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ORIGINAL RESEARCH

Trial Conduct, Baseline Characteristics, and Symptom Burden of Patients in the ARISE Study

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ABSTRACT

***Introduction*:** ARISE was a global clinical trial designed to generate evidence demonstrating the utility of the patient-reported outcome instruments Quality of Life–Bronchiectasis (QOL-B) [Respiratory Domain (RD) only] and Patient-Reported Outcomes Measurement Information System Short Form v1.0-Fatigue 7a (PROMIS F SF-7a) in patients with newly diagnosed or recurrent *Mycobacterium avium* complex lung disease (MACLD). Here, we describe trial conduct, patient characteristics, and patient-reported symptoms at baseline among patients enrolled in ARISE.

***Methods*:** Adult patients with newly diagnosed or recurrent non-cavitary MACLD who had not initiated antibiotic treatment for their current MAC infection were enrolled; data including comorbidities and prior MACLD history were collected during screening. Symptom burden was assessed using QOL-B, PROMIS F SF-7a, and Functional Assessment of Chronic Illness Therapy (FACIT) questionnaires.

Prior Presentation This manuscript is based on work that has been previously presented at the ATS International Conference, 17–22 May 2024, San Diego, CA, USA, and the 7th World Bronchiectasis Conference, 4–6 July 2024, Dundee, Scotland.

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Results: Of 99 patients from 12 countries enrolled in ARISE, the median age was 69.0 years; most were white (80.8%) and female (77.8%). This was the first diagnosis of MACLD for 72.7% of patients. Patients frequently reported having a comorbid respiratory disorder: bronchiectasis (49.5%), asthma (21.2%), and chronic obstructive pulmonary disease (16.2%). At baseline, mean (± SD) and median QOL-B RD scores were 65.0 (± 15.3) and 66.7; PROMIS F SF-7a T-scores were 53.8 (± 8.2) and 55.1; and FACIT-Fatigue scores were 35.0 (± 9.6) and 37.0.
Conclusions: Patients in ARISE were representative of a real-world patient population with MACLD. Comorbid chronic respiratory diseases were common in patients with new or recurrent MACLD, and substantial disease burden at the time physicians initiated MACLD treatment was evidenced by impairment across measures of fatigue and QOL-B domains.
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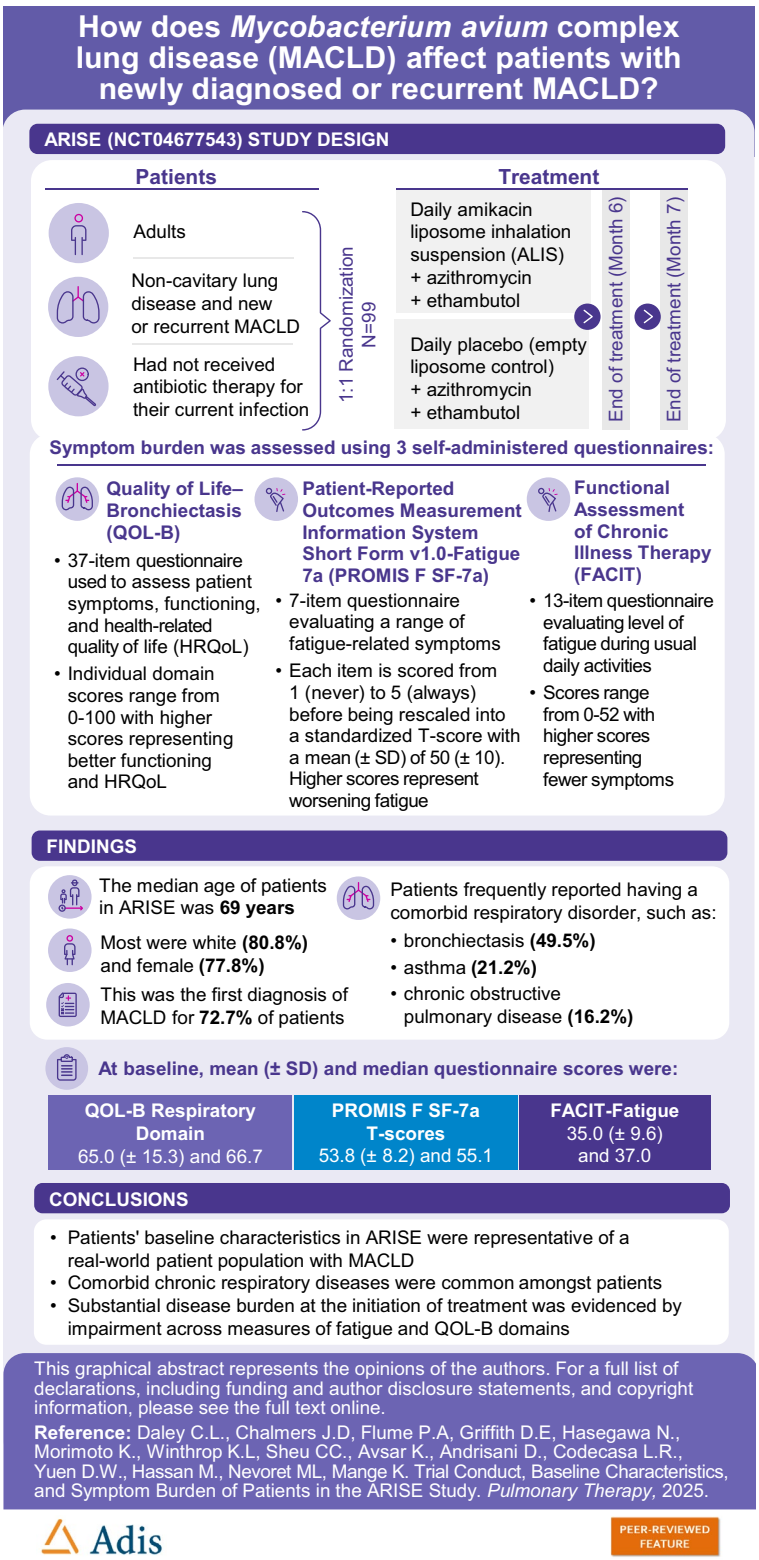
Graphical Abstract:



