Platform trial of two embedded (parallel group), randomised, double blind, placebo controlled, treatment approaches in patients stratified into T2-High/T2-Low severe asthma phenotypes (using blood eosinophil levels): BEyond Allergic Th2 Severe Asthma

T2-LOW Treatment Cohort

End of Study Report

Trial registration: ISRCTN57935812

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Reviewers: Cassey Brookes, Shaun Barber and Professor Salman Siddiqui

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End of Study Report approval for finalised version:

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		29/07/2024
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	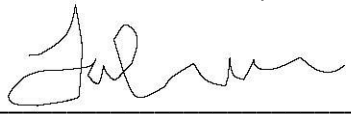	30.08.2024
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1. Introduction

The statistical analysis was carried out in accordance with the BEAT-SA T2-LOW Statistical Analysis Plan v2.2. Data reported in this report was extracted from the MACRO database after the 29th February 2024, which is the database lock date.

BEyond Allergic Th2 Severe Asthma (BEAT-SA) is a platform study made-up of 26 participants, with 13 participants allocated to the Doxycycline group and another 13 being allocated to the Placebo group. The trial was closed to recruitment following review by the funder at the end of the funded grant period having failed to reach the recruitment target in the post covid era. A total of 2 (7.7%) participants attended the last dispensing visit at 365 days follow-up while 24 (92.3%) participants attended the Safety Follow-up visit.

Due to the premature closure and the small numbers randomized the SAP was amended to reflect the fact only mostly descriptive statistics could be presented. It was not possible to conduct any powered statistical hypothesis testing/modelling, as originally planned in the protocol, due to a lack of data.

The primary analysis of the primary and secondary outcomes was conducted using the Intention-to-treat (ITT) population on a complete case basis.

The populations defined for statistical analyses are as follows:

ITT population: includes all participants who were randomised into the Trial. Participants were analysed based on the treatment to which they were randomly allocated, regardless of the treatment received or any protocol deviations.

Safety population: includes all participants who had treatment administered. Participants were considered to be in the treatment arm corresponding to the intervention they received the majority of the time, regardless of their randomised allocation.

