Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Validate Patient-Reported Outcome Instruments in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by Mycobacterium avium Complex (MAC)

Summary

EudraCT number	2020-002545-42
Trial protocol	DK DE HU AT NL GR IT
Global end of trial date	09 May 2023

Results information

Result version number	v1 (current)
This version publication date	24 May 2024
First version publication date	24 May 2024

Trial information

Trial identification

Sponsor protocol code	INS-415

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04677543
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Insmed Incorporated
Sponsor organisation address	700 US Highway 202/206, Bridgewater, NJ, United States, 08807-1704
Public contact	Insmed Medical Information, Insmed Incorporated, medicalinformation@Insmed.com
Scientific contact	Insmed Medical Information, Insmed Incorporated, medicalinformation@insmed.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to generate evidence demonstrating the domain specification (via modern psychometric methods), reliability, validity, and responsiveness (within-subject meaningful change) of the Patient-Reported Outcome (PRO) endpoints.

Protection of trial subjects:

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy:

Background Regimen (Azithromycin + Ethambutol)

Evidence for comparator: -

Actual start date of recruitment	22 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	99
EEA total number of subjects	32

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	65
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants took part in this multi-centre study at different investigative sites from 22 December 2020 to 09 May 2023.

Pre-assignment

Screening details:

A total of 99 participants with mycobacterium avium complex (MAC) lung infection were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	ALIS + Background Regimen (Azithromycin + Ethambutol)

Arm description:

Participants received 590 mg of amikacin liposome inhalation suspension (ALIS) once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 milligrams per kilogram (mg/kg) tablets orally, once daily.

Arm type	Active comparator
Investigational medicinal product name	Amikacin Liposome Inhalation Suspension
Investigational medicinal product code	
Other name	ALIS, ARIKAYCE®
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ALIS 590 mg once daily

Arm title	ELC + Background Regimen (Azithromycin + Ethambutol)

Arm description:

Participants received empty liposome control (ELC), a matching placebo to ALIS, once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 mg/kg tablets orally, once daily.

Arm type	Placebo
Investigational medicinal product name	Empty Liposome Control
Investigational medicinal product code	
Other name	ELC
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ELC, a matching placebo to ALIS, once daily.

Number of subjects in period 1	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)
Started	48	51
Completed	44	48
Not completed	4	3
Consent withdrawn by subject	4	1
Physician decision	-	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ALIS + Background Regimen (Azithromycin + Ethambutol)
Reporting group description:	
Participants received 590 mg of amikacin liposome inhalation suspension (ALIS) once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 milligrams per kilogram (mg/kg) tablets orally, once daily.	
Reporting group title	ELC + Background Regimen (Azithromycin + Ethambutol)
Reporting group description:	
Participants received empty liposome control (ELC), a matching placebo to ALIS, once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 mg/kg tablets orally, once daily.	

Reporting group values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)	Total
Number of subjects	48	51	99
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	69.0	65.9	
standard deviation	± 9.51	± 12.27	-
Sex: Female, Male Units: Participants			
Female	32	45	77
Male	16	6	22
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	12	18
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	41	39	80
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	3	3	6
Not Hispanic or Latino	45	48	93
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	ALIS + Background Regimen (Azithromycin + Ethambutol)
Reporting group description:	
Participants received 590 mg of amikacin liposome inhalation suspension (ALIS) once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 milligrams per kilogram (mg/kg) tablets orally, once daily.	
Reporting group title	ELC + Background Regimen (Azithromycin + Ethambutol)
Reporting group description:	
Participants received empty liposome control (ELC), a matching placebo to ALIS, once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 mg/kg tablets orally, once daily.	

Primary: Psychometric Cross-Sectional Validation of Patient Reported Outcome (PRO): Patient Global Impression of Severity (PGI-S) Respiratory Scale Score at Baseline

End point title	Psychometric Cross-Sectional Validation of Patient Reported Outcome (PRO): Patient Global Impression of Severity (PGI-S) Respiratory Scale Score at Baseline[1]
End point description:	
The PGI-S respiratory symptom is a self-reported scale to measure the severity of illness based on symptoms using a 5-point scale ranging from 1 to 5, (1=not at all, 2=mild, 3=moderate, 4=very severe, 5=extremely severe). Considering different aspects of breathing symptoms like congestion, cough, mucus, wheezing, shortness of breath, participants rated their symptom severity on the PGI-S respiratory symptom scale. Higher scores indicate greater symptom severity. ITT Analysis Set comprises all participants who were randomised.	
End point type	Primary
End point timeframe:	
Baseline	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical data were planned for this endpoint.