PLAIN LANGUAGE SUMMARY

People with a disease called *Mycobacterium avium* complex lung disease (MACLD) experience many symptoms, including cough, fatigue, and shortness of breath, which can impact their quality of life. It is not clear what symptoms people with new or repeating MACLD may have before they start antibiotic treatment for their disease. This publication describes the design of a study called ARISE, characteristics of people with MACLD who participated, and the symptoms they reported when they started the study. Overall, 99 people with a first, second, or third diagnosis of MACLD, who had not started taking antibiotics, participated in the study. People in the study were on average 69 years old and most were female (78%). This was the first diagnosis of MACLD for more than 70% of people who participated in ARISE. In addition to MACLD, many people also had other respiratory diseases, including bronchiectasis, asthma, and chronic obstructive pulmonary disease. At the start of the study, people completed three questionnaires that measured their symptoms, quality of life, and the severity and frequency of fatigue in their daily life. In these questionnaires, people with MACLD reported that, before starting treatment, they had a high burden of symptoms that impacted their daily lives and quality of life. They also reported more fatigue than people without MACLD. The results from this study were similar to those seen in people with MACLD from registries and other clinical studies. The results also showed that people with MACLD have a large symptom burden before starting treatment.

Keywords: Amikacin liposome inhalation suspension; *Mycobacterium avium* complex lung disease; Nontuberculous mycobacterial lung disease; Patient-reported outcomes; Clinical trial

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.28581332

Key Summary Points

Why carry out this study?

Mycobacterium avium complex lung disease (MACLD), a leading cause of nontuberculous mycobacterial lung disease, is associated with significant respiratory symptoms and high all-cause mortality.

There are limited data characterizing the symptom burden of patients with newly diagnosed or recurrent MACLD who have not yet initiated antibiotic treatment.

What was learned from the study?

Patients in ARISE were representative of a real-world patient population with MACLD.

Substantial disease burden was seen at the time MACLD treatment was initiated, as demonstrated by impairment in patient-reported outcome measures.

INTRODUCTION

Mycobacterium avium complex (MAC) is the leading cause of nontuberculous mycobacterial lung disease (NTMLD) [1–3], a progressive disease associated with a high symptom burden, including cough, sputum production, fatigue, shortness of breath, fever, weight loss, and hemoptysis [4, 5]. MAC lung disease (MACLD) often complicates other chronic, debilitating, underlying lung diseases such as bronchiectasis, asthma, or chronic obstructive pulmonary disease (COPD), and is linked to increased all-cause and disease-specific mortality [2, 6, 7]. Additionally, due to limited disease awareness and heterogeneity in approach to disease management, including the use of "watchful waiting," many patients may not

receive treatment until their disease has progressed [6].

Although some data are available on patients with refractory MACLD, there is limited understanding of the burden of disease among patients with newly diagnosed or recurrent MACLD who have not yet initiated antibiotic treatment [8].