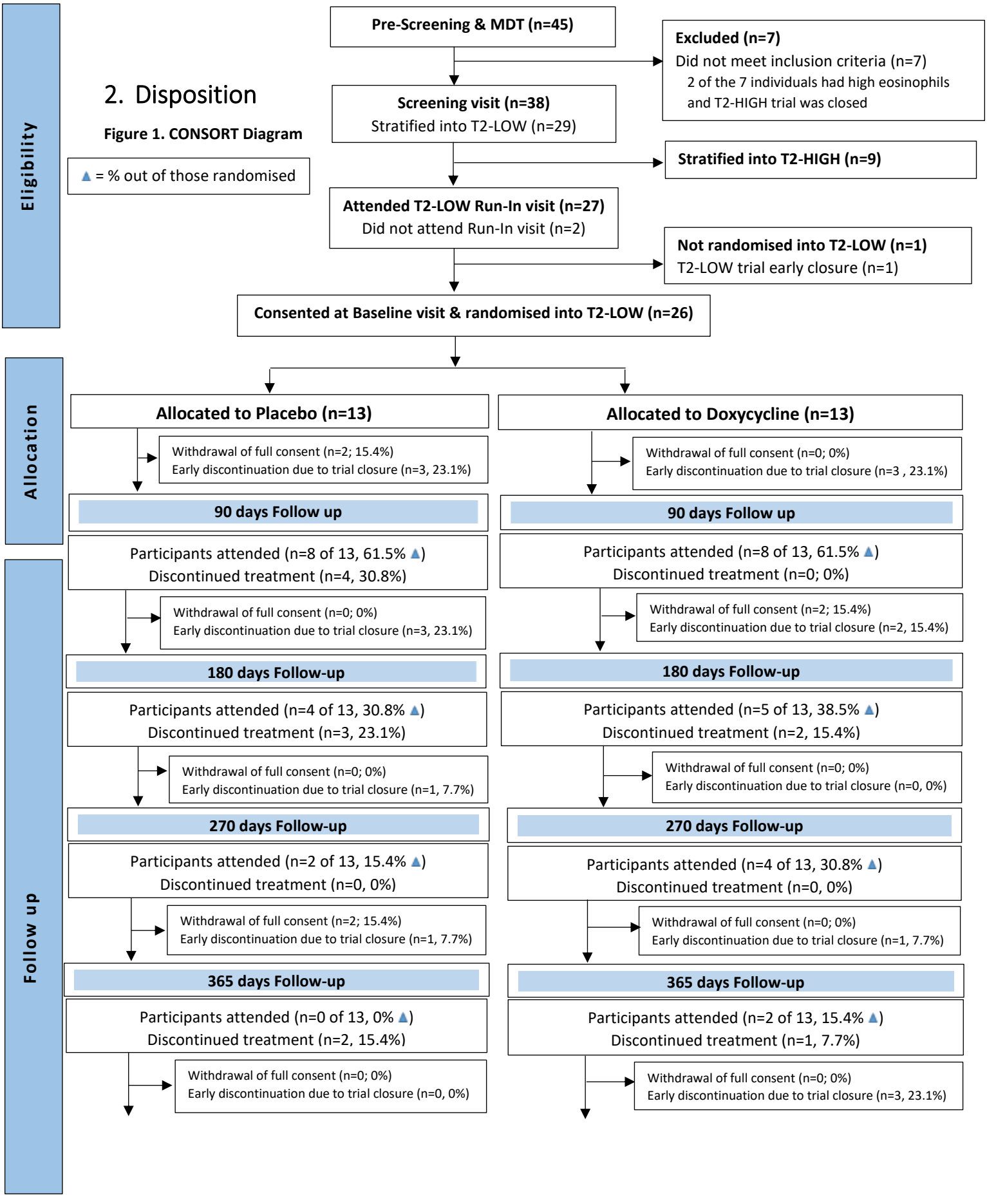
Deviations from the SAP

- Descriptive statistics of the Mechanistic Outcomes were calculated using nasal swabs and nasosorption data as no participants produced sputum either by induction or spontaneously.
- Descriptive statistics were calculated instead of the planned correlations between the Exploratory Outcomes using nasal swabs and nasosorption data as no participants produced sputum either by induction or spontaneously.
- Analyses in section 11.5 were not specified in the SAP and were carried out post-hoc at the request of the co-Chief Investigators to placate reviewers of the paper submission

2. Disposition

Figure 1. CONSORT Diagram

▲ = % out of those randomised



Safety Follow-up
Participants attended (n=12 of 13, 92.3% ▲)
Analysis of the Primary Outcome Participants included in the Primary (ITT) analysis (n=13) Participants included in the Safety analysis (n=13)

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Participants attended (n=12 of 13, 92.3% ▲)
Analysis of the Primary Outcome Participants included in the Primary (ITT) analysis (n=13) Participants included in the Safety analysis (n=13)

Please note the following:

- Pre-Screening & MDT figures and reasons for exclusion were obtained from the Screening Logs provided by sites to the LCTU.
- Run-In visit: the reason for not attending this visit is unknown for one individual whereas the other individual was no longer eligible due to a change in their asthma medication during the run-in period. The latter was obtained from the Screening Logs provided by sites to the LCTU.
- Discontinuation of treatment: figures reported correspond to participants who discontinued their allocated treatment in the period prior to the visit (i.e. between previous and indicated visit).
- Safety Follow-up visits were required to ensure the participants' safety. Participants may have attended their Safety Follow-up visit after withdrawing their full consent.
- Early discontinuation due to trial closure figures were calculated using the number of participant IDs listed in the File Note produced by the Trial Coordinator prior to the T2-LOW trial closing down to recruitment.