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: score on scale				
arithmetic mean (standard deviation)	2.5 (± 0.82)	2.4 (± 0.90)		

Statistical analyses

No statistical analyses for this end point

Primary: Psychometric Cross-Sectional Validation of PRO: PGI-S Fatigue Scale Score at Baseline

End point title	Psychometric Cross-Sectional Validation of PRO: PGI-S Fatigue Scale Score at Baseline[2]

End point description:

The PGI-S fatigue is a self-reported scale to measure the severity of illness based on symptoms using a 5-point scale ranging from 1 to 5, (1=not at all, 2=mild, 3=moderate, 4=very severe, 5=extremely severe). Participants rated the severity of their fatigue on the PGI-S fatigue scale. Higher scores indicate greater fatigue severity. ITT Analysis Set comprises all participants who were randomised.

End point type	Primary

End point timeframe:

Baseline

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical data were planned for this endpoint.

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: score on scale				
arithmetic mean (standard deviation)	2.5 (± 0.99)	2.5 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Primary: Psychometric Cross-Sectional Validation of PRO: Patient-Reported Outcome Measurement Information System - Fatigue-Short Form 7a (PROMIS F-SF 7a) Score at Baseline

End point title	Psychometric Cross-Sectional Validation of PRO: Patient-Reported Outcome Measurement Information System - Fatigue-Short Form 7a (PROMIS F-SF 7a) Score at Baseline[3]

End point description:

The PROMIS F-SF 7a is a self-administered questionnaire assessing a range of self-reported symptoms over the past 7 days, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one’s ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities over 7 items. Response options are on a 5-point Likert scale, ranging from 1=never to 5=always. Total scores range from 7 to 35 and low scores represent less fatigue interference i.e., better symptoms. The ITT Analysis Set comprises all participants who were randomised.

End point type	Primary

End point timeframe:

Baseline

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical data were planned for this endpoint.

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: score on scale				
arithmetic mean (standard deviation)	18.3 (± 5.76)	18.6 (± 4.76)		

Statistical analyses

No statistical analyses for this end point

Primary: Response Rate as Assessed by Within-Subject Meaningful Change (WSMC) for QOL-B Respiratory Symptoms Final Score Estimated via Anchor-Based Methods and Validated via Empirical Cumulative Distribution Functions (eCDFs)

End point title	Response Rate as Assessed by Within-Subject Meaningful Change (WSMC) for QOL-B Respiratory Symptoms Final Score Estimated via Anchor-Based Methods and Validated via Empirical Cumulative Distribution Functions (eCDFs)

End point description:

WSMC was estimated via change scores computed between Baseline and end of study (EOS) (Month 7). The estimated WSMC threshold of 14.81 points for the QOL-B Respiratory Symptom score (9-item scale ranging from 0 to 100, higher scores=fewer symptoms and better quality of life) as derived from anchor-based methods supplemented with eCDF curves was used for analysis. The percentage of participants and confidence intervals were estimated by standardized logistic regression with treatment group and history of mycobacterium avium complex (MAC) lung infection as factors in the model. Missing change from baseline at Month 7 was imputed by multiple imputation. The mean of all imputed values was used to derive response according to WSMC. Response rate was expressed in terms of percentage of participants and the percentages are rounded off to the nearest decimal. The ITT Analysis Set comprises all participants who were randomised.

End point type	Primary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: percentage of participants				
number (confidence interval 95%)	43.8 (29.8 to 57.8)	33.3 (20.4 to 46.2)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ELC + Background Regimen (Azithromycin + Ethambutol) v ALIS + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2819
Method	Standardized Logistic Regression
Parameter estimate	Percentage Difference
Point estimate	10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	29.5

Primary: Assessment of TRTR Reported as the ICC Coefficient Estimate Among Participants Reporting no Change on Fatigue PGI-S Score Applied to PROMIS F-SF 7a Score Between Screening and Baseline

End point title	Assessment of TRTR Reported as the ICC Coefficient Estimate Among Participants Reporting no Change on Fatigue PGI-S Score Applied to PROMIS F-SF 7a Score Between Screening and Baseline[4]