A recent study of patients with newly diagnosed MACLD showed improvement in health-related quality of life (HRQoL) with initiation of any treatment [9]. However, there is a need to better characterize comorbidities, disease-related symptoms, and impact on HRQoL among these individuals. Collectively, such data would provide a better picture of disease burden and assist physicians in determining when to initiate treatment.

There are limited data on the validity of patient-reported outcome (PRO) measures in MACLD. The randomized, multicenter ARISE study (NCT04677543) was designed to generate evidence on measurement properties of PRO instruments, including the domain specifications, reliability, validity, and responsiveness (i.e., within-patient meaningful change), supporting validation of PRO endpoints in patients with MACLD. In addition, ARISE offers an opportunity to understand the symptom burden among this patient population and to fill these data gaps.

This manuscript describes trial conduct, baseline characteristics, and baseline patient-reported burden among patients enrolled in the ARISE trial whom physicians have deemed ready to initiate treatment. Patients in the study completed the Quality of Life–Bronchiectasis (QOL-B) questionnaire [9–11], the Patient-Reported Outcomes Measurement Information System-Short Form v1.0-Fatigue 7a (PROMIS F SF-7a) [12–14], and the Functional Assessment of Chronic Illness Therapy (FACIT) questionnaires, each of which captured patient-reported burden of disease prior to treatment initiation.

METHODS

ARISE Study Design and Endpoints

ARISE was a randomized, placebo-controlled, active comparator, double-blind, multicenter international study designed to generate evidence demonstrating the domain specification, reliability, validity, and responsiveness (where responsiveness is defined as within-patient meaningful change) of the QOL-B Respiratory Symptoms domain (RD) and PROMIS F SF-7a instruments in patients with MACLD. Figure 1 details the overarching study design. Regions (countries) with ARISE study sites included North America (United States), Europe (Germany, Italy, Spain, Denmark, Austria, and Israel), and the Rest of the World (Taiwan, Republic of Korea, Australia, New Zealand, and Argentina). Additional study objectives included evaluation of the effect of

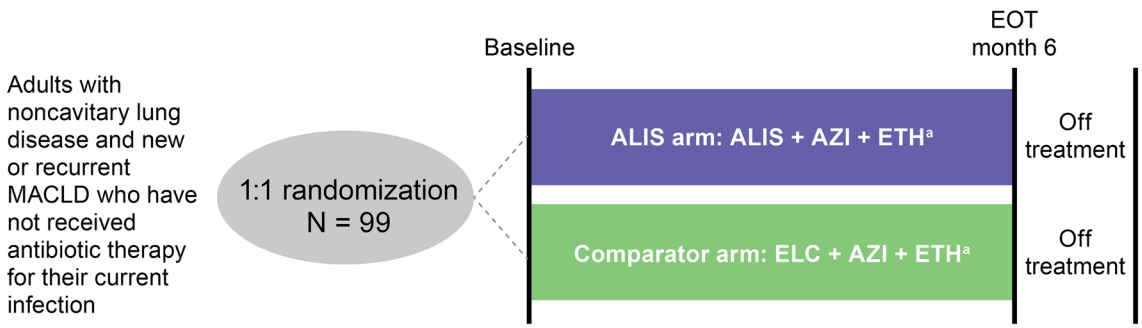


Fig. 1 ARISE study design. *ALIS* amikacin liposome inhalation suspension, *AZI* azithromycin, *ELC* empty liposome control, *EOS* end of study, *EOT* end of treatment, *ETH* ethambutol, *MACLD Mycobacterium avium* complex lung disease, *PO* oral administration, *QD* daily. [a]ALIS 590 mg QD or placebo (ELC) QD plus AZI 250 mg QD and ETH 15 mg/kg QD PO

each study treatment arm on patient-reported respiratory and fatigue symptoms, microbiologic outcomes, and safety.

PATIENTS

Key Inclusion and Exclusion Criteria

A complete, detailed description of all inclusion and exclusion criteria can be found in Table S1 in the supplementary material. Briefly, patients eligible for ARISE were adults aged 18 years or older (19 years or older in the Republic of Korea) with a new or recurrent (second or third) diagnosis of MACLD who had not initiated antibiotic therapy. Patients were required to have a positive sputum culture for MAC within 6 months prior to screening as well as a positive sputum culture at screening. Patients had documented respiratory signs and symptoms at screening which the investigator attributed to the current MAC lung infection, and patients were required to have an average QOL-B RD score of ≤ 85 from assessments collected at screening and on the day of randomization. Underlying lung disease had to have been managed according to best local standard of care and patients had to be on stable maintenance therapy for at least 4 weeks before randomization. Patients with cystic fibrosis, with any pulmonary cavity ≥ 2 cm in diameter, current smokers, or those with a history of more than 3 MAC lung infections, refractory disease (defined as positive cultures for MAC despite ≥ 6 months of treatment), or relapsed MAC infection (defined as positive cultures for MAC < 6 months after completing treatment) were excluded.