T2-LOW Recruitment Figures

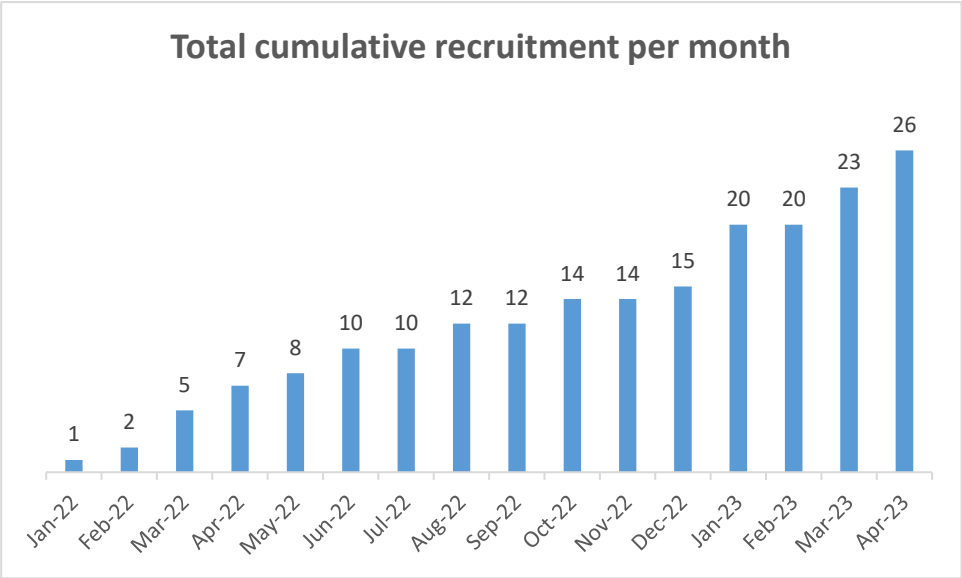

Table 1. T2-LOW Recruitment Figures per Site

Site	Participants recruited into T2-LOW Treatment Cohort
Birmingham	1
Glasgow	1
Leicester	3
Nottingham	5
Portsmouth	6
Liverpool	3
St Mary's (London)	1
Southampton	3
St Bartholomew's (London)	1
Manchester	2
Total	26

Table 2. Disposition of participants and withdrawals

		Placebo n=13	Doxycycline n=13	Total n=26
At Baseline	Provided consent, n(%)	13 (100%)	13 (100%)	26 (100%)
	Entered trial and provided data, n(%)	13 (100%)	13 (100%)	26 (100%)
At 90 days follow-up	Attended and provided data, n(%)	8 (61.5%)	8 (61.5%)	16 (61.5%)
At 180 days follow-up	Attended and provided data, n(%)	4 (30.8%)	5 (38.5%)	9 (34.6%)
At 270 days follow-up	Attended and provided data, n(%)	2 (15.4%)	4 (30.8%)	6 (23.1%)
At 365 days follow-up	Attended and provided data, n(%)	0 (0%)	2 (15.4%)	2 (7.7%)
Safety Follow-up	Attended and provided data, n(%)	12 (92.3%)	12 (92.3%)	24 (92.3%)
Discontinued treatment early, n (%)		9 (69.2%)	3 (23.1%)	12 (46.2%)
Ceased all physical participation but did not withdraw full consent, n(%)		1 (7.7%)	0 (0%)	1 (3.85%)
Withdrew full consent from the trial, n(%)		4 (30.8%)	2 (15.4%)	6 (23.1)
Early discontinuation due to Trial's early closure, n(%)		8 (61.5%)	9 (69.2%)	17 (65.4%)

NB: Figures for provision of data account for participants who completed and provided any data at each individual time point. Please note that participants randomised into the trial had the option to withdraw their consent for one or more than one trial activity at the same time or at a different time point. Participants who withdrew full consent may have also ceased all physical participation. Early discontinuation due to trial closure figures were calculated using the number of participant IDs listed in the File Note produced by the Trial Coordinator prior to the T2-LOW trial closing down to recruitment.

Table 3. Summary of Primary Outcome Results | Primary Outcome: Annual Rate of Severe Exacerbations

	Number of participants		Annual Rate of Severe Exacerbations Median (IQR)	
	Placebo	**Doxycycline**	**Placebo**	**Doxycycline**
Primary Analysis				
Intention to Treat	12	12	2.51 (0, 7.47)	2.34 (0, 4.58)