End point description:

TRTR consists of measuring degree to which an instrument yield reproducible score at different points in time assessed across a fixed and common time interval for all subjects. TRTR co-relations were based on two-way mixed effect intraclass co-relation coefficient estimated using inter-rater reliability package, version 0.84.1. TRTR estimate of 0.7 and above indicated better retest reliability. TRTR was estimated using mean PROMIS F-SF 7a scores from participants who were stable as defined by a PGI-S-Fatigue change score of zero between screening and baseline. As pre-specified in SAP, to adequately power planned MPMs cross-sectional validation sample was composed of a total of 98 participants enrolled in INS-415 study who provided item-level PROMIS F-SF 7a data and Screening/Baseline data from first 132 participants enrolled in INS-416 study to yield a total sample of n=230. Due to EudraCT database constraints data cannot be entered here, please refer to the table attachment.

End point type	Primary

End point timeframe:

From Screening to Baseline (Day -70 to Day 1)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical data were planned for this endpoint.

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: ICC estimate				
number (not applicable)				

Notes:

[5] - Data is not presented due to EudraCT database constraints.

[6] - Data is not presented due to EudraCT database constraints.

Attachments (see zip file)	Assessment_of_TRTR_Reported_as_the_Intraclass_Co-

Statistical analyses

No statistical analyses for this end point

Primary: Assessment of Test-Retest Reliability (TRTR) Reported as the Intraclass Co-relation (ICC) Estimate Among Participants Reporting no Change on Respiratory PGI-S Score Applied to QOL-B Respiratory Domain Score Between Screening and Baseline

End point title	Assessment of Test-Retest Reliability (TRTR) Reported as the Intraclass Co-relation (ICC) Estimate Among Participants Reporting no Change on Respiratory PGI-S Score Applied to QOL-B Respiratory Domain Score Between Screening and Baseline[7]

End point description:

TRTR consists of measuring degree to which instrument yield reproducible score at different points in time assessed across fixed and common time interval for all subjects.TRTR was assessed among subjects reporting no change on PGI-S between screening and baseline.PGI-S anchors are PRO specific,with respiratory PGI-S(scale ranging from 1=not at all to 5=extremely severe,Higher scores=greater symptom severity) applied to QOL-B respiratory domain(9-item scale ranging from 0 to 100,higher scores=fewer symptoms and better quality of life).As pre-specified in SAP,to adequately power planned modern psychometric methods(MPMs)cross-sectional validation sample was composed of a total of 97 subjects enrolled in INS-415 study who provided item-level QOL-B Respiratory domain data and Screening/Baseline data from first 132 subjects enrolled in INS-416 study(NCT04677569) to yield a total sample of n=229.Due to EudraCT database constraints data cannot be entered here,refer to table attachment.

End point type	Primary

End point timeframe:

From Screening to Baseline (Day -70 to Day 1)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical data were planned for this endpoint.

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: ICC estimate				
number (not applicable)				

Notes:

[8] - Data is not presented due to EudraCT database constraints.

[9] - Data is not presented due to EudraCT database constraints.

Attachments (see zip file)	Assessment_of_TRTR_Reported_as_the_Intraclass_Co-

Statistical analyses

No statistical analyses for this end point

Primary: Psychometric Cross-Sectional Validation of PRO: Quality of Life Questionnaire - Bronchiectasis (QoL-B) Respiratory Symptoms Scale Score at Baseline

End point title	Psychometric Cross-Sectional Validation of PRO: Quality of Life Questionnaire - Bronchiectasis (QoL-B) Respiratory Symptoms Scale Score at Baseline[10]

End point description:

The QOL-B is a self-administered, PRO questionnaire used to assess symptoms, functioning, and health related quality of life in adults with lung conditions. The respiratory symptom domain of the QOL-B contains 9 items describing patient's self-assessment of her/his respiratory symptoms that affect daily life. For each of the 8 items (chest congestion, coughing, cough up mucus, shortness of breath with greater activity, wheezing, chest pain, shortness of breath when talking, woken up during night due to cough), scores ranged from 1 to 4(1=lot, 2=moderate, 3=little, 4=not at all) and the sputum item based on the color ranged from 0=don't know,1=green with traces of blood/brownish dark,2=yellowish-green,3=clear to yellow,4=clear. The item scores were summed and then standardized on a 0 to 100-point scale to derive the domain score with higher scores representing fewer symptoms or better functioning and quality of life. The ITT Analysis Set comprises all participants who were randomised.