Study Procedures

Patients were randomized 1:1 via a central Interactive Web Response System to receive amikacin liposome inhalation suspension (ALIS, 590 mg) or empty liposome control (ELC, comparator), along with azithromycin (250 mg) and ethambutol (15 mg/kg), once daily for 6 consecutive months; this was followed by 1 month of follow-up off-treatment. Randomization was stratified by region (North America, Europe, and the Rest of the World) and history of MAC lung infection (initial or subsequent; "subsequent" was defined as a second or third MAC lung infection). Investigators, including evaluators/raters and other clinicians providing care, the sponsor, and patients/caregivers were blinded to treatment group assignment throughout the duration of the study. Unblinding was only to occur at the conclusion of the study or in case of patient emergencies.

At screening, informed consent was obtained, followed by PRO questionnaires, including QOL-B, PROMIS F SF-7a, and FACIT along with other validating PROs. Other assessments then proceeded, including medical history, physical examination, vital signs and pulse oximetry, forced expiratory volume in 1 s (FEV_1), an audiogram, concomitant medications, sputum collection for microbiology, safety laboratories, and a pregnancy test for all women of child-bearing potential. Additional safety assessments, such as echocardiogram and ophthalmological exam, were conducted as required by local labeling guidance for azithromycin and/or ethambutol.

Patient assessments were conducted in clinic at screening and baseline (day of randomization/treatment initiation); followed by 1, 3, 5, 6, and 7 months post-treatment initiation. Patients exited the study at 7 months, which was 1 month post-treatment completion. Additional assessments were conducted at 2 and 4 months post-treatment initiation, with flexibility in mode of assessment (in clinic, virtual, or telephone). Baseline assessments included all screening assessments (except audiograms) and evaluation for adverse events.

Ethics

A data monitoring committee periodically monitored the safety of patients in the study. ARISE was approved by the Advarra Institutional Review Board under protocol reference number Pro00045468 on 12 August 2020. ARISE also received ethics approval from all study sites. Participants and/or their legally authorized representative were informed that their

participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent which met the requirements of 21 CFR 50, local regulations, ICH guidelines, and HIPAA requirements. Participants did not consent for publication as no individual patient data are included. ARISE was conducted in compliance with its protocol and the ethical principles derived from international guidelines (Declaration of Helsinki [15], the Council for International Organizations of Medical Sciences International Ethical Guidelines [16)], and applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines [17], as well as applicable local laws and regulatory requirements.

Quality of Life Assessments

Two of the primary HRQoL instruments evaluated in the study were the QOL-B and the PROMIS F SF-7a. The QOL-B is a self-administered questionnaire used to assess patient symptoms, functioning, and HRQoL which has been validated in adult patients with non-cystic fibrosis bronchiectasis (NCFBE) [10, 18]. This instrument measures PROs over a recall period of 1 week using 37 items across 8 scales, typically referred to as "domains" (physical, role, emotional, and social functioning; vitality; treatment burden; health perceptions; and respiratory symptoms). As burden related to the treatments used in ARISE could not be reliably assessed at baseline (i.e., pre-treatment initiation), that domain was not included in the analyses presented here. For each domain item, patients select from 4 responses ranging from "never" to "always." Each response is scored from 1 to 4; each domain score is then standardized on a 0- to 100-point scale; higher scores represent better functioning and HRQoL.

The PROMIS F SF-7a is a self-administered, 7-item questionnaire evaluating a range of fatigue-related symptoms over a recall period of 7 days which has been validated in patients with conditions such as COPD [19], rheumatoid arthritis [20], and Crohn's disease and ulcerative colitis [21], but has not been assessed in NTMLD [12, 13, 22]. Symptoms evaluated range from mild subjective feelings of tiredness to extreme fatigue and exhaustion which interfere with activities of daily living and normal familial and social functioning. Each item is scored from 1 (never) to 5 (always). Item scores are summed into a total raw score before being rescaled into a standardized T-score with a mean (± SD) of 50 (± 10). The PROMIS Fatigue item bank divides fatigue into the experience of fatigue (i.e., frequency, duration, and intensity) and impact on physical, mental, and social functioning. To our knowledge, no other studies in MACLD have reported PROMIS T-scores.

