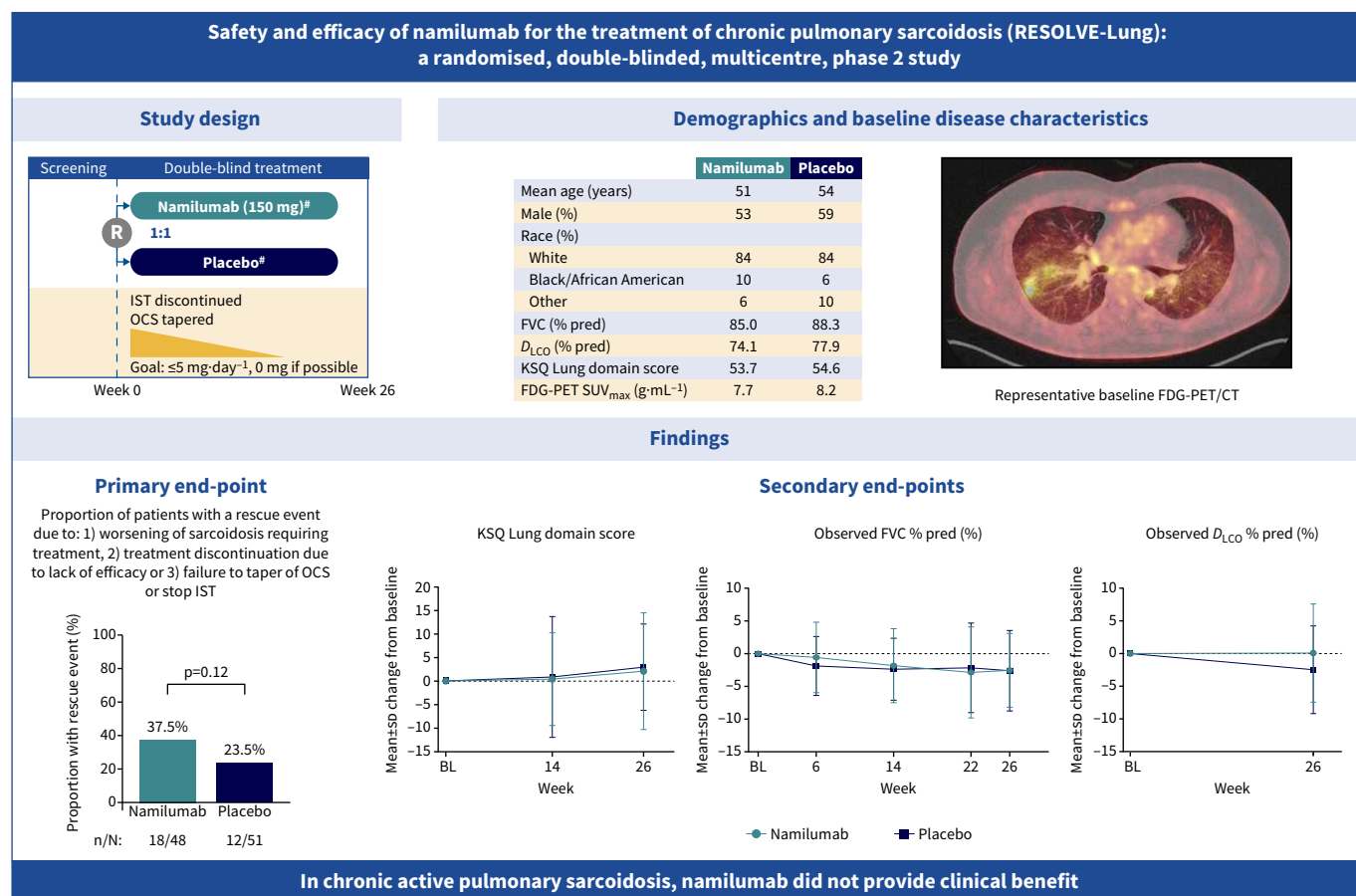


Safety and efficacy of namilumab for the treatment of chronic pulmonary sarcoidosis (RESOLVE-Lung): a randomised, double-blinded, multicentre, phase 2 study

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GRAPHICAL ABSTRACT Overview of the study. #: once every 4 weeks, subcutaneously. R: randomisation; IST: immunosuppressive therapies; OCS: oral corticosteroids; FVC: forced vital capacity; D_{LCO} : diffusing capacity of the lung for carbon monoxide; KSQ: King's Sarcoidosis Questionnaire; FDG-PET: ¹⁸F-fluorodeoxyglucose positron emission tomography; SUV_{max} : maximum standardised uptake value; CT: computed tomography; BL: baseline (in x-axis labels).



Safety and efficacy of namilumab for the treatment of chronic pulmonary sarcoidosis (RESOLVE-Lung): a randomised, double-blinded, multicentre, phase 2 study

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Shareable abstract (@ERSpublications)

Namilumab, an anti-GM-CSF antibody, was not efficacious in chronic pulmonary sarcoidosis, yet its novel design and findings may help guide future end-point selection and trial design for new sarcoidosis therapies. <https://bit.ly/49Ouglj>

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Abstract

Background Treatment options for chronic pulmonary sarcoidosis are limited in efficacy and by tolerability concerns. Namilumab, an investigational humanised monoclonal antibody inhibiting granulocyte-macrophage colony-stimulating factor, was hypothesised to downregulate the granulomatous response in pulmonary sarcoidosis.

Methods RESOLVE-Lung was a double-blind, placebo-controlled trial in participants with chronic active pulmonary sarcoidosis on oral corticosteroids (OCS) and/or immunosuppressive therapies (IST). Participants were randomised (1:1) to receive 150 mg namilumab or placebo *via* subcutaneous injection every 4 weeks and were required to stop IST and/or taper OCS. End-points were assessed at week 26. The primary end-point was the proportion of participants with a rescue event, such as disease worsening necessitating treatment. Secondary end-points included safety, lung function assessments and corticosteroid burden. The trial was registered at ClinicalTrials.gov (NCT05314517).

Results Of 209 participants screened, 107 were randomised to receive namilumab (n=53) or placebo (n=54). The proportion of participants with a rescue event was higher for the namilumab group (37.5%) compared with the placebo group (23.5%) (stratified difference 13.6 (90% CI -1.5–28.7) percentage points; p=0.12). The least squares (LS) mean change from baseline in forced vital capacity % predicted was -3.3 (90% CI -5.1–-1.5) percentage points for namilumab and -2.9 (90% CI -4.5–-1.3) percentage points for placebo (LS mean difference -0.4 (90% CI -2.7–2.0) percentage points). The proportion of participants successfully achieving OCS taper was 53.3% for namilumab and 76.9% for placebo (difference -19.4 (90% CI -47.5–8.7) percentage points). Treatment-emergent adverse events were reported in 94% in both groups, most being mild or moderate in severity.