End point type	Primary

End point timeframe:

Baseline

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical data were planned for this endpoint.

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: score on scale				
arithmetic mean (standard deviation)	63.04 (± 14.824)	66.90 (± 15.673)		

Statistical analyses

No statistical analyses for this end point

Primary: Response Rate as Assessed by WSMC for PROMIS Fatigue Final Score Estimated via Anchor-Based Methods and Validated via eCDFs

End point title	Response Rate as Assessed by WSMC for PROMIS Fatigue Final Score Estimated via Anchor-Based Methods and Validated via eCDFs

End point description:

WSMC was estimated via change scores computed between Baseline and EOS (Month 7). The percentage of participants and confidence intervals were estimated by standardized logistic regression with treatment group and history of MAC lung infection as factors in the model. Missing change from baseline at Month 7 was imputed by multiple imputation. The mean of all imputed values was used to derive response according to WSMC. The estimated WSMC threshold of -4.00 points for the PROMIS Fatigue score as derived from anchor-based methods supplemented with eCDF curves was used for analysis. Response rate was expressed in terms of percentage of participants and the percentages are

rounded off to the nearest decimal. The ITT Analysis Set comprises all participants who were randomised.

End point type	Primary
End point timeframe:	
Baseline to Month 7	

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: percentage of participants				
number (confidence interval 95%)	35.5 (22.2 to 48.7)	29.4 (17.1 to 41.6)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ALIS + Background Regimen (Azithromycin + Ethambutol) v ELC + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.508
Method	Standardized Logistic Regression
Parameter estimate	Percentage Difference
Point estimate	6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	24.1

Secondary: Percentage of Participants Achieving Culture Conversion by Month 6

End point title	Percentage of Participants Achieving Culture Conversion by Month 6

End point description:

Culture conversion by Month 6 was defined as no MAC growth on agar media and broth media in all sputum cultures at 2 consecutive visits up to Month 6. Percentage of participants and confidence intervals were estimated by standardized logistic regression with treatment group and history of MAC lung infection as factors in the model. For the purpose of the estimation missing conversion status by Month 6 was imputed by multiple imputation. Percentages are rounded off to the nearest decimal. The ITT Analysis Set comprises all participants who were randomised.

End point type	Secondary
End point timeframe:	
Baseline to Month 6	

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: percentage of participants				
number (confidence interval 95%)	80.6 (68.7 to 92.6)	63.9 (50.2 to 77.6)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ALIS + Background Regimen (Azithromycin + Ethambutol) v ELC + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0712
Method	Standardized Logistic Regression
Parameter estimate	Percentage Difference
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	34.9

Secondary: Change from Baseline in QOL-B Respiratory Symptom Score at Month 7

End point title	Change from Baseline in QOL-B Respiratory Symptom Score at Month 7

End point description:

QOL-B is a self-administered, PRO questionnaire used to assess symptoms, functioning, and health related quality of life in adults with lung conditions. Respiratory symptom domain of QOL-B contains 9 items describing patient's self-assessment of her/his respiratory symptoms that affect daily life. For each of the 8 items(chest congestion, coughing, cough up mucus, shortness of breath with greater activity, wheezing, chest pain, shortness of breath when talking, woken up during night due to cough), scores ranged from 1 to 4(1= lot, 2= moderate, 3= little, 4= not at all) and sputum item based on color ranged from 0=don't know,1=green with traces of blood/brownish dark,2=yellowish-green,3=clear to yellow,4=clear.Item scores were summed and then standardized on a 0 to 100-point scale to derive domain score with higher scores representing fewer symptoms or better functioning and quality of life. The ITT Analysis Set comprises all participants who were randomised.