The QOL-B and PROMIS F SF-7a were the first and second assessments completed at prespecified study visits, respectively, to minimize bias and questionnaire fatigue, as these were the instruments being validated. Additional PRO instruments were administered after the PROMIS F SF-7a. These additional instruments included an anchor [Patient Global Impression of Severity (PGI-S), data not shown] and domain-specific questionnaires for the 2 key symptom concepts being assessed: respiratory {Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and St. George's Respiratory Questionnaire (SGRQ), data not shown] and fatigue (FACIT).

The FACIT-Fatigue, described here as FACIT, is a self-administered questionnaire comprising 13 items that was used in ARISE as a convergent validator for the QOL-B RD and PROMIS instruments. It assesses an individual's level of fatigue during their usual daily activities during the past week. The FACIT scale is graded from 0 to 52, with a higher score indicating fewer symptoms. FACIT data are included here, as the PROMIS F SF-7a did not appear to adequately measure fatigue in the patients in this trial.

Necessary permissions were obtained to use all PRO questionnaires in this study.

Statistical Analysis

Longitudinal validation required approximately 100 patients to adequately power the planned within-subject meaningful change methods.

Descriptive statistics of the pooled data from the intent-to-treat population, comprised of all randomized patients, were used to describe different patient and disease characteristics at baseline. Continuous variables were summarized using mean, median, SD, range, and interquartile range (IQR). Item and domain scoring for the QOL-B was completed according to instrument instructions (e.g., some items require reverse scoring, and the respiratory symptoms domain was computed across 8 or 9 items depending on item response). Total score domains were also derived for non-respiratory domains. All statistical analyses were done with Statistical Analysis System (SAS) software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient and Baseline Disease Characteristics

Patient recruitment for the ARISE study occurred between December 2020 and October 2022. A total of 99 patients from 12 countries were enrolled and randomized to either the ALIS or the comparator arm (Table 1). The median age of patients was 69.0 years. Of the 99 patients, 77.8% (n = 77) were female and 80.8% (n = 80) were white (Table 1). Mean body mass index (BMI) was 21.87 kg/m^2 and mean percent predicted FEV_1 was 78.8%. The majority of patients enrolled were located either in North America (39.4%, n = 39) or Europe (38.4%, n = 38; Table 1). For 72.7% (n = 72) of the patients, this was their first MAC infection. At baseline, *M. avium* was isolated in 32.3% of patients (n = 32); *M. intracellulare* in 43.4% of patients (n = 43); other speciated MAC in 23.2% of patients (n = 23); and unspeciated MAC in 6.1% of patients (n = 6).

Comorbidities at Baseline

Based on each patient's source documentation and medical history, along with the investigator's clinical assessment, the most commonly reported pre-existing respiratory

Table 1 Patient demographics and characteristics

Parameter	Overall (n = 99)
Age (median)	69.0
≥ 65 years, n (%)	67 (67.7)
Female, n (%)	77 (77.8)
Race	
White, n (%)	80 (80.8)
Asian, n (%)	18 (18.2)
Black, n (%)	1 (1.0)
Ethnicity	
Hispanic or Latino, n (%)	6 (6.1)
Non-Hispanic/Latino	93 (93.9)
BMI (kg/m^2), mean ± SD	21.87 ± 4.059
FEV_1 % predicted, mean ± SD	78.8 ± 19.37
Region (as per IRT), n (%)	
North America[a]	39 (39.4)
Europe[b]	38 (38.4)
Rest of the World[c]	22 (22.2)
MAC infection at baseline, n (%)	
M. avium	32 (32.3)
M. intracellulare	43 (43.4)
Other speciated MAC[d]	23 (23.2)
Unspeciated MAC	6 (6.1)
History of MAC (initial), n (%)	
Initial	72 (72.7)
Subsequent	27 (27.3)
Duration (years) since last MAC infection, mean ± SD)	2.86 ± 2.82
Duration (years) since last MAC infection, median (IQR)	2.00 (1.02–4.15)

BMI body mass index, *FEV_1* forced expiratory volume in 1 s, *IQR* interquartile range, *IRT* interactive response technology, *MAC Mycobacterium avium* complex

[a]United States, 39 (39.4%)

[b]Germany, 12 (12.1%); Italy, 9 (9.1%); Israel, 6 (6.1%); Spain, 6 (6.1%); Denmark, 4 (4.0%); Austria 1 (1.0%)

[c]Taiwan, 8 (8.1%); the Republic of Korea, 7 (7.1%); Australia, 3 (3.0%); New Zealand, 3 (3.0%); Argentina, 1 (1.0%)

Table 1 continued

[d]Other speciated MAC: *M. bouchedurhonense*: 1 (1.0%); *M. intracellulare* subsp chimera: 15 (15.2%); *M. marseillense*: 2 (2.0%); *M. intracellulare* subsp yongonense: 5 (5.1%)

Table 2 Patient comorbidities and symptoms at baseline in > 10% of patients

	Overall (*n* = 99) ***n*** **(%)**
Respiratory symptoms and comorbidities	
Bronchiectasis	49 (49.5)
Asthma	21 (21.2)
COPD	16 (16.2)
Cough	16 (16.2)
Pneumonia	15 (15.2)
Allergic rhinitis	11 (11.1)
Dyspnea	10 (10.1)
Non-respiratory comorbidities	
GERD	29 (29.3)
Hypertension	28 (28.3)
Osteoporosis	19 (19.2)
Hypothyroidism	16 (16.2)
Osteoarthritis	14 (14.1)
Anxiety disorder	14 (14.1)
Hyperlipidemia	13 (13.1)
Insomnia	13 (13.1)
Depressive disorder	12 (12.1)
Arthritis	11 (11.1)
Migraine	11 (11.1)
Seasonal allergy	11 (11.1)
Headache	10 (10.1)

COPD chronic obstructive pulmonary disorder, *GERD* gastro-esophageal reflux disease

conditions (≥ 15% overall) were bronchiectasis (49.5%, *n* = 49), asthma (21.2%, *n* = 21), COPD (16.2%, *n* = 16), and previous pneumonia (15.2%, *n* = 15) (Table 2). The most frequently reported non-respiratory conditions (≥ 15% overall) included gastro-esophageal reflux disease (29.3%, *n* = 29), hypertension (28.3%, *n* = 28), osteoporosis (19.2%, *n* = 19), and hypothyroidism (16.2%, *n* = 16) (Table 2).

Prior Medications of Interest

Overall, 99% of patients used medications for comorbidities prior to the first dose of study drug and 21.2% had prior exposure to macrolides. Prior macrolide use may have been for prior MAC infections. The prior medications

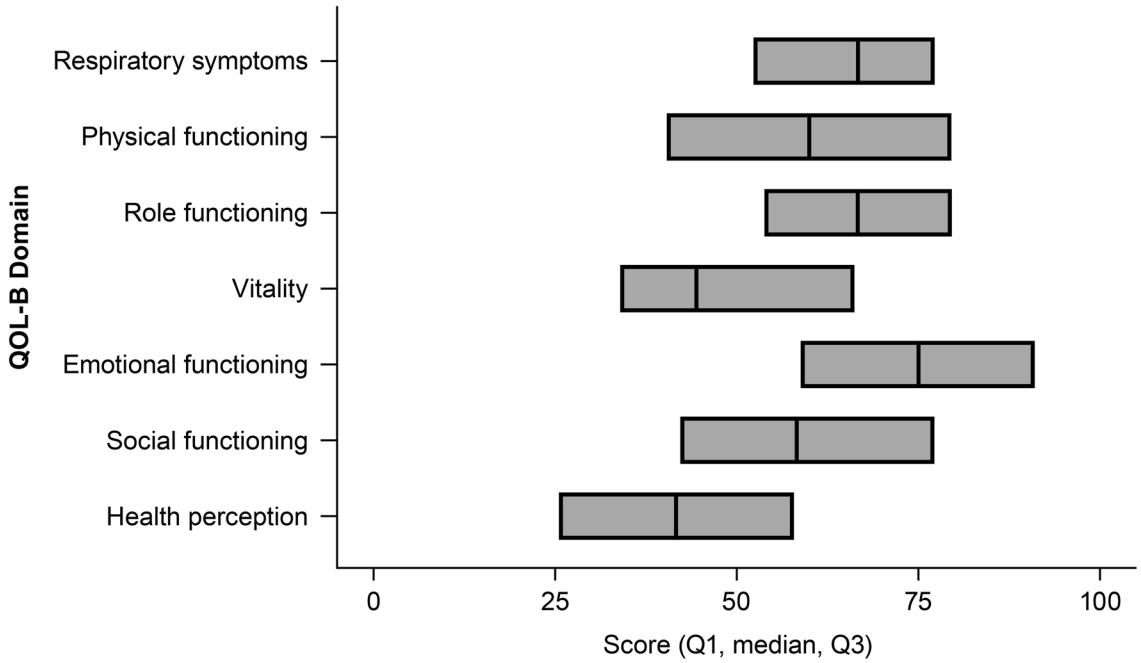
Table 3 Most commonly used prior medications: ATC level 4 class