Conclusion In participants with chronic active pulmonary sarcoidosis, namilumab did not provide clinical benefit.

Introduction

Sarcoidosis is an inflammatory disorder characterised by the presence of non-necrotising granulomas of unknown aetiology. Typically, this condition affects the lungs and lymphatic tissues (known as pulmonary sarcoidosis), but less frequently can affect other organ systems. Pulmonary sarcoidosis usually presents with symptoms such as dyspnoea, cough, fatigue and pain [1, 2]. While it may spontaneously resolve in a number of cases, patients with chronic, active disease can experience progression to lung dysfunction, fibrosis and, eventually, respiratory failure [1]. Treatments remain limited and aim to relieve symptoms through suppressing inflammation and modulating the immune system, rather than specifically targeting underlying disease pathology. Currently, the recommended treatments for pulmonary sarcoidosis include oral corticosteroids (OCS), *e.g.* prednisone, and off-label immunosuppressive therapies (IST), *e.g.* methotrexate [3]. However, these options often have limited efficacy and can be associated with significant side-effects [2]. The development of new, effective and well-tolerated treatments is critical to improve patient care.

To date, there have been few large, randomised trials or prospective cohort studies conducted in patients with pulmonary sarcoidosis; clinical data are mainly derived from case reports and retrospective therapeutic series. This limits our ability to adequately understand and classify patient population phenotypes in this clinically heterogeneous disorder, as well as the natural history of these phenotypes, and the end-points responsive to change within these different patient groups. This reality has not only limited our advancements in understanding sarcoidosis, but inadvertently reduces the focus on and ability to develop novel therapies to treat the disease.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) is an important activator of the innate and adaptive immune system, and is involved in several inflammatory and autoimmune processes, including granuloma formation [4, 5]. Pre-clinical data suggest an important role for GM-CSF in sarcoidosis through stimulating activation of macrophages in the target tissue, mobilisation of monocytes and macrophages from bone marrow, and facilitating cross-talk with inflammatory T-cells [6, 7]. In line with these observations, clinical studies evaluating anti-GM-CSF monoclonal antibodies have also demonstrated efficacy, and were well tolerated, in patients with rheumatoid arthritis, suggesting this approach may offer clinical benefit in other inflammatory conditions, including pulmonary sarcoidosis [8].

Further, upregulation of GM-CSF has been observed in lesioned tissues from patients with sarcoidosis [9], and GM-CSF levels have also been shown to be elevated in the serum [9], skin [4], lungs [10, 11] and bronchoalveolar fluid [12] of these patients. Notably, this increased expression of GM-CSF is also positively correlated with disease activity [12], suggesting that GM-CSF could be a disease driver and therefore represent a potential therapeutic target in patients with pulmonary sarcoidosis.

Namylumab is a potent, human, investigational anti-GM-CSF monoclonal antibody (immunoglobulin (G1κ)) which has previously demonstrated activity and tolerability in clinical studies across a range of indications, including rheumatoid arthritis [8] and COVID-19 [13].

Here, we report the results from RESOLVE-Lung, which assessed the safety and efficacy of namylumab over a 26-week period in patients with chronic active pulmonary sarcoidosis, utilising a unique study design novel to sarcoidosis clinical studies.

Methods

Study design and participants

RESOLVE-Lung was a randomised, double-blind, placebo-controlled, multicentre trial assessing namylumab *versus* placebo over 26 weeks in patients with chronic active pulmonary sarcoidosis. The trial was conducted in 42 locations across Europe, Turkey and the USA (supplementary table S1). Participants were randomised 1:1 to receive either namylumab 150 mg or placebo, using an interactive response technology system. At the randomisation visit, participants were required to stop any IST treatment (including methotrexate, mycophenolate mofetil, azathioprine and hydroxychloroquine) and start tapering OCS treatment. Those with a baseline OCS dose of >5 to ≤ 10 mg·day⁻¹ prednisone (or equivalent) were required to reduce the dose to ≤ 5 mg·day⁻¹ by the end of week 6, and for those with baseline OCS dose >10 mg·day⁻¹ prednisone (or equivalent), the taper goal of ≤ 5 mg·day⁻¹ was to be achieved by the end of week 10. The tapering schedule and goal of 5 mg·day⁻¹ was designed to minimise the potential of adrenal insufficiency. At the investigator's discretion, the taper could continue below 5 mg·day⁻¹, based on tolerability. After randomisation, study drug (namylumab 150 mg or placebo) was administered *via* subcutaneous injection on day 1 (baseline visit (week 0)), week 2 and then at every 4 weeks (seven doses). Participants who completed the 26-week double-blind treatment period were eligible to continue to an

open-label extension in which participants received namilumab 150 mg every 4 weeks (seven doses), regardless of treatment in the double-blind period.

Written informed consent was obtained from all patients participating in the study. Participants were ≥ 18 years of age, with a ≥ 6 -month biopsy-proven history of pulmonary sarcoidosis, a high-resolution computed tomography (HRCT) scan at screening consistent with pulmonary sarcoidosis of the lung parenchyma and $\leq 20\%$ estimated percentage of fibrosis by a central reader (an experienced thoracic radiologist). Evidence of symptomatic, active, pulmonary sarcoidosis must have been present, defined as: a score of ≥ 2 on the Medical Research Council Dyspnoea scale, while currently on OCS, IST or a combination of both, or documentation that they have taken OCS or IST in the past 2 years for pulmonary sarcoidosis and stopped them for tolerance, ineffectiveness or refusal reasons, and one or more of the following: 1) a screening ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) scan showing pulmonary parenchymal uptake consistent with active sarcoidosis, with a maximum standardised uptake value (SUV_{max}) ≥ 3 ; 2) worsening of pulmonary sarcoidosis as evident from a decline in lung function or imaging of the chest in the past 12 months as documented in the patient medical records; 3) tapering of OCS and/or IST resulted in an increase in pulmonary sarcoidosis symptoms, signs or other measures of activity requiring an increase in dose of OCS and/or IST. Forced vital capacity (FVC) $\geq 50\%$ predicted and haemoglobin-corrected diffusing capacity of the lung for carbon monoxide (D_{LCO}) $\geq 40\%$ predicted at screening were also required. Participants with extrapulmonary sarcoidosis, such as cardiac sarcoidosis or neuro-sarcoidosis, requiring continued treatment were excluded. Full inclusion and exclusion details are listed in supplementary appendix S1.0.

RESOLVE-Lung was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice Guideline, and all other applicable laws and regulations. All relevant documents were approved by the respective institutional review board or ethics committee and health authorities. The study was reviewed and approved by the WCG Institutional Review Board (#20220115). An independent data monitoring committee provided oversight. The study was registered at ClinicalTrials.gov (NCT05314517) and at EU Clinical Trials (2024-511115-25-00), and has been completed.