End point type	Secondary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: score on scale				
least squares mean (confidence interval 95%)	12.24 (7.96 to 16.53)	7.76 (3.76 to 11.77)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ALIS + Background Regimen (Azithromycin + Ethambutol) v ELC + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1073
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	4.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	9.93

Secondary: Time to First Culture Conversion

End point title	Time to First Culture Conversion

End point description:

Time to first culture conversion was the number of months between first study drug intake and date of the first negative culture at or before Month 6 after adjustment for non-productivity. Participants without conversion at or before Month 6 are considered censored at the last visit with available culture assessment at or before Month 6. The ITT Analysis Set comprises all participants who were randomised. Number of subjects analysed is the number of participants with culture conversion who had data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: months				
median (full range (min-max))	1.0 (1 to 5)	2.0 (1 to 5)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ALIS + Background Regimen (Azithromycin + Ethambutol) v ELC + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3542
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.92

Secondary: Time to First Negative Culture

End point title	Time to First Negative Culture

End point description:

Time to first negative culture was the number of months from the date of first dose of study drug(s) to the date of first MAC culture negative post-baseline. Participants without negative culture were considered censored at the last visit with available culture assessment or at Month 7 whichever occurred first. The ITT Analysis Set comprises all participants who were randomised. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: months				

median (full range (min-max))	1.0 (1 to 3)	1.0 (1 to 7)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ALIS + Background Regimen (Azithromycin + Ethambutol) v ELC + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1583
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2.06

Secondary: Change from Baseline in PROMIS F-SF 7a Score at Month 7

End point title	Change from Baseline in PROMIS F-SF 7a Score at Month 7

End point description:

The PROMIS F-SF 7a is a self-administered questionnaire assessing a range of self-reported symptoms over the past 7 days, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities over 7 items. Response options are on a 5-point Likert scale, ranging from 1=never to 5=always. Total scores range from 7 to 35 and low scores represent less fatigue interference i.e., better symptoms. The ITT Analysis Set comprises all participants who were randomised.

End point type	Secondary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: score on a scale				
least squares mean (confidence interval 95%)	-2.1 (-3.4 to -0.8)	-1.6 (-2.9 to -0.3)		

Statistical analyses

Statistical analysis title	ALIS vs ELC
Comparison groups	ALIS + Background Regimen (Azithromycin + Ethambutol) v ELC + Background Regimen (Azithromycin + Ethambutol)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.613
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	1.3

Secondary: Percentage of Participants Who Develop a MAC Isolate With Amikacin Minimum Inhibitory Concentration (MIC) ≥ 128 micrograms per millliliter (µg/mL) at More Than 1 Visit

End point title	Percentage of Participants Who Develop a MAC Isolate With Amikacin Minimum Inhibitory Concentration (MIC) ≥ 128 micrograms per millliliter (µg/mL) at More Than 1 Visit
End point description:	
The ITT Analysis Set comprises all participants who were randomised.	
End point type	Secondary
End point timeframe:	
Up to Month 7	

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: percentage of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence of MAC (New Infection) Assessed as Percentage of Participants Who Achieved Culture Conversion With a Subsequent at Least One MAC Positive Culture in Agar Media or Broth Media in at Least 2 Consecutive Visits

End point title	Recurrence of MAC (New Infection) Assessed as Percentage of Participants Who Achieved Culture Conversion With a Subsequent at Least One MAC Positive Culture in Agar Media or Broth Media in at Least 2 Consecutive Visits

End point description:

Culture conversion for this outcome measure was defined as MAC culture negative at 2 consecutive visits before or at Month 5 during the treatment period. The positive culture was defined as at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits. Percentages are rounded off to the nearest decimal. The ITT Analysis Set comprises all participants who were randomised. Number of subjects analysed is the number of participants who had conversion before or at Month 5 with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: percentage of participants				
number (not applicable)	5.1	25.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experience any Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experience any Treatment-emergent Adverse Event (TEAE)

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAEs are AEs that occurred on or after the date of first dose of study drugs and within 28 days after the end of treatment. The Safety Analysis Set comprises all participants who were randomised and received at least 1 dose of ALIS, ELC, azithromycin or ethambutol.