	Overall (*n* = 99) ***n*** **(%)**
Adrenergics in combination with anticholinergics including triple combinations with corticosteroids	15 (15.2)
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	11 (11.1)
Inhaled corticosteroids[a]	6 (6.1)
COVID-19 vaccines	81 (81.8)
Glucocorticoids	11 (11.1)
HMG-COA reductase inhibitors	23 (23.2)
Macrolides	21 (21.2)
Mucolytics	28 (28.3)
Proton pump inhibitors	25 (25.3)
Selective beta-2-adrenoreceptor agonists	28 (28.3)
Vitamin D and analogs	29 (29.3)

ATC anatomical therapeutic chemical, *HMG-COA* 3-hydroxy-3-methylglutaryl coenzyme A

[a]Inhaled corticosteroids used alone, not in combination with other treatment

a



QOL-B domain	Mean (±SD)
Respiratory symptoms	65.0 (±15.3)
Physical functioning	56.9 (±28.9)
Role functioning	65.3 (±21.0)
Vitality	48.7 (±20.7)
Emotional functioning	76.4 (±20.4)
Social functioning	58.0 (±25.1)
Health perception	41.3 (±21.3)

b

	Overall (N=99)	
	Mean (±SD)	Median (Q1, Q3)
PROMIS F SF-7a T-score	53.8 (±8.2)	55.1 (47.6, 59.2)
FACIT-Fatigue subscale score	35.0 (±9.61)	37.0 (28, 42)

◂**Fig. 2** Symptom burden at baseline assessed by QOL-B, PROMIS F SF-7a, and FACIT-Fatigue. **a** Median, Q1, Q3, of QOL-B domain scores with mean (± SD) presented in the table below. Overall n = 99. Higher scores represent better functioning and QoL. **b** PROMIS F SF-7a T-score and FACIT-Fatigue subscale score mean (± SD), median (Q1, Q3) presented. In PROMIS F SF-7a, higher scores represent worsening fatigue. In FACIT-Fatigue, higher scores represent fewer symptoms. PROMIS F SF-7a Patient-Reported Outcomes Measurement Information System Short Form v1.0-Fatigue 7a, Q quartile, QOL-B Quality of Life–Bronchiectasis questionnaire

most commonly reported were COVID-19 vaccines (81.8%), vitamin D and analogs (29.3%), mucolytics (28.3%), selective beta-2-adrenoreceptor agonists (28.3%), and proton pump inhibitors (25.3%) (Table 3).

Quality of Life Assessments

Mean baseline scores for the QOL-B are summarized in Fig. 2a. The median (Q1–Q3) QOL-B scores for respiratory symptoms [66.7 (51.9–77.8)], physical functioning [60.0 (40.0–80.0)], social functioning [58.3 (41.7–77.8)], and role functioning [66.7 (53.3–80.0)] suggest that patients experience impairment in breathing, functioning at home and in social environments, and energy to perform routine tasks of daily living. Scores on emotional functioning items, including those related to anxiety and depression, were notably higher than the scores for the physical and social functioning domains. The mean (± SD) and median PROMIS F SF-7a T-scores were 53.8 (± 8.2) and 55.1 and the mean (± SD) and median FACIT-Fatigue scores were 35.0 (± 9.61) and 37.0, respectively (Fig. 2b).

DISCUSSION

We have described the baseline patient characteristics and patient-reported symptom burden among patients with MACLD enrolled in the ARISE study, as captured using the QOL-B, PROMIS F SF-7a, and FACIT-Fatigue instruments. These patients are representative of the real-world population of patients with MACLD [23, 24]. As previously shown in patients with MACLD, comorbid chronic respiratory disease was common in patients with new or recurrent MACLD in ARISE [4]. The observed scores for the QOL-B RD (role, social, and physical functioning, and vitality and health perception domains) suggest that patients with MACLD have a high symptom burden at the time when physicians initiate antibiotic treatment following a new diagnosis of MACLD. The data presented here represent a key point in time when physicians have determined that antibiotic treatment is necessary.

Patients in ARISE had similar QOL-B domain scores to patients with NCFBE and a Gram-negative endobronchial infection which were included in the Quittner et al. study, which validated the QOL-B as a PRO tool for the patient population [10], suggesting a burden of symptoms in patients with MACLD that is as high as in patients with an acute pulmonary infection in the presence of bronchiectasis. The ARISE patients and the patients from the clinical trials used in the Quittner et al. validation study may overlap due to disease comorbidities. However, in Quittner et al., the patients from the clinical trials used in the analysis were modestly younger, included a greater proportion of men, and mean BMI was higher than in ARISE, although these population differences did not impact QOL-B domain scores [10].

Patients in ARISE also had similar characteristics to those with NTMLD reported by Pravosud et al., with 58.2% of patients over 65 years (vs. 67.7% in ARISE) and 93.1% female (vs. 77.8% in ARISE) [25]. However, this study did not specify the NTM species present and had limited geographic scope. Pravosud et al. also showed that patients on active treatment experienced substantial symptom burden, similar to the ARISE population that was identified as requiring treatment for their MACLD [25].