Procedures

Efficacy assessments included pulmonary function tests (PFTs), patient-reported outcomes (PROs) and biomarker analysis. PFTs were performed at weeks 0, 6, 14, 22 and 26, and included spirometry (forced expiratory volume in 1 s (FEV_1) (L), FEV_1 % pred, FVC (L), FVC % pred and FEV_1/FVC) and haemoglobin-adjusted D_{LCO} % pred testing (weeks 0 and 26) [14]. Spirometry was performed using standardised equipment and software. D_{LCO} testing was performed using the site's equipment. All PFTs were electronically transmitted for central overread of quality. PROs were collected at weeks 0, 14 and 26, and included the King's Sarcoidosis Questionnaire (KSQ; increase=improvement), a multi-organ health status measure consisting of five modules (General Health Status, Lung, Medications, Skin and Eye) [15]. Additional questionnaires included the St George's Respiratory Questionnaire (SGRQ; increase=improvement) [16] and Leicester Cough Questionnaire (LCQ; increase=improvement) [17]. Blood for the analysis of circulating disease-specific, pathway-specific and other inflammatory biomarkers was collected throughout the double-blind period and analysed using the Olink Explore platform (<https://olink.com>). High-sensitivity C-reactive protein (hsCRP) was analysed using an immunochemiluminometric assay (Labcorp, Burlington, NC, USA) and serum amyloid A (SAA) was analysed using an electrochemiluminescence assay (Labcorp). Safety assessments included vital signs, physical examinations, ECGs, clinical laboratory measurements, adverse event (AE) reporting and anti-drug antibody to namilumab.

End-points

The primary end-point was the proportion of patients with a rescue event during the double-blind period. Rescue events were defined as a clinically significant worsening of pulmonary or extrapulmonary sarcoidosis requiring rescue treatment, as determined by the investigator, with prednisone (or equivalent), start of an IST or use of prohibited medication. In addition, treatment discontinuation due to lack of efficacy and failure to comply with specific protocol-defined requirements for use of concomitant medications, including failure to taper of OCS, were also considered rescue events. All rescue events were reviewed by a blinded internal committee for data completeness and accuracy, and if needed (for treatment discontinuation due to lack of efficacy) for adjudication. Secondary end-points included time to first rescue event, the proportion of patients achieving OCS taper without a rescue event, change from baseline in FVC % pred and KSQ Lung domain (logit score) at week 26, as well as safety and tolerability. Exploratory end-points included D_{LCO} % pred corticosteroid-free days and other OCS use-related end-points, and PROs

such as such KSQ subscales, SGRQ and LCQ. Additionally, population pharmacokinetic and exposure–response relationships for namilumab as well as change from baseline in prespecified exploratory biomarkers at week 26 were assessed. The prespecified disease-specific biomarkers included interferon- γ , interleukin (IL)-2 receptor A, IL-6, IL-15, CXCL10, SAA and tumour necrosis factor- α . The prespecified pathway-specific biomarkers included IL-1 β , IL-4, IL-27 and CXCL9.

Statistical analysis

RESOLVE-Lung was planned for around 50 patients per arm. Assuming a placebo rescue event rate of 40% and dropout rate of 10%, 90 evaluable patients (45 per arm) provided ~80% power to detect an absolute treatment difference of 25 percentage points at a two-sided significance level of 0.10, based on Fisher's exact test [18]. The between-group comparison for the primary efficacy end-point was assessed using a Cochran–Mantel–Haenszel test, stratified by use of IST at baseline. The difference in proportions between treatment groups and the 90% confidence intervals were calculated using the stratified Miettinen–Nurminen method.

No formal interim analyses were planned for this study. The first database lock and subsequent analyses were conducted at the end of the double-blind period, as outlined in the protocol and Statistical Analysis Plan (<https://clinicaltrials.gov/study/NCT05314517>).

Details of the statistical analyses performed in this study have been reported previously [19]. Briefly, efficacy analyses were conducted in the modified intent-to-treat population (mITT), which included all randomised patients who received any quantity of double-blind study treatment. Participants with study quality events (potential accidental unblinding of study treatment assignment) were excluded from the mITT population, as prespecified in the SAP. These patients were still included in the sensitivity analysis and in the safety analysis.

Participants who prematurely discontinued treatment during the double-blind period without a rescue event per adjudication were excluded from the primary analysis (assumed missing at random). Analyses of safety data were conducted in the safety population, defined as all randomised patients who received any amount of study drug. Details in relation to missing data sensitivity are presented in supplementary appendix S2.0.

Results

Study disposition and baseline characteristics

Between 4 August 2022 and 28 March 2024, 209 participants were screened. The data cut-off was 17 October 2024 and data were unblinded, as planned, on 13 November 2024, following completion of the 26-week double-blind period.

Overall, 107 participants were randomised 1:1 to receive namilumab (n=53) or placebo (n=54). Reasons for screening failures are summarised in supplementary table S2. The most common reasons for screen failure were lack of abnormalities on HRCT consistent with pulmonary parenchymal disease, lack of evidence of active, symptomatic disease and not meeting lung function criteria. One participant in the namilumab group was not dosed, resulting in 52 participants in the namilumab group and 54 participants in the placebo group in the safety population. In the mITT population, after excluding six participants due to study quality events, there were 49 participants in the namilumab group and 51 participants in the placebo group (figure 1).

Overall, 56% of participants were male and the mean age was 53 years (range 26–79 years) (table 1). Baseline characteristics were comparable between the namilumab and placebo groups, with three exceptions: the proportion of patients on OCS was higher in the namilumab group (61% (30/49)) than in the placebo group (49% (25/51)), the observed duration of the disease was longer in the namilumab group (mean 9.1 years (range 1–36 years)) compared with the placebo group (mean 5.4 years (range 0–22 years)) and medical history of extrapulmonary sarcoidosis was more common in the namilumab group, including skin (24.5% versus 5.9%), lymph (14.3% versus 7.8%) and ocular (10.2% versus 0%) sarcoidosis (table 1).

Primary end-point

The proportion of participants with a rescue event at week 26 was 37.5% (18/48) in the namilumab group and 23.5% (12/51) in the placebo group (stratified difference 13.6 (90% CI –1.5–28.7) percentage points; p=0.12) (figure 2).