End point type	Secondary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: participants	44	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence of MAC (Relapse) Assessed as Percentage of Participants Who Achieved Culture Conversion With a Subsequent at Least One MAC Positive Culture in Agar Media or Broth Media in at Least 2 Consecutive Visits

End point title	Recurrence of MAC (Relapse) Assessed as Percentage of Participants Who Achieved Culture Conversion With a Subsequent at Least One MAC Positive Culture in Agar Media or Broth Media in at Least 2 Consecutive Visits

End point description:

Culture conversion for this outcome measure was defined as MAC culture negative at 2 consecutive visits before or at Month 5 during the treatment period. The positive culture was defined as at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits. Percentages are rounded off to the nearest decimal. The ITT Analysis Set comprises all participants who were randomised. Number of subjects analysed is the number of participants who had conversion before or at Month 5 with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to Month 7

End point values	ALIS + Background Regimen (Azithromycin + Ethambutol)	ELC + Background Regimen (Azithromycin + Ethambutol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: percentage of participants				
number (not applicable)	5.1	22.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Month 7

Adverse event reporting additional description:

The Safety Analysis Set comprises all participants who were randomised and received at least 1 dose of ALIS, ELC, azithromycin or ethambutol.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	ELC + Background Regimen (Azithromycin + Ethambutol)

Reporting group description:

Participants received ELC, a matching placebo to ALIS, once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 mg/kg tablets orally, once daily.

Reporting group title	ALIS + Background Regimen (Azithromycin + Ethambutol)

Reporting group description:

Participants received 590 mg of ALIS once daily. Participants also received the background regimen of azithromycin 250 mg and ethambutol 15 mg/kg tablets orally, once daily.

Serious adverse events	ELC + Background Regimen (Azithromycin + Ethambutol)	ALIS + Background Regimen (Azithromycin + Ethambutol)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 51 (5.88%)	7 / 48 (14.58%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			

subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ELC + Background Regimen (Azithromycin + Ethambutol)	ALIS + Background Regimen (Azithromycin + Ethambutol)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 51 (64.71%)	38 / 48 (79.17%)	
Investigations			

Weight decreased			
subjects affected / exposed	0 / 51 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 51 (9.80%)	2 / 48 (4.17%)	
occurrences (all)	5	3	
Headache			
subjects affected / exposed	6 / 51 (11.76%)	5 / 48 (10.42%)	
occurrences (all)	8	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 51 (11.76%)	5 / 48 (10.42%)	
occurrences (all)	6	7	
Asthenia			
subjects affected / exposed	5 / 51 (9.80%)	2 / 48 (4.17%)	
occurrences (all)	5	2	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	4 / 51 (7.84%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 51 (5.88%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 51 (1.96%)	4 / 48 (8.33%)	
occurrences (all)	1	4	
Abdominal pain			
subjects affected / exposed	4 / 51 (7.84%)	4 / 48 (8.33%)	
occurrences (all)	4	4	
Nausea			
subjects affected / exposed	4 / 51 (7.84%)	5 / 48 (10.42%)	
occurrences (all)	4	5	
Diarrhoea			

subjects affected / exposed	13 / 51 (25.49%)	13 / 48 (27.08%)	
occurrences (all)	15	22	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	2 / 51 (3.92%)	20 / 48 (41.67%)	
occurrences (all)	2	31	
Cough			
subjects affected / exposed	4 / 51 (7.84%)	13 / 48 (27.08%)	
occurrences (all)	4	18	
Dyspnoea			
subjects affected / exposed	4 / 51 (7.84%)	5 / 48 (10.42%)	
occurrences (all)	6	7	
Haemoptysis			
subjects affected / exposed	3 / 51 (5.88%)	5 / 48 (10.42%)	
occurrences (all)	3	8	
Oropharyngeal pain			
subjects affected / exposed	2 / 51 (3.92%)	5 / 48 (10.42%)	
occurrences (all)	2	6	
Sputum increased			
subjects affected / exposed	2 / 51 (3.92%)	4 / 48 (8.33%)	
occurrences (all)	2	5	
Wheezing			
subjects affected / exposed	0 / 51 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 51 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 51 (3.92%)	3 / 48 (6.25%)	
occurrences (all)	2	3	
Arthralgia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 48 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			

COVID-19			
subjects affected / exposed	5 / 51 (9.80%)	6 / 48 (12.50%)	
occurrences (all)	5	6	
Nasopharyngitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	4	
Urinary tract infection			
subjects affected / exposed	3 / 51 (5.88%)	2 / 48 (4.17%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 51 (3.92%)	5 / 48 (10.42%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2021	The following changes were made as per Amendment 01 - 1. AZI+ETH were moved to background regimen. 2. Updated objectives and endpoints 1, 2, 3, 4, 5, 6, and 9. 3. Updated inclusion and exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported