Response assessed across the full assessment period using interpolated curve after application of prespecified imputation rules[^]	Non-responder classification assigned if withdrew before month 6
COMPARE	TP 3 TP 6 TP 3 & 6	Selected missing sUA values imputed using baseline values or averaging of observed prior timepoint values[^]	Response assessed across the full assessment period using interpolated curve after application of prespecified imputation rules[^]	Non-responder classification assigned if discontinuation before completion of assessment period or ULT initiation
DISSOLVE I/II	TP 6	No imputation for sUA values	The proportion of the assessment period with sUA below 6 mg/dL was estimated across TP 6 using interpolation between available assessments (including eligible unscheduled and post-TP6 assessments when needed) to derive response through TP 6 Day 28; response evaluation considered missing if assessment coverage was insufficient	Non-responder classification assigned if stopping rule, ULT initiation, study drug discontinuation due to AE, or death; Multiple imputation used for missing response evaluations

Abbreviations: AE, adverse event; sUA, serum uric acid; TP, treatment period; UA, uric acid; ULT, urate-lowering therapy

* In COMPARE and DISSOLVE I/II, the schedule of assessments was defined by treatment period rather than calendar month. Each treatment period corresponded to 28 days and was therefore broadly comparable to one month

[+] SAP specified multiple imputation (MI) to be used for missingness due to COVID-related site closure. However, the CSR reported that there was no COVID site closure-related missingness and therefore MI was not implemented.

^ Imputation rules are summarized for brevity; full details are provided in each study's statistical analysis plan

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[redacted]

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[redacted]

8.2 Effect Measures

ORs will be used as the relative effect measure for binary outcomes, including treatment response [redacted]

8.3 Obtain Estimates from Individual Studies

For MAIC analyses of treatment response, baseline characteristics and outcome data will be obtained from the IPD of MIRROR RCT and AgD of COMPARE. Values derived from the IPD of MIRROR RCT will be cross-validated against CSRs and published or publicly available aggregate summaries, where available. For COMPARE, baseline characteristics and outcomes will be extracted at the study-arm level from published and publicly available sources.

For exploratory analyses using NMA, published and publicly available aggregate outcome data will be used where available for each contributing trial. Where required outcome data is not publicly reported for a study with available IPD, the corresponding estimates will be derived from the IPD. In particular, the LS mean estimate of [redacted] for C405/C406 will be derived from the IPD using the same MMRM approach applied in MIRROR RCT (Section 8.1.3.2).

When extracting AgD, event counts and corresponding sample sizes for categorical baseline and outcome variables (e.g., baseline tophi, treatment response) will be extracted directly when reported. Where only proportions and sample sizes are reported, event counts will be back-calculated from the reported values. For continuous baseline variables, mean and standard deviation (SD) are the preferred summary statistics; where continuous variables are reported in alternative formats (e.g., median and interquartile range), mean and SD values will be derived using published method, where appropriate [14]. For [redacted], arm-level LS means for CFB and the corresponding standard errors (SE) will be extracted.

To preserve the uncertainty of the underlying estimates, directly reported values will be prioritized over derived or back-calculated values, and model-based and observed summaries will not be combined for the same outcome within a given analysis. Values derived from multiple imputation-based results (i.e., DISSOLVE I/II treatment response, for which observed responder counts are not available) will be treated with particular caution, as reconstructed event counts may not fully preserve the uncertainty of the

original model-based estimates. All derived, back-calculated, or reconstructed values will be clearly documented, and independently quality controlled by a second analyst.

8.4 Heterogeneity

Heterogeneity across the included trials was evaluated during the feasibility assessment along three dimensions: study design and conduct (Section 8.1.1), study populations (Section 8.1.2), and outcome definitions and derivation (Section 8.1.3). Clinically and methodologically relevant differences identified during this assessment are described in the corresponding sections and were used to determine the feasibility of comparative analyses for each outcome.

The validity of anchored indirect comparisons relies on the transitivity assumption that the included trials are sufficiently similar in the distribution of treatment effect modifiers (or have been adequately controlled for) such that differences in outcomes can be attributed to the treatments rather than to cross-study heterogeneity. Residual imbalance in treatment effect modifiers may bias indirect treatment comparisons, while adjustment for prognostic factors may improve the precision of estimated treatment effects. Because the network comprises a small number of trials, formal statistical assessment of between-study heterogeneity is not feasible, and comparability was therefore evaluated primarily through the qualitative and covariate-level assessments described above.

To mitigate the impact of cross-trial differences on the primary treatment response analyses, population adjustment will be applied for potential treatment effect modifiers. A previous ITC comparing pegloticase + MTX with placebo identified a comprehensive set of potential treatment effect modifiers and prognostic factors through regression analyses of IPD from C405/C406 and MIRROR RCT, supplemented by input from Amgen clinical experts (Section 8.6.4). This set was re-evaluated during the feasibility assessment and informed the selection of adjustment covariates for the population-adjusted analyses. Population adjustment can account only for effect modifiers that are measured and reported across studies; the potential for residual confounding from unmeasured or unadjusted effect modifiers, particularly variables not reported by the comparator studies, will be considered when interpreting the findings.

8.5 Missing Data

Baseline Characteristics

Missing baseline data is only relevant for analyses requiring population adjustment (i.e., the MAIC analyses of treatment response); the exploratory NMAs are unadjusted and

are therefore not affected by missing baseline covariate data. Among the studies contributing to the primary MAIC network, no missing baseline covariate data were reported by COMPARE. In MIRROR RCT, two participants had missing BMI values and one had missing race information.

To preserve the randomized intention-to-treat (ITT) population for the primary MAIC analyses, participants with missing baseline covariate data will be retained. Missing BMI values will be imputed by calculating BMI using observed body weight and the sex-specific mean height of the study population. Missing race will be grouped with the non-White/other category for analyses. Sensitivity analyses excluding participants with missing baseline covariate data will be conducted to evaluate the impact of these assumptions on the estimated treatment effects (8.6.7).

Outcomes

For treatment response, the reported outcome data in both the IPD and AgD already reflect the study-specific missing data handling approaches prespecified in the original study protocols or SAPs. As described in Section 8.1.3.1, these approaches included non-responder imputation (MIRROR RCT, C405/C406, and COMPARE) and multiple imputation (DISSOLVE I/II).

CCI [redacted]

CCI [redacted] CCI [redacted] The only exception is C405/C406, for which model-derived CCI [redacted] was not originally reported. For this study, month 6 CCI [redacted] estimates will be derived using the methodology specified in the MIRROR RCT SAP: participants without post-baseline assessments will be assigned a CFB value of 0 at the first post-baseline visit, and subsequent missing values will be handled within the MMRM framework. As discussed in section 8.1.3.2, this differs from the multiple imputation approach used in DISSOLVE I/II. COMPARE is not included in the evidence network for this outcome because it reported only a non–model-based, complete-case estimate.

8.6 Statistical Analysis

8.6.1 Primary Analysis Set

As described in Section 8.1, the primary analysis set for treatment response will consist of MIRROR RCT and COMPARE. These studies provide the basis for the covariate-adjusted MAIC analyses of treatment response during month 6 (primary timepoint),

month 3, and months 3 & 6 combined. Expanded networks incorporating C405/C406 and/or DISSOLVE I/II (in addition to MIRROR RCT and COMPARE) will be used only for exploratory analyses, and only where outcome-specific feasibility has been established. The specific evidence network applied to each analysis is summarized in Section 8.6.7.

8.6.2 Primary Outcome

The primary outcome for assessing the comparative efficacy of pegloticase + MTX versus NASP is treatment response, defined as maintaining sUA <6 mg/dL for ≥80% of the assessment period. The primary analysis will evaluate treatment response at month 6 (primary timepoint), consistent with the primary endpoint timing in MIRROR RCT, with additional supportive analyses conducted for month 3 and months 3 & 6 combined. Relative treatment effects will be expressed as ORs with 95% CIs, with NASP as the reference group.

8.6.3 Exploratory Outcomes

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[redacted]

8.6.4 Covariates

The selection of adjustment covariates was informed by a previous ITC comparing pegloticase + MTX with placebo, which identified age, body weight, CKD status, baseline sUA, and presence of baseline tophi as potential treatment effect modifiers and prognostic factors based on regression analyses of IPD from C405/C406 and MIRROR RCT, supplemented by clinical input. This set was refined based on the comparability and availability of the corresponding AgD in COMPARE, the comparator study in the primary MAIC network.

Body weight was not reported in COMPARE; BMI was therefore used as a proxy as it was consistently reported across MIRROR RCT and COMPARE. CKD status could not be included because corresponding AgD was not reported in COMPARE. Based on these considerations, together with additional clinical input, age, BMI, baseline sUA, and baseline tophi were selected as the primary adjustment covariates. These variables were considered clinically relevant potential effect modifiers and were reported consistently across MIRROR RCT and COMPARE.

Additional variables considered during the feasibility assessment included sex, race, alcohol use, duration of disease, number of acute gout flares in the prior year, and chronic synovitis or arthropathy. Of these, only sex and race were reported in both MIRROR RCT and COMPARE and will therefore be evaluated as part of sensitivity analyses assessing broader covariate adjustment. The remaining variables were not reported in COMPARE and therefore could not be incorporated into the population-adjusted analyses.

Because population adjustment can account only for effect modifiers that are measured and reported across studies, the MAIC cannot address potential imbalances in variables unavailable in the COMPARE AgD (e.g., CKD status, alcohol use, disease duration, prior flare frequency, and chronic synovitis or arthropathy) or in unmeasured effect modifiers. The potential for residual confounding will be considered when interpreting the treatment response findings.

8.6.5 Matching-Adjusted Indirect Comparisons (MAIC)

An anchored MAIC will be performed for the primary outcome (treatment response) to account for baseline population differences between trials. MAIC is a population-adjustment method that uses non-parametric re-weighting to balance baseline characteristics between trial populations and enable a valid indirect comparison [15]. In the analysis for treatment response, we will leverage IPD from MIRROR RCT and AgD from COMPARE, adjusting for the key covariates identified in Section 8.6.4 to align patient characteristics across trials.

8.6.5.1 Estimation of Weights

The MAIC will be conducted in line with EU Joint Clinical Assessment (JCA) guidance and NICE DSU TSD 18 [11, 16]. The first step in conducting the MAIC involves deriving balancing weights such that the average baseline characteristics of MIRROR RCT after re-weighting match the published aggregate-level baseline characteristics of COMPARE. The weights will be estimated using a propensity score-type logistic regression model that predicts whether a patient originated from the index trial or the comparator study as a function of the baseline covariates. The model will be estimated based on IPD from MIRROR RCT and the published summary data from COMPARE. Data for weight estimation will be taken from the total study population (intervention + placebo/comparator arms) since anchored ITC will make use of all relevant arms within each study. Specifically, the weights will be estimated by the odds calculated as $w_i = exp(\alpha + x_i'\beta)$, where x_i' is the vector of baseline variables controlled for in the analyses

and α is the intercept. In line with the NICE DSU recommendations, the β coefficients will be estimated using a method of moments and the quasi-Newton optimization Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm rather than maximum likelihood (as is usually the case), since only AgD is available for the comparator study [11].

Once the coefficients are estimated, the equation will be applied to the individuals from MIRROR RCT to calculate the individual patient weights. These weights will then be used to calculate the effective sample size (ESS) achieved as $(\sum w_i)^2/(\sum w_i^2)$ where w_i is the calculated weight for the i^{th} individual. If the populations are perfectly balanced before adjustment, all individuals would have $w_i = 1$, and the ESS would be equal to the original size of individuals in MIRROR RCT. Adjustments for population differences will assign individuals uneven weights, leading to a reduction in the ESS that is proportional to the degree of between-trial differences in the distribution of baseline covariates.

The ESS will be used as a diagnostic measure to assess the degree of overlap between the MIRROR RCT and COMPARE populations. Although no universally accepted threshold defines an adequate ESS, a substantial reduction in ESS relative to the original sample size will be interpreted as evidence of limited population overlap and reduced precision of the MAIC estimate. If the ESS is substantially reduced, the corresponding MAIC results will be considered potentially unstable and interpreted cautiously as supportive rather than definitive evidence.

The use of rescaled weights aids interpretation; a scaled weight of > 1 means that an individual carries more weight in the re-weighted sample than in the original sample, and a scaled weight of < 1 means that an individual carries less weight. The rescaled weights will be calculated by dividing each w_i by their sum $(\sum w_i)$ and then multiplying by the original sample size. The distribution of the rescaled weights will be inspected using histograms to identify influential observations. No trimming of the weights will be performed in the current analyses.

8.6.5.2 Anchored Comparison

With the weights derived from the matching procedure, outcomes will be compared between balanced trial populations using analyses that incorporate the derived weights. To perform the indirect comparison in terms of treatment response (binary outcome), the effect of treatment A (i.e., pegloticase + MTX) vs treatment B (i.e., NASP) in the comparator's study population will be estimated as follows:

$$d_{AB(AgD)} = d_{AC(AgD)} - d_{BC(AgD)}$$

$$Var(d_{AB(AgD)}) = Var(d_{AC(AgD)}) + Var(d_{BC(AgD)})$$

where $d_{AB(AgD)}$ is the logOR comparing treatment A vs B in the comparator's study population; $d_{AC(AgD)}$ is the logOR for treatment A compared to C (i.e., pegloticase) in the comparator's study population estimated from the IPD, and $d_{BC(AgD)}$ is the logOR for treatment B compared to C (i.e., pegloticase) reported by the comparator trial. $d_{AC(AgD)}$ is estimated using weighted logistic regression with a robust variance estimator to estimate $Var(d_{AC(AgD)})$. Naïve (unadjusted) comparisons will also be conducted without the MAIC weights.

8.6.5.3 Reporting of Results

Summary statistics for the baseline characteristics will be reported for MIRROR RCT before and after MAIC matching, as well as for COMPARE. Percentages will be reported for categorical variables and means will be reported for continuous variables. The ESS and the percentage of ESS compared to the original sample size will also be reported for the index trials. Although no universally accepted ESS threshold exists, the following criteria will guide interpretation: ESS ≥50% of the original sample size will be considered adequate; 25-50% will warrant cautious interpretation with close inspection of the weight distribution; and <25%, or a very small absolute ESS, will be considered indicative of limited overlap such that the adjusted estimate may be unstable or unreliable.

Estimates of the relative treatment effect comparing pegloticase + MTX and NASP (i.e., ORs) along with 95% CIs will be presented in data tables. For all analyses, NASP will be coded as the reference group. For treatment response, an OR >1 favors pegloticase + MTX and indicates that pegloticase + MTX is associated with higher odds of achieving treatment response relative to NASP.

8.6.6 Network Meta-Analysis

8.6.6.1 Bayesian NMA

NMA will serve as analytical framework for all exploratory analyses. The analysis will follow the general linear modeling approach outlined in the NICE DSU TSD 2 [17]. All analyses will be conducted in R using the multinma package, which implements Bayesian modeling via Stan [12]. For binary outcomes (treatment response CCI [redacted]), arm-level event counts and sample sizes will be used; CCI [redacted] Posterior distributions of model parameters will be estimated using Markov Chain Monte Carlo (MCMC) sampling. Four MCMC chains will be run, each with 5,000

iterations following a 2,500-iteration warm-up. Median posterior values will be reported as point estimates, and 95% credible intervals (CrIs) will be defined by the 2.5th and 97.5th percentiles of the posterior distributions.

Fixed-effect models will serve as the primary analysis for all NMAs, given the small number of studies contributing to each network (2-4 studies). Random-effects models will be explored as sensitivity analyses where convergence and model stability permit.

Vague (non-informative) priors will be used for treatment effects and study-specific intercepts:

- Treatment effects: Normal(0, 100)
- Study intercepts: Normal(0, 10)
- Between-study standard deviation (random-effects only): Half-Normal(0, 5)

Model specifications, including the choice of link function, likelihood, and effect measure, will be determined by outcome type:

- For binary outcomes (i.e., treatment response CCI), ORs will be estimated using a binomial likelihood with a logit link function
- CCI

8.6.6.2 Assessment of Model Fit

Model fit will be evaluated using the deviance information criterion (DIC), residual deviance (Dres), and the effective number of parameters (pD). The DIC will be calculated as DIC = Dres + pD. Lower DIC values indicate better model fit, with a difference of more than 5 points considered meaningful improvement in fit.

8.6.6.3 Assessment of Model Convergence

Convergence of MCMC chains will be assessed using the potential scale reduction factor (PSRF), also known as the Gelman-Rubin statistic. A PSRF value close to 1.00 indicates convergence, while values above 1.10 suggest potential convergence issues. In such cases, trace plots will be visually inspected, and additional iterations (e.g., 5,000) will be run as needed to achieve convergence.

8.6.6.4 Reporting of Results

Results from each NMA will be presented in summary tables and forest plots. For binary outcomes, relative treatment effects will be reported as ORs with 95% CrIs. For the continuous outcome, relative treatment effects will be reported as MDs with 95% CrIs.

All estimates will be presented as pegloticase + MTX relative to each comparator (pegloticase, placebo, NASP, NASP low-dose).

For treatment response, ORs >1 favor pegloticase + MTX. For CCI [redacted], ORs <1 favor pegloticase + MTX. For CCI [redacted], MDs <0 favor pegloticase + MTX and indicate greater reductions in sUA relative to the comparator.

8.6.7 Primary, Sensitivity, and Exploratory Analyses

The full list of planned analyses is summarized in Table 11.

Primary analyses

The primary analyses will evaluate treatment response during month 6 (primary timepoint), using anchored MAICs adjusting for core baseline covariates (age, BMI, baseline sUA, and baseline tophi). Additional supportive analyses will evaluate treatment response during month 3 and months 3 & 6 combined using the same anchored MAIC approach and covariate adjustment strategy. These analyses will leverage the MIRROR RCT and COMPARE network, with pegloticase monotherapy as the common comparator, to estimate the relative effect of pegloticase + MTX versus NASP.

Sensitivity analyses

Three sensitivity analyses are planned for treatment response, using the same MIRROR RCT and COMPARE network as the primary analyses. First, anchored MAICs will be repeated using an expanded covariate set that additionally adjusts for sex and race, to assess the robustness of results to broader population adjustment. Second, the primary analyses will be repeated without imputing the values for missing baseline characteristics in MIRROR RCT. Third, unadjusted NMAs will be conducted using the same MIRROR RCT and COMPARE network to assess the impact of population adjustment on the estimated treatment effects.

Exploratory analyses

CCI [redacted]

CCI



Table 11. List of planned primary, sensitivity and exploratory analyses

Analysis	Method	Covariates	Network
Treatment response, month 6 (primary timepoint) **Treatment response, month 3 / months 3 & 6 (additional timepoints)**			
Primary analysis	MAIC	Age, BMI, Baseline sUA, Baseline tophi	
Sensitivity 1	MAIC	Age, BMI, Baseline sUA, Baseline tophi, Sex, Race	
Sensitivity 2	MAIC	Age, BMI, Baseline sUA, Baseline tophi (excluding participants with missing baseline covariate data)	
Sensitivity 3	NMA	No adjustment	

CCI

[redacted]

Abbreviations: BMI; body mass index; MAIC, matching-adjusted indirect comparison; MTX, methotrexate; NASP, nanoencapsulated sirolimus plus pegadricase; NMA, network meta-analysis; NR, not reported; SAE, serious adverse event; sUA, serum uric acid; TEAE, treatment-emergent adverse event

CCI

[redacted]

9. STUDY LIMITATIONS

This ITC is subject to several limitations related to the available evidence and methodology. First, although the evidence network is anchored through common comparators (pegloticase monotherapy and placebo), the indirect comparisons rely on the assumption of transitivity. Transitivity assumes that the included trials are sufficiently comparable in populations, design, and outcome definitions such that differences in results can be attributed to treatments rather than study heterogeneity. In practice, the trials do show some differences in design and context, for example, the open-label design of COMPARE vs double-blind designs in the other trials, varying trial periods (with C405/C406 conducted over a decade earlier than the others), and different geographic scopes (DISSOLVE II included Eastern Europe). These differences are potential sources of heterogeneity that cannot be fully adjusted and may affect the comparability of results across studies. In addition, the small number of trials in the network further limits the ability to estimate and account for between-study heterogeneity.

Second, ITC can leverage the IPD from pegloticase trials (MIRROR RCT and C405/C406) with AgD from NASP trials (COMPARE, DISSOLVE I/II). The availability of IPD has enabled adjustment for key baseline covariates (i.e., age, BMI, baseline sUA, baseline tophi) to mitigate known differences between certain trials. However, since only published AgD is available for the NASP trials, any unmeasured or unreported differences in patient characteristics (e.g., CKD, prior flare frequency, disease duration, or other unknown effect modifiers) cannot be adjusted for, leaving risk of residual confounding. Furthermore, the ESS reduction inherent to the MAIC re-weighting process (especially given the moderate differences in baseline characteristics observed) might reduce statistical precision of the adjusted analyses. The results of the covariate-adjusted MAIC for treatment response outcome are therefore reliant on the assumption that all major effect modifiers have been adjusted; any unobserved differences between trials could still bias the results despite the adjustments.

Third, there are limitations specific to certain outcomes, which have been included for exploratory analysis rather than primary inference. The treatment response endpoint was selected as the primary outcome specifically because it is consistently defined and reported across all trials and demonstrates a connected network through common comparators. However, MIRROR RCT and COMPARE had minor differences in their handling of missing sUA data and response derivation. These differences are expected

to apply only to a small subset of individuals, such as those with missing sUA measurements who neither discontinued treatment nor met protocol-defined stopping criteria, and are therefore unlikely to materially affect the overall treatment response estimates. C405/C406 could not be included in the network due to a zero responder rate in its placebo arm (precluding an anchored relative effect estimate); by excluding this older trial, the base-case analysis focuses on the most relevant and comparable evidence (MIRROR RCT and COMPARE). CCI



Lastly, the results of this ITC primarily reflect adults with severe, uncontrolled gout - the intended target population for both pegloticase + MTX and NASP. This focus on refractory disease supports internal validity but limits generalizability beyond adults with similarly severe gout. Regional factors (e.g., all trials predominately enrolled patients in North America) and temporal differences (e.g., C405/C406 conducted in 2006-2007 vs other trials conducted after 2019) may further affect external validity by reflecting variations in clinical practice patterns and patient demographics. The MAIC approach aligns the MIRROR RCT population to that of COMPARE, such that the primary estimates reflect treatment effects in a weighted, trial-matched population rather than a broader real-world population. In addition, because the regimen under evaluation is pegloticase + MTX and the underlying IPD are derived from MIRROR RCT, the primary MAIC estimate is most applicable to patients for whom MTX co-therapy is clinically appropriate and tolerated, consistent with the population enrolled in MIRROR RCT. As a result, the MAIC-adjusted findings are not intended to be generalizable beyond adults with characteristics similar to those observed in COMPARE and for whom MTX co-therapy is appropriate. Exploratory analyses based on NMA are further limited by the small number of studies contributing to the networks, restricting the range of patient populations and clinical settings represented.

10. ETHICAL AND REGULATORY CONSIDERATIONS

This study is a secondary analysis of previously collected clinical trial data and published or publicly available aggregate evidence. There will be no prospective enrollment, direct subject contact, or collection of additional subject-level data. The analyses will be conducted using existing de-identified study data where IPD are available, and published or publicly available aggregate data where IPD are not available. Therefore, additional institutional review board/ethics committee approval and informed consent are not required for this study.

10.1 Adverse Events

Reporting of individual AE, product complaints (PCs), and other safety findings are not applicable for SLR and ITC, which involve published literature sources, as the safety data from the studies identified will have been previously reported to regulatory agencies, institutional review boards, and ethics committees in accordance with local regulations and routine pharmacovigilance practices.

10.2 Subject Confidentiality

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omit subject identification. Any publications and reports will not include subject identifiers.

11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Study Amendments and Study Termination

Amendments to the study protocol must be made only with prior written approval of Amgen and IQVIA. Study termination will be governed by the contractual agreement between IQVIA and Amgen.

11.2 Study Documentation and Archive

Retention of study documents will be governed by the contractual agreement between Amgen and IQVIA and will be maintained pursuant to Amgen’s records retention schedule.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Publication Plan

The study results will be submitted for publication to a peer-reviewed scientific journal and/or to a scientific congress/conference. Publications resulting from this study will comply with recognized ethical standards concerning publications and authorship, as described below.

Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

1. When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

2. Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.

3. All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

4. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review.

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