Table 4. Summary of Continuous Secondary Outcome Results

	Number of participants		**Primary Analysis:** Intention to Treat Median (IQR)	
Secondary Outcome	**Placebo**	**Doxycycline**	**Placebo**	**Doxycycline**
Time to first Severe Exacerbation (days)	13	13	86 (54, 131)	80 (47, 155)
Annual Rate of Severe Exacerbations defined as the use of systemic steroid only	12	12	1.26 (0, 3.98)	0 (0, 2.34)
Annual Rate of Severe Exacerbations defined as the use of antibiotic only	12	12	0 (0, 0)	0 (0, 0)
Annual Rate of Severe Exacerbations defined as the use of systemic steroid and antibiotic only	12	12	0 (0, 0)	0 (0, 1.31)
Annual Rate of Severe Exacerbations defined as admission to hospital or emergency department	12	12	0 (0, 0)	0 (0, 0)
Change in ACQ 6-IA from Baseline to:				
90 days follow-up	8	8	0.4 (-0.5, 1.0)	-0.4 (-1.0, 0.5)
180 days follow-up	4	5	0.6 (0.3, 1.1)	0.2 (0.0, 0.3)
270 days follow-up	2	4	0.2 (-0.5, 1.0)	-0.1 (-0.2, 0.3)
365 days follow-up	0	2	-	-0.2 (-0.5, 0.0)
Change in AQLQ S-IA from Baseline to:				
90 days follow-up	8	8	0.2 (-0.2, 0.6)	0.2 (-0.5, 0.8)
180 days follow-up	4	5	-0.7 (-1.1, 0.0)	0.2 (0.0, 0.3)
270 days follow-up	2	4	-0.6 (-0.7, -0.5)	0.4 (-0.5, 0.7)
365 days follow-up	0	2	-	0.4 (0.3, 0.5)
Change in post-bronchodilator FEV_1 from Baseline to 365 days follow-up	0	2	-	0.0 (-0.1, 0.1)
Change in post-bronchodilator FEV_1/FVC from Baseline to 365 days follow-up	0	2	-	1.5 (1.0, 2.1)
Change in absolute blood Eosinophil from Baseline to:				
90 days follow-up	6	8	-0.05 (-0.09, 0.02)	0.02 (-0.00, 0.05)

Secondary Outcome	Number of participants		Primary Analysis: Intention to Treat Median (IQR)	
	Placebo	Doxycycline	Placebo	Doxycycline
180 days follow-up	3	5	-0.06 (-0.08, 0.02)	0.03 (0.02, 0.05)
270 days follow-up	1	4	-0.11 (-0.11, -0.11)	0.00 (-0.01, 0.05)
365 days follow-up	0	1	-	0.03 (0.03, 0.03)
Change in absolute blood Neutrophil from Baseline to:				
90 days follow-up	6	8	0.97 (-0.10, 2.59)	-0.67 (-0.90, 0.50)
180 days follow-up	3	5	1.11 (-0.26, 6.39)	-0.17 (-0.39, 0.07)
270 days follow-up	1	4	0.05 (0.05, 0.05)	-0.23 (-2.48, 0.68)
365 days follow-up	0	2	-	-6.45 (-12.39, -0.50)
Change in FeNO from Baseline to:				
90 days follow-up	8	8	-0.5 (-2.2, 7.5)	-0.8 (-3.0, 14.2)
180 days follow-up	4	5	-0.2 (-4.8, 3.0)	-0.5 (-0.5, 6.0)
270 days follow-up	2	4	7.0 (5.5, 8.5)	0.2 (-5.0, 6.5)
365 days follow-up	0	2	-	-0.8 (-3.5, 2.0)
Change in SNOT-22 score from Baseline to:				
90 days follow-up	8	8	7.0 (-10.5, 11.5)	-3.5 (-7.0, 4.5)
180 days follow-up	4	5	5.0 (1.0, 10.0)	2.0 (1.0, 3.0)
270 days follow-up	2	4	2.5 (-8.0, 13.0)	-2.5 (-8.5, 21.5)
365 days follow-up	0	2	-	-8.0 (-14.0, -2.0)
Change in VAS score from Baseline to:				
90 days follow-up	8	8	3.5 (-20.0, 7.5)	-3.0 (-40.5, 7.0)
180 days follow-up	4	5	-17.5 (-57.5, 79.0)	3.0 (0.0, 3.0)
270 days follow-up	2	4	-17.0 (-37.0, 3.0)	2.5 (-9.0, 46.5)
365 days follow-up	0	2	-	-19.0 (-38.0, 0.0)
Change in EQ-5D-5L VAS score from Baseline to 365 days follow-up	0	2	-	-17.5 (-30.0, -5.0)
Change in EQ-5D-5L utility score from Baseline to 365 days follow-up	0	2	-	-0.1 (-0.2, 0.0)
WPAI: Change in % of work time missed due to asthma from Baseline to 365 days follow-up	0	1	-	0.0 (0.0, 0.0)
WPAI: Change in % of impairment while working due to asthma from Baseline to 365 days follow-up	0	1	-	10.0 (10.0, 10.0)
WPAI: Change in % of overall work impairment due to asthma from Baseline to 365 days follow-up	0	1	-	10.0 (10.0, 10.0)
WPAI: Change in % of activity impairment due to asthma from Baseline to 365 days follow-up	0	2	-	-10.0 (-20.0, 0.0)