The mean baseline QOL-B RD score in ARISE was similar to previously reported scores in patients with NTMLD. In an analysis of patients enrolled in the Northwest NTM Biobank, 25 individuals with NTMLD who were initiating

treatment had a mean (± SD) QOL-B RD score of 57.6 (± 22.6), compared with 65.03 (± 15.3) in ARISE [26]. Similarly, in an interim analysis of 228 patients with newly diagnosed non-cavitary MACLD from an ongoing MAC clinical trial, the mean (± SD) QOL-B RD score was 64.7 (± 17.0) [9]. In another study, among 72 patients with refractory MACLD, the mean (± SD) QOL-B RD score was 68.2 (± 18.8), suggesting that patients with untreated MACLD experience respiratory symptoms as severe as those with refractory disease [27].

Anxiety and depression are frequently reported comorbidities in patients with chronic respiratory disease [28]. However, within ARISE, scores for the emotional function domain of QOL-B, which includes questions related to anxiety and depression, were not as affected as scores in other domains. While patients may have anxiety and depression symptoms, they may not attribute these to their MACLD. As the emotional function domain includes 1 item regarding anxiety and 2 around depression, it may be useful to screen this population for emotional distress using a separate and specific tool.

Concept elicitation research previously completed indicated that respiratory and fatigue symptoms are the most prevalent and bothersome to patients with newly diagnosed MACLD [29]. In the previously completed psychometric validation analysis from ARISE, PROMIS F SF-7a was found to have adequate reliability, validity, and responsiveness for assessing fatigue symptoms in patients with MACLD [14]. However, the mean baseline PROMIS F SF-7a T-scores in ARISE did not suggest that patients experienced substantial fatigue, as their scores were similar to those for a US adult general population [mean (± SD) PROMIS T-score of 50 (± 10) vs. 53.8 (± 8.2) in ARISE] [30, 31]. In contrast, the FACIT scale, which was used as a validating PRO for the psychometric validation analyses of the QOL-B RD and PROMIS F SF-7a instruments in the ARISE study, showed a greater degree of fatigue in ARISE patients than the PROMIS F SF-7a. At baseline, the mean FACIT score for the ARISE population was 35.0, substantially lower than the mean of 43.5 ± 8.3 reported in a general adult population [32]. This lower FACIT score could be due to FACIT being a fatigue severity index, whereas PROMIS F SF-7a items focus on assessing the frequency of fatigue feelings. Another reason that this instrument appeared to better elucidate the patients' fatigue symptoms is that FACIT captured a greater number of items (13) allowing for more targeted questions, and items of a different nature compared to PROMIS F SF-7a (e.g., "I need help doing my usual activities" vs. "How often did your fatigue limit you at work (include work at home)?").

The ARISE study has a strength in geographic diversity with patients enrolled across 12 countries. Additionally, the QOL-B RD and PROMIS instruments, based on previously completed qualitative evidence, reflected the respiratory and fatigue symptom concepts known to be prevalent and important to patients with MACLD. However, qualitative work was not available to support the relevance of other QOL-B domains to the MACLD population to evaluate physical or social functioning, anxiety, or depression. Due to disease burden being assessed in a clinical trial setting with strict inclusion/exclusion criteria and a small sample size, the results may not be reflective of the day-to-day burden experienced by a range of real-world patients with MACLD.

CONCLUSIONS

Overall, patients in ARISE were representative of a real-world patient population with MACLD. These patients experienced considerable symptom burden impacting various aspects of their lives at the time of treatment initiation, as reported via the QOL-B questionnaire. Patients in ARISE were found to experience greater fatigue than the general population and equivalent to the refractory MACLD population, as identified with the FACIT tool. Future research using symptom-specific tools to better understand individual QoL aspects and evaluating change in symptom burden in response to treatment in the MACLD population could aid physicians with understanding the potential HRQoL benefit for real-world clinical practice.

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Data Availability. The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy.

Declarations

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Ethical Approval. A data monitoring committee periodically monitored the safety of

patients in the study. ARISE was approved by the Advarra Institutional Review Board under protocol reference number Pro00045468 on 12 August 2020. ARISE also received ethics approval from all study sites. Participants and/or their legally authorized representative were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements. Participants did not consent for publication as no individual patient data are included. ARISE was conducted in compliance with its protocol and the ethical principles derived from international guidelines (Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines), and applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines, as well as applicable local laws and regulatory requirements.

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