When assessed by type of rescue event, the number of participants with rescue events at week 26 due to worsening of sarcoidosis as assessed by the investigator was similar between groups (20.8% (10/48) for

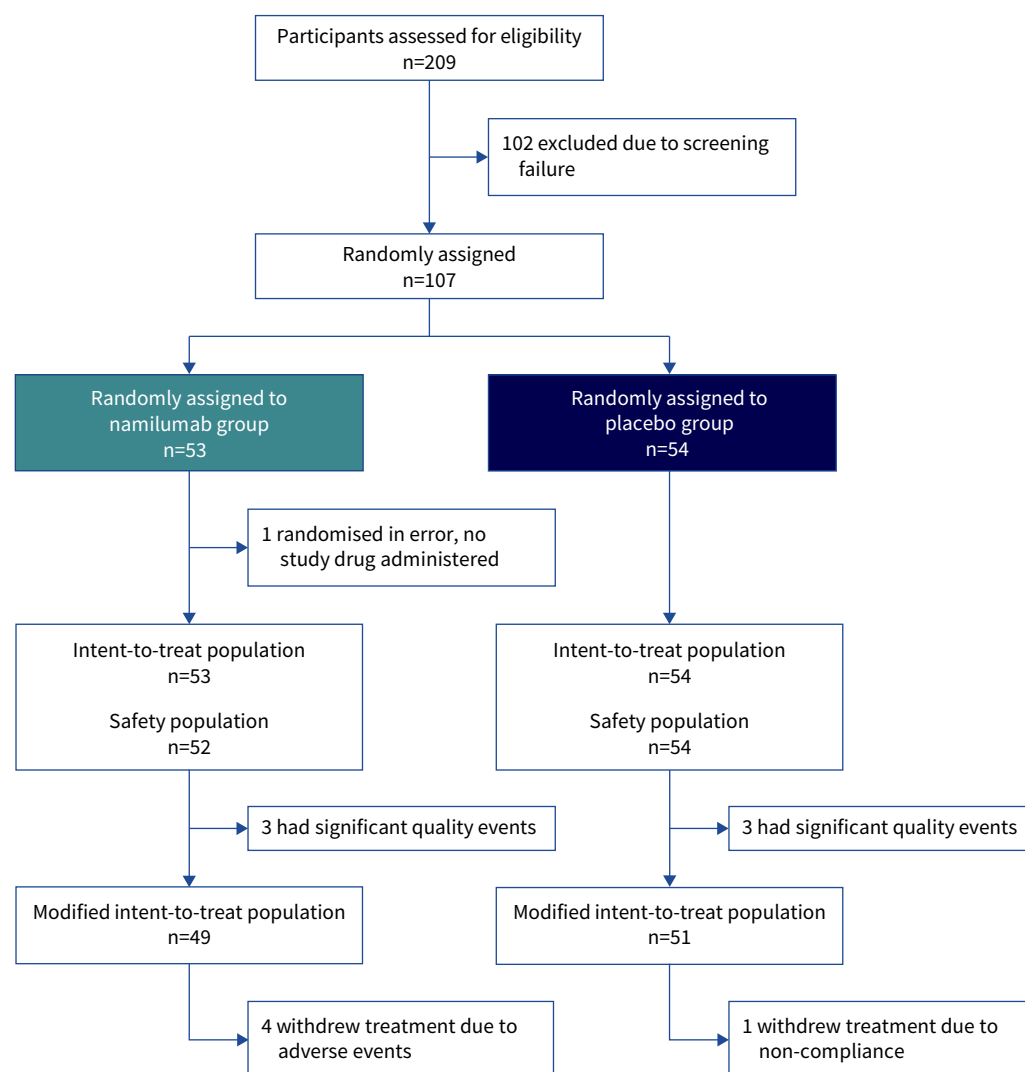


FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) diagram for RESOLVE-Lung. Reasons for screen failures are provided in supplementary table S2. Reasons for treatment discontinuations are provided in supplementary table S5. One participant who was randomised to the namilumab group did not receive study drug and thus was excluded from the safety population.

namilumab compared with 23.5% (12/51) for placebo) (supplementary figure S1). In the namilumab group, 10 participants had a rescue event due to worsening of sarcoidosis as assessed by the investigator: six due to pulmonary sarcoidosis, two due to extrapulmonary sarcoidosis, and two due to both extrapulmonary and pulmonary sarcoidosis. In the placebo group, 12 participants had a rescue event due to worsening of sarcoidosis: 11 due to pulmonary sarcoidosis and one due to extrapulmonary sarcoidosis. Further, numerically more rescue events due to failure to comply with specific protocol-defined requirements for use of concomitant medications were observed in the namilumab group compared with the placebo group (14.3% (7/49) *versus* 0.0%) (supplementary figure S1). In a sensitivity analysis including all six participants with a study quality event, the proportion of participants with a rescue event at week 26 was 37.3% (19/51) for the namilumab group and 25.9% (14/54) for the placebo group (stratified difference 11.1 (90% CI −3.7–25.9) percentage points).

In a subgroup analysis considering IST use at baseline, the proportion of participants with rescue events at week 26 was higher for the namilumab group compared with the placebo group, whether they were using IST at baseline (33.3% (6/18) for namilumab and 23.5% (4/17) for placebo; difference 9.2 (90% CI −15.9–34.2) percentage points) or not (40.0% (12/30) for namilumab and 23.5% (8/34) for placebo; difference 16.1 (90% CI −2.8–35.0) percentage points). In subgroup analysis for participants using OCS at

TABLE 1 Participant demographics and baseline disease characteristics

	Namimumab (n=49)	Placebo (n=51)	Total (n=100)
Age (years)	51.4±12.2	54.3±10.4	52.9±11.4
Range	26–79	34–72	26–79
Male[#]	26 (53)	30 (59)	56 (56)
Race[¶]			
White	41 (84)	43 (84)	84 (84)
Black or African American	5 (10)	3 (6)	8 (8)
Other	3 (6)	5 (10)	8 (8)
Duration of disease (years)	9.1±8.6	5.4±5.1	7.2±7.2
Range	1–36	0–22	0–36
Prior medication for pulmonary sarcoidosis	48 (98)	49 (96)	97 (97)
FVC % pred	85.0±15.9	88.3±16.2	86.7±16.1
FEV₁ % pred	74.7±14.4	73.6±18.5	74.2±16.5
FEV₁/FVC ratio	0.7±0.1	0.7±0.1	0.7±0.1
D_{LCO} % pred	74.1±15.0	77.9±15.2	76.0±15.1
FDG-PET SUV_{max} (g·mL⁻¹)	7.7±4.8	8.2±4.3	8.0±4.5
KSQ Lung score	53.7±9.38	54.6±13.93	54.2±11.87
KSQ General Health Status score	56.8±12.72	56.0±10.28	56.4±11.48
LCQ Total score	16.1±4.22	16.5±4.33	16.3±4.26
SGRQ Total score	44.9±18.45	40.2±18.74	42.5±18.65
OCS⁺			
Yes	30 (61)	25 (49)	55 (55)
≤5 mg	15 (31)	12 (24)	27 (27)
>5 mg	15 (31)	13 (25)	28 (28)
No	19 (39)	26 (51)	45 (45)
OCS dose[§] (mg·day⁻¹)	9.2±7.1	8.1±5.0	8.7±6.2
IST use			
Yes	19 (39)	17 (33)	36 (36)
No	30 (61)	34 (67)	64 (64)
Use of OCS and IST			
OCS alone	20 (41)	17 (33)	37 (37)
OCS and IST	10 (20)	8 (16)	18 (18)
IST alone	9 (18)	9 (18)	18 (18)
No OCS or IST	10 (20)	17 (33)	27 (27)
Extrapulmonary sarcoidosis			
Skin	12 (25)	3 (6)	15 (15)
Lymph	7 (14)	4 (8)	11 (11)
Spleen	5 (10)	3 (6)	8 (8)
Bone	3 (6)	3 (6)	6 (6)
Eyes	5 (10)	0	5 (5)
Liver	3 (6)	1 (2)	4 (4)
Joint and muscle	2 (4)	0	2 (2)
Parotid	0	1 (2)	1 (1)

Data are presented as mean±SD or n (%), unless otherwise stated. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide (corrected for haemoglobin); FDG-PET: ¹⁸F-fluorodeoxyglucose positron emission tomography; SUV_{max}: maximum standardised uptake value; KSQ: King's Sarcoidosis Questionnaire; LCQ: Leicester Cough Questionnaire; SGRQ: St George's Respiratory Questionnaire; OCS: oral corticosteroids; IST: immunosuppressive therapies. [#]: data are reported as sex at birth and were self-reported by participants; [¶]: as reported by participants; ⁺: prednisolone equivalent; [§]: mean dose for those participants receiving OCS at baseline.

baseline, the proportion of participants with rescue events at week 26 in the namilumab group was higher than in the placebo group (46.7% (14/30) *versus* 24.0% (6/25); difference 22.7 percentage points). In patients not using OCS at baseline, the proportion of participants with rescue events was similar between groups (22.2% (4/18) for namilumab and 23.1% (6/26) for placebo; difference −0.85 percentage points) (supplementary figure S2).

Overall, when analysed by baseline treatment regimen (OCS alone, OCS and IST, IST alone, or no OCS or IST), the proportion of participants with rescue events at week 26 was generally consistent with the overall

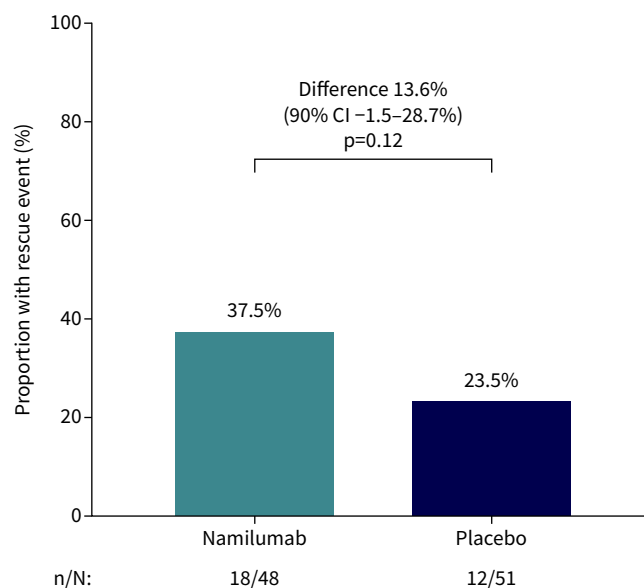


FIGURE 2 Primary end-point: proportion of participants with a rescue event. Higher proportion of rescue events indicates a worse outcome. It should be noted that one participant in the namilumab arm prematurely discontinued treatment without a rescue event per adjudication and was excluded from the primary analysis (assumed missing at random).

trial population (supplementary figure S3). Subgroup analyses of rescue events by baseline PET SUV_{max} (median <7.0 or ≥7.0), FVC % pred (<80% or ≥80%), *D*_{LCO} % pred (<80% or ≥80%) and KSQ Lung domain score (median <52.6 or ≥52.6) were also consistent with the overall trial population (supplementary figure S4).

Secondary and exploratory end-points

For participants who had a rescue event, the median (interquartile range (IQR)) time to first rescue event was 11.0 (1.0–26.6) weeks for namilumab and 12.9 (3.0–22.1) weeks for placebo (hazard ratio (HR) 1.7, 90% CI 0.9–3.2) (figure 3a). In participants using OCS >5 mg·day⁻¹ at baseline, the proportion of participants successfully achieving OCS taper without a rescue event at week 26 was 53.3% (8/15) for namilumab and 76.9% (10/13) for placebo (difference -19.4 (90% CI -47.5–8.7) percentage points) (figure 3b).

Exploratory end-points related to OCS use were consistent with primary and secondary outcomes; the mean±SD proportion of OCS-free days at week 26 was 52.8±40.1% for namilumab and 61.9±39.0% for placebo (supplementary figure S5a). The mean±SD OCS dose for any participants who used OCS during the study (including those who started OCS after randomisation) while being on OCS was 8.7±8.2 mg·day⁻¹ for namilumab and 7.1±4.9 mg·day⁻¹ for placebo.

Pulmonary function end-points

There were no significant differences in pulmonary function based on the secondary end-point of FVC % pred and exploratory end-point of *D*_{LCO} % pred between the namilumab and placebo groups at week 26. The least squares (LS) mean change from baseline to week 26 in FVC % pred was -3.3 (90% CI -5.1–-1.5) percentage points for namilumab and -2.9 (90% CI -4.5–-1.3) percentage points for placebo (LS mean difference -0.4 (90% CI -2.7–2.0) percentage points) (figure 3c). *Post hoc* analysis indicated a mean±SD increase of 5.0±7.8% in observed FVC % pred in participants receiving rescue treatment from the last observed data-point before initiation of rescue treatment to the last observed data-point for the 3 months after initiation of rescue treatment until week 26 (supplementary table S3). The LS mean change from baseline to week 26 in *D*_{LCO} % pred was 0.1 (90% CI -2.4–2.6) percentage points for namilumab and -2.3 (90% CI -4.4–-0.3) percentage points for placebo (LS mean difference 2.5 (90% CI -0.7–5.6) percentage points) (figure 3d).

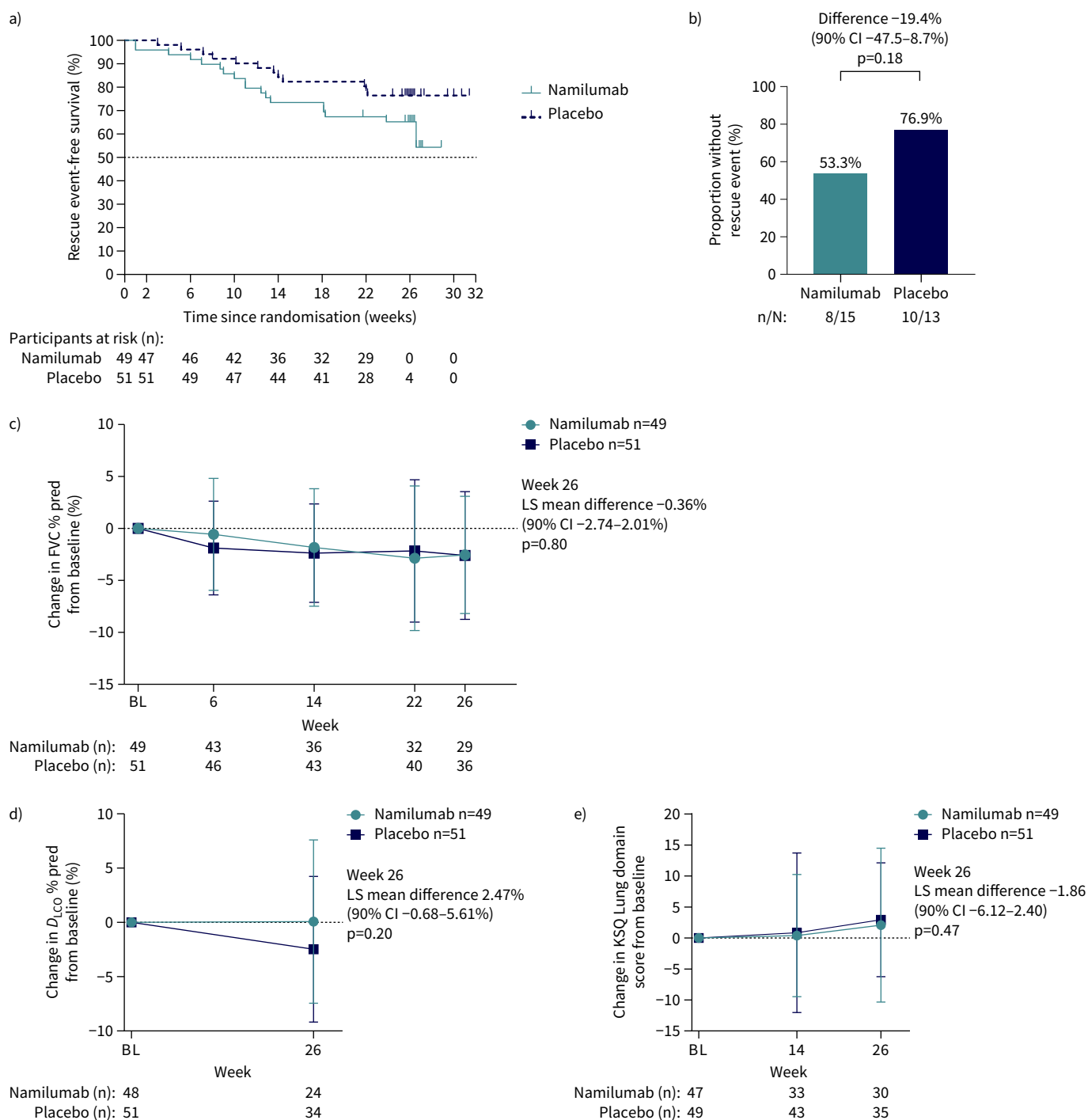


FIGURE 3 Secondary and exploratory end-points. **a)** Kaplan-Meier plot for time to first rescue event in all participants, including all participants with study quality event. (For participants who did not enrol in the extension, rescue events were captured through week 30, 8 weeks after the last dose at week 22.) **b)** Proportion of patients who completed oral corticosteroid taper (≤ 5 mg·day⁻¹) without a rescue event. **c)** Mean $\pm$ SD change from baseline in observed forced vital capacity (FVC) % predicted. **d)** Mean $\pm$ SD change from baseline in observed diffusing capacity of the lung for carbon monoxide (D_{LCO}) % predicted. **e)** Mean $\pm$ SD change from baseline in observed King's Sarcoidosis Questionnaire (KSQ) Lung domain score. LS: least squares; BL: baseline (in x-axis labels). Missing baseline values account for the differences in participant numbers.

Patient-reported end-points

The secondary end-point of LS mean change from baseline to week 26 in KSQ Lung domain score was +1.6 (90% CI -1.5-4.7) for namilumab and +3.5 (90% CI 0.5-6.4) for placebo (LS mean difference -1.9,

TABLE 2 Safety end-points

	Namulumab (n=52)	Placebo (n=54)	Total (n=106)
Any TEAEs	49 (94)	51 (94)	100 (94)
Leading to discontinuation of study treatment	4 (8)	0	4 (4)
Any TEAEs by maximum severity[#]			
Mild	21 (40)	23 (43)	44 (42)
Moderate	24 (46)	26 (48)	50 (47)
Severe	4 (8)	2 (4)	6 (6)
Any study treatment-related TEAEs[¶]	20 (38)	16 (30)	36 (34)
Leading to discontinuation of study treatment	1 (2)	0	1 (1)
Leading to death	0	0	0
Any TSEAEs	3 (6)	3 (6)	6 (6)
Leading to discontinuation of study treatment	2 (4)	0	2 (2)
Leading to death	0	0	0
Any study treatment-related TSEAEs	0	0	0

Data are presented as n (%). TEAE: treatment-emergent adverse event; TSEAE: treatment-emergent serious adverse event. [#]: TEAE severities are based on investigator assessment of mild, moderate or severe (severe TEAEs include unknown/missing severity); [¶]: study treatment-related TEAEs are events definitely or possibly related to study treatment or with unknown/missing relationship to study treatment.

90% CI -6.1 – 2.4) (figure 3e). *Post hoc* analysis indicated a mean $\pm$ SD increase of 6.7 ± 11.7 in observed KSQ Lung domain score in patients receiving rescue treatment from the last observed data-point before initiation of rescue treatment to the last observed data-point for the 3 months after initiation of rescue treatment until week 26 (supplementary table S3).

The mean change from baseline to week 26 in KSQ General Health Status domain score was $+4.1$ (90% CI 1.5 – 6.8) for namulumab and $+0.1$ (90% CI -3.1 – 3.2) for placebo (mean difference 4.1 , 90% CI -0.0 – 8.1) (supplementary figure S5b). At baseline, the mean $\pm$ SD LCQ Total score was 16.1 ± 4.2 for namulumab and 16.5 ± 4.3 for placebo. The mean $\pm$ SD baseline SGRQ Total score was 44.9 ± 18.5 for namulumab and 40.2 ± 18.7 for placebo. Both the LCQ Total score and SGRQ Total score changes from baseline to week 26 were consistent with primary end-point outcomes and did not show benefit of namulumab (supplementary figure S5c and d). Analysis of fatigue as measured by KSQ fatigue items 2, 3, 4 and 10, and LCQ items 3 and 15 also did not show a treatment benefit for namulumab (supplementary figure S6).

Pharmacokinetic and biomarker analysis

The pharmacokinetic profile of namulumab was consistent with previous studies of namulumab (supplementary figure S7) [8].

Disease-specific biomarkers were generally elevated at week 26 compared with baseline in both treatment groups, except for IL-6 and IL-15 in the placebo group (supplementary figure S8). Disease-specific biomarkers were also generally numerically higher in the namulumab group than in the placebo group at week 26. Pathway-specific biomarkers (IL-4 and CXCL9) were generally elevated at week 26 compared with baseline in both treatment groups, and were generally higher at week 26 in the namulumab group than the placebo group, except IL-1 β (where there was no change).

At baseline, the mean $\pm$ SD levels of hsCRP were 5.02 ± 6.43 mg $\cdot$ L $^{-1}$ for namulumab and 3.8 ± 5.2 mg $\cdot$ L $^{-1}$ for placebo. The hsCRP mean $\pm$ SD change from baseline to week 26 was similar between treatment groups, at 3.3 ± 12.1 mg $\cdot$ L $^{-1}$ for namulumab compared with 2.0 ± 13.7 mg $\cdot$ L $^{-1}$ for placebo (mean difference 1.3 (90% CI -3.8 – 6.5) mg $\cdot$ L $^{-1}$). At baseline, the mean $\pm$ SD levels of SAA were $12\,377.2\pm 13\,921.9$ ng $\cdot$ mL $^{-1}$ for namulumab and $12\,993.3\pm 24\,782.1$ ng $\cdot$ mL $^{-1}$ for placebo. The SAA mean $\pm$ SD change from baseline to week 26 was $7114.9\pm 46\,115.9$ ng $\cdot$ mL $^{-1}$ for namulumab compared with $-2530.6\pm 244\,496.6$ ng $\cdot$ mL $^{-1}$ for placebo (mean difference 9645.4 (90% CI -5869.3 – $25\,160.2$) ng $\cdot$ mL $^{-1}$).

Safety end-points

Treatment-emergent AEs (TEAEs) were reported for 94% of participants in both the namulumab (49/52) and placebo (51/54) groups, with most being mild or moderate in severity (table 2). Overall, the most common TEAEs (affecting $\geq 10\%$ participants) were cough (25.5%), dyspnoea (18.9%), fatigue (15.1%), upper respiratory tract infection (15.1%), arthralgia (12.3%) and pulmonary sarcoidosis (10.4%)

(supplementary table S4). TEAEs associated with sarcoidosis were numerically higher in the namilumab group *versus* the placebo group, *e.g.* fatigue (19.2% *versus* 11.1%), arthralgia (17.3% *versus* 7.4%), myalgia (5.8% *versus* 3.7%) and pulmonary sarcoidosis (13.5% *versus* 7.4%) (supplementary table S4).

The most common treatment-related TEAEs determined by the trial investigator in the namilumab group were injection site pain (9.6%), eosinophilia and dyspnoea (each 5.8%). The most common study treatment-related TEAE in the placebo group was fatigue (5.6%).

In the namilumab group, three participants reported a total of six serious AE (SAEs): one participant reported three SAEs, one each of hypoglycaemia, seizure and worsening of pulmonary sarcoidosis; one participant reported two SAEs of acute respiratory failure; and one participant reported a lower respiratory tract infection. In the placebo group, three participants reported a total of five SAEs: one participant reported two SAEs of ventricular fibrillation and one SAE of atrioventricular block; one participant reported one SAE of chronic spontaneous urticaria; and one participant reported an SAE of intestinal adenocarcinoma (supplementary table S5).

No TEAEs of pulmonary alveolar proteinosis were reported. No TEAEs of allergic or hypersensitivity reactions were reported in the namilumab group. Overall, the incidence of anti-drug antibodies was <1%. The TEAEs of injection site reactions were generally mild and did not lead to treatment discontinuation (supplementary table S4).

Overall, liver-related TEAEs including hepatobiliary and liver laboratory abnormalities (*e.g.* alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transferase and bilirubin) were infrequent, mostly mild in severity and numerically higher in the namilumab group. In the namilumab group, seven participants reported a total of seven liver-related TEAEs, none of which were assessed by the investigator as related to trial treatment. In the placebo group, three participants reported a total of four liver-related TEAEs, all of which were assessed by the investigator as possibly related to trial treatment.

Reports of neutropenia as an AE were low and generally balanced between treatment groups. TEAEs of eosinophilia and eosinophil count increased were reported as four events in the namilumab group and no events in the placebo group. All reports were mild in severity, assessed by the investigator as possibly related to trial treatment and did not lead to treatment discontinuation.

At week 26, 90.6% (48/53) participants in the namilumab group and 98.1% (53/54) participants in the placebo group completed treatment as planned. Overall, four participants discontinued study drug in the namilumab group, all due to AEs (supplementary table S6); these included respiratory failure, altered mood, worsening pulmonary sarcoidosis and liver sarcoidosis. In the placebo group, one participant was discontinued from treatment by the study investigator due to non-compliance with the study protocol (supplementary table S6).

Discussion

By the end of the 26-week double-blind period, the RESOLVE-Lung trial did not demonstrate a treatment benefit of namilumab on the primary end-point (proportion of participants with a rescue event) or on the secondary outcomes including measures of pulmonary physiology, PROs or biomarkers in participants with chronic pulmonary sarcoidosis. Considering these findings, the open-label phase was terminated early following sponsor review of the double-blind study results.

A total of 107 participants were enrolled globally, representing a patient population with chronic, symptomatic, active pulmonary sarcoidosis. Notably, this study was among the first randomised placebo-controlled trials to use FDG-PET/CT for selecting patients with active granulomatous inflammation. Nearly all participants had a centrally confirmed $SUV_{max} \geq 3$ in the sarcoidosis-affected pulmonary parenchyma, with a mean SUV_{max} of 8.0 despite the majority receiving background OCS and/or IST treatment. Based on the current study it remains unclear if FDG-PET/CT uptake reflects meaningful disease activity, which might be amenable to further suppression by add-on or novel therapy when considering the design of future clinical trials. In addition, whether such suppression would translate to improved clinical outcomes is uncertain. The study employed an IST withdrawal/OCS taper design element that, although used in other fields and in line with recent World Association for Sarcoidosis and other Granulomatous Disorders (WASOG) recommendations to consider OCS tapering as an end-point, is novel for sarcoidosis studies [20, 21]. To safeguard study participants, patients with a requirement for ongoing treatment (*e.g.* cardiac sarcoidosis or neuro-sarcoidosis) were excluded from study participation. In addition, participants were closely monitored with weekly clinic or phone visits during the IST withdrawal/OCS

taper period of 10–18 weeks. This design aimed to increase the likelihood of being able to assess therapeutic benefit, as well as explore a range of other end-points, to inform a possible phase 3 study [22, 23]. The use of a rescue-event-based primary end-point, within a tapering OCS/IST design, offered a means of capturing clinically meaningful worsening in a heterogeneous disease for which no broadly accepted or validated trial end-point exists.

The proportion of rescue events in the placebo group was somewhat lower than modelled, likely a reflection of the limited data in the literature available at the time of the trial's design. The data from this study may hopefully add to this nascent literature and aid in designing future clinical trials in this area. Of note, few rescue events were due to worsening or development of extrapulmonary sarcoidosis (five events in five participants); however, these events are important to consider for future studies as this highlights how sarcoidosis in other tissues may influence determination of disease progression, response to treatment and study end-points in this systemic disorder.

Notably, a large proportion of the placebo group was able to successfully taper OCS (achieve $\leq 5 \text{ mg} \cdot \text{day}^{-1}$) during the study without a rescue event. Although an interesting finding, this does not necessarily reflect that patients enrolled in the study were on too high doses of OCS, as there were signs of disease worsening during the study even if this did not require a rescue, *e.g.* as evident from decline in FVC. Reasons for missing the OCS taper goal, as well as increase in OCS dose, were carefully monitored in the study as part of the rescue event review process, and no events of adrenal insufficiency were reported, supporting that the tapering schedule was effective.

While FVC has become the standard end-point in interstitial lung disease trials, its utility in sarcoidosis is less established, as prior sarcoidosis studies showed only modest or no change in FVC % pred in placebo arms [24, 25]. In this trial, the overall participant population showed a mean FVC decline of $\sim 3\%$ at week 26, with post-rescue data censored, while *post hoc* analysis indicated $\sim 5\%$ improvement in FVC % pred among those receiving rescue treatment, an effect size comparable to that seen with first-line OCS therapy [26–28]. These data validate that our trial design was sufficiently sensitive to detect these changes, and can indeed provide an adequate window for detecting clinical improvement. Similarly, a mean improvement of 6.7 in KSQ Lung domain scores was observed post-rescue, exceeding the reported minimal clinically important difference of 4 for this measure [29]. Together, these data support that FVC and KSQ Lung domain scores may be responsive end-points within the context of this trial design.

The safety profile of namilumab in RESOLVE-Lung was generally consistent with prior studies, indicating good overall tolerability [30], and the most common AEs were related to disease progression. Consistent with the efficacy end-points, AEs of sarcoidosis worsening, or constitutional symptoms associated with sarcoidosis, were more prevalent in the namilumab group.

This study was placebo-controlled, and incorporated several elements needed to evaluate a clinical effect of namilumab, including reasonable powering assumptions appropriate for a phase 2 study to provide confirmation of the role of GM-CSF in pulmonary sarcoidosis. The study overall performed as expected. Namilumab, a potent and specific monoclonal antibody against GM-CSF, reached expected concentrations which had shown biological activity in other inflammatory indications [8, 13]. The high degree of consistency across end-points supports the scientific robustness of the study; however, contrary to our hypothesis and existing evidence, the study data do not support a pathogenic role for GM-CSF in pulmonary sarcoidosis. Indeed, several outcomes, including the proportion of participants with a rescue event or able to taper OCS, change from baseline in FVC % pred and biomarkers, as well as AEs associated with sarcoidosis worsening, suggest possible worsening in the namilumab group to a greater extent than in the placebo group. Although, overall, the treatment groups were well balanced, some imbalances in participant characteristics at baseline suggest that the namilumab group may have had more severe disease that could have contributed to this observation. Alternatively, these observations raise the possibility of an unknown feedback mechanism, redundancy in pathways or even a protective role of GM-CSF in pulmonary sarcoidosis and highlight that the role of GM-CSF in this disease is not yet fully understood.

This study did have some limitations. Few studies were available to understand the incidence and characteristics of rescue events, although assumptions on frequency generally held. While the end-point of rescue events was pragmatic and reflective of real-world clinical decision making, it may have been influenced by investigator and patient preference or regional treatment differences in the absence of objective thresholds to determine treatment initiation. In addition, timing of initiation of rescue treatment may have been influenced by the absence of a standardised diagnosis of disease worsening, *e.g.* a variable

observation period to rule out intercurrent events may have played a role in determining whether to start rescue treatment or not.

Notwithstanding its outcome, RESOLVE-Lung offers several important contributions to the field. First, it enrolled one of the largest cohorts of patients with active pulmonary sarcoidosis, overcoming recruitment barriers inherent to rare, heterogeneous diseases [30]. Second, the use of PET-based imaging to define disease activity is a methodological advance that should inform future trial designs. Third, the trial reinforces the importance of end-point selection, tapering strategies and accounting for extrapulmonary disease when evaluating therapeutic interventions in sarcoidosis. While this study does not support targeting GM-CSF as a therapeutic strategy in pulmonary sarcoidosis, it provides valuable evidence that can guide mechanistic research and future drug development. Hypotheses regarding the complex role of GM-CSF in sarcoidosis pathophysiology remain speculative, but the data suggest caution in suppressing this pathway without a clearer understanding of its systemic and tissue-specific effects.

Conclusion

RESOLVE-Lung demonstrates that namilumab does not confer clinical benefit in patients with chronic, active pulmonary sarcoidosis. The findings suggest that targeting GM-CSF may not be a viable strategy in this setting and highlight the need for deeper mechanistic understanding. Nonetheless, the study advances clinical research methodology in sarcoidosis and lays a foundation for future trial design in similarly complex inflammatory conditions.

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Data availability: The data supporting this study can be accessed on the ClinicalTrials.gov website: <https://clinicaltrials.gov/study/NCT05314517>. Subsequent analysis will be made available on request to the corresponding author.

This clinical trial was prospectively registered with ClinicalTrials.gov as NCT05314517.

Ethics statement: RESOLVE-Lung was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice Guideline, and all other applicable laws and regulations. All relevant documents were approved by the respective institutional review board or ethics committee and health authorities. The study was reviewed and approved by the WCG Institutional Review Board (#20220115).

Author contributions: N. Mogulkoc, S. Nayci Atis, R. Gupta, J. Guiot, S.P. Hart and E.M. Carmona Porquera are RESOLVE-Lung site investigators who enrolled patients into the study. B. Van Den Blink, H.B. Koeller, N. Arocho, C.M. Petit, J. Denning, M. Lin and T.F. Reiss were involved in the design, data curation and analysis of the study. S.S. Birring, R.P. Baughman and M. Wijsenbeek-Lourens were involved in design and interpretation of the results. All authors were involved in the drafting of the manuscript and provided approval of the final submitted draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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