3 Demographics and Screening data Summary

A total of 38 eligible individuals attended the Screening visit and consented to have their blood analysed for stratification with a view to participating in either the T2-LOW or T2-HIGH treatment cohorts. Of these individuals, 29 had their severe asthma subtype classed as T2-LOW and 9 as T2-HIGH. Data corresponding to all participants screened is reported in this section of the report.

Table 5. Demographics and Screening data summary

		Total (n=38)
Demographics		
Age (years)	N	38
	Mean (SD)	52.3 (11.2)
	Median (IQR)	52 (46, 62)
	Min, Max	28, 76
Sex	Male, n(%)	10 (26.3%)
	Female, n(%)	28 (73.7%)
Ethnicity	White, n(%)	36 (94.7%)
	Asian/Asian British, n(%)	1 (2.6%)
	Black/African/Caribbean/Black British, n(%)	1 (2.6%)
	Mixed/Multiple Ethnic Groups, n(%)	0 (0%)
	Other Ethnic Group, n(%)	0 (0%)
Asthma History		
Asthma confirmed by one or more of the following objective criteria ***(recorded within a 10 year period of screening)***		
A positive treatment trial to an inhaled steroids recorded by the treating clinician or GP (defined as 200ml improvement in FEV1 and 12% in FEV1 following initiation with inhaled steroids), n(%)		6 (15.8%)
i) Peak flow variation of ≥20% over a two-week period, n(%)		11 (28.9%)
ii) A methacholine or histamine PC20 of ≤8mg/ml, mannitol PD15 achieved after <635mg of cumulative dosing, n(%)		4 (10.5%)
iii) Bronchodilator reversibility of at least 200mls (FEV1) and 12% following the administration of 400mcg of Salbutamol or an equivalent bronchodilator, n(%)		14 (36.8%)
iv) Variability of FEV1 of ≥200ml and 12% between stable asthma spirometry records over a two-year period prior to screening, n(%)		9 (23.7%)
A positive response to an oral steroid trial defined as an improvement in lung function of at least 200mls and 12% (FEV1) after treatment with systemic steroids at any dose over a period of ≥10 days, n(%)		4 (10.5%)
Participant's GINA treatment intensity category:		
	Step 3, n(%)	0 (0%)
	Step 4, n(%)	11 (28.9%)
	Step 5, n(%)	26 (68.4%)
	Missing, n(%)	1 (2.6%)
Has the participant had a severe asthma diagnosis confirmed by the MDT or non-English equivalent trial team?		
	Yes, n(%)	37 (97.4%)

	Total (n=38)
MDT or non-English equivalent trial team confirmed adherence to current asthma therapies using one or more of the following criteria:	
Prescription refill records (≥75% adherence to ICS, ICS/LABA therapy) within 365 days of screening, n(%)	34 (89.5%)
BOTH recordable serum prednisolone and supressed cortisol levels (as determined at the discretion of the Investigator) in patients taking regular systemic corticosteroids. We will capture whether local tests evaluating serum prednisolone and cortisol levels are performed via High Performance Liquid Chromatography (HPLC) or non-HPLC, n(%)	1 (2.6%)
Testing method used:	
HPLC, n(%)	1 (2.6%)
Non-HPLC, n(%)	0 (0%)
A FeNO of <45ppb at screening or a negative FeNO suppression testing in selected patients (FeNO ≥45ppb). FeNO suppression testing can be delivered according to local service level arrangements, including INCA based monitoring, other SMART devices or directly observed inhaler therapy, n(%)	16 (42.1%)
Does the participant have a family history of asthma?	
Yes, n(%)	30 (78.9%)
Have there been any deaths in the family due to asthma?	
Yes, n(%)	1 (2.6%)
Does the participant have an asthma action plan?	
Yes, n(%)	30 (78.9%)
Does the participant have any of the following:	
Allergies (to common seasonal or perennial allergens (confirmed by either skin prick test or immunocap testing/equivalent within 10 years of screening), n(%)	14 (36.8%)
Triggers: Participant reported triggers for asthma exacerbations e.g. aspirin/NSAIDS, grass pollen, dust exposure, etc., n(%)	37 (97.4%)
Polyps: Nasal polyps confirmed by visual nasal examination, nasendoscopy or CT sinus imaging, n(%)	4 (10.5%)
Has the participant had any previous nasal polyp resection surgery?	
Yes, n(%)	3 (7.9%)
Aspirin/NSAID sensitivity	
Yes, n(%)	10 (26.3%)
In the 365 days prior to screening, has the participant:	
Had courses of oral steroids?	
Yes, n(%)	37 (97.4%)
Had any unscheduled visits to their GP/A&E due to airways disease?	
Yes, n(%)	25 (65.8%)

		Total (n=38)
Had any ITU admissions due to airways disease?	Yes, n(%)	2 (5.3%)
Has the participant received treatment with a biologic (s) within 4 months prior to screening?		
	No, n(%)	38 (100%)
Has the participant received/completed bronchial thermoplasty treatment within 180 days of screening?		
	No, n(%)	38 (100%)
Is the participant currently receiving long term treatment (≥90 days) with macrolides for asthma?		
	No, n(%)	38 (100%)
Smoking History		
Has the participant ever smoked (including e-cigarettes)?		
	Yes, n(%)	12 (31.6%)
How many years did the participant smoke for (including e-cigarettes)?		
	N	12
	Mean (SD)	8.7 (6.7)
	Median (IQR)	6 (3.5, 14)
	Min, Max	1, 22
How many cigarettes did the participant smoke per day?		
	N	12
	Mean (SD)	10 (5.8)
	Median (IQR)	10 (7.5, 11)
	Min, Max	1, 20
Number of pack-years previously smoked		
	N	12
	Mean (SD)	5.1 (4.4)
	Median (IQR)	3.5 (1.5, 8)
	Min, Max	0, 14
Highest Blood Eosinophil Level (if known, in the year prior to screening)		
Blood eosinophil result ($x10^9$ L cells)		
	N	32
	Mean (SD)	0.2 (0.2)
	Median (IQR)	0.1 (0.1, 0.3)
	Min, Max	0.0, 0.9
Medical History		
COPD, n(%)		0 (0%)
Atopic dermatitis, n(%)		4 (10.5%)
Bronchiectasis (reported by CT imaging), n(%)		5 (13.2%)
Allergic Bronchopulmonary Aspergillosis (ABPA), n(%)		1 (2.6%)
Urticaria (e.g. Idiopathic, autoimmune, n(%)		2 (5.3%)
Previous anaphylaxis or angioedema, n(%)		4 (10.5%)

		Total (n=38)
EpiPen usage, n(%)		3 (7.9%)
Eosinophilic esophagitis, n(%)		0 (0%)
Seasonal or perennial rhinitis (please specify), n(%)		28 (73.7%)
	Seasonal rhinitis, n(%)	19 (50.0%)
	Perennial rhinitis, n(%)	9 (23.7%)
Immunodeficiency (CVID or specific antibody deficiency confirmed by immunology services, n(%)		0 (0%)
Ischaemic Heart disease, n(%)		2 (5.3%)
Previous Myocardial infarction, n(%)		0 (0%)
Previous Stroke (ischaemic or haemorrhagic), n(%)		0 (0%)
Diabetes, n(%)		4 (10.5%)
	Diabetes type 2, n(%)	4 (10.5%)
Hypertension, n(%)		13 (34.2%)
Pulmonary hypertension, n(%)		0 (0%)
Epilepsy, n(%)		0 (0%)
High cholesterol, n(%)		9 (23.7%)
Chronic kidney disease, n(%)		0 (0%)
Liver Disease, n(%)		1 (2.6%)
Depression, n(%)		12 (31.6%)
Anxiety, n(%)		15 (39.5%)
GORD, n(%)		21 (55.3%)
Blindness/Glaucoma, n(%)		2 (5.3%)
Malignancy**,** n(%)		3 (7.9%)
Drug allergy, n(%)		18 (47.4%)
Other medical conditions, n(%)		29 (76.3%)

		Total (n=38)
Total IgE (if assessment done, within the previous 365 days prior to Screening)		
Total IgE (kU/L)		
	N	19
	Mean (SD)	76.8 (182.3)
	Median (IQR)	30.0 (8.0, 55.0)
	Min, Max	2.0, 813.0
COVID-19 Status		
Has the participant previously had COVID-19 based on a PCR test?		
	Yes, n(%)	18 (47.4%)
Has the participant received a COVID-19 vaccine?		
	Yes, n(%)	37 (97.4%)
Has the participant had (or will be receiving) a second dose of a COVID-19 vaccine?		
	Yes, n(%)	36 (94.7%)
Has the participant received any further COVID-19 'booster' vaccinations?		
	Yes, n(%)	34 (89.5%)
Has the participant been shielding due to COVID-19 at any point in the last 365 days?		
	Yes, n(%)	10 (26.3%)
If Yes, approximately, how many months has the participant been shielding for within the last 365 days?		
	N	10
	Mean (SD)	6.9 (4.6)
	Median (IQR)	6 (2, 12)
	Min, Max	2, 12
Blood Stratification Sample Result		
BEAT-SA Central Management Team confirmed Eosinophil level ($x10^9$ L cells)		
	N	38
	Mean (SD)	0.2 (0.2)
	Median (IQR)	0.1 (0.1, 0.3)
	Min, Max	0.0, 0.8
BEAT-SA Central Management Team confirmed severe asthma sub-type according to eosinophil level		
	T2-HIGH, n(%)	9 (23.7%)
	T2-LOW, n(%)	29 (76.3%)

4 Run-In data Summary of T2-LOW Cohort

Of the 29 individuals whose severe asthma sub-type was confirmed as T2-LOW at the Screening stage, 2 of them did not attend the Run-In visit (reason for not attending is unknown for one individual whereas the other individual was no longer eligible due to a change in their asthma medication during the run-in period).

Table 6. Run-In data Summary T2-LOW cohort

		Total (n=27)
Participant Information Sheet		
Has the participant been provided with the relevant Stage 2 Participant Information Sheet? V4.0, Date 18/01/2021		
	Yes, n(%)	27 (100%)
Stable Disease Assessment		
Is the participant currently exacerbating?		
	Yes, n(%)	1 (3.7%)
Asthma Action Plan Review		
Has the participant's asthma action plan been clinically reviewed by a trained practitioner?		
	Yes, n(%)	26 (96.3%)
Is the Research Nurse/treating Clinician satisfied that the participant understands how to identify, manage and report exacerbations?		
	Yes, n(%)	27 (100%)
ICS, ICS/LABA Assessment		
Has the participant's maintenance ICS, ICS/LABA technique been clinically reassessed by a trained practitioner/trial team?		
	Yes, n(%)	27 (100%)
Has the participant's ICS, ICS/LABA technique been clinically confirmed as adequate by a trained practitioner/trial team?		
	Yes, n(%)	27 (100%)
Micro Diary		
The participant has been trained in how to use the micro diary		
	Yes, n(%)	27 (100%)
The participant has been provided with the micro diary questions and user guide		
	Yes, n(%)	27 (100%)

5 Baseline data Summary of T2-LOW Cohort

Table 7. Baseline data Summary T2-LOW cohort

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Vital Signs				
Height, cm	N	13	13	26
	Mean (SD)	166.3 (9.4)	168.4 (7.6)	167.3 (8.4)
	Median (IQR)	163.0 (160.0, 173.0)	166.0 (164.0, 174.0)	165.5 (160.0, 174.0)
	Min, Max	155.0, 186.0	158.0, 183.0	155.0, 186.0
Weight, kg	N	13	13	26
	Mean (SD)	91.4 (19.3)	89.3 (20.4)	90.4 (19.4)
	Median (IQR)	90.0 (75.6, 102.6)	91.0 (76.4, 105.0)	90.5 (75.6, 105.0)
	Min, Max	67.4, 121.8	47.0, 116.7	47.0, 121.8
BMI, kg/m^2	N	13	13	26
	Mean (SD)	32.9 (5.5)	31.8 (7.3)	32.3 (6.3)
	Median (IQR)	31.1 (28.0, 36.7)	31.4 (26.9, 38.8)	31.2 (27.7, 37.6)
	Min, Max	25.7, 43.7	17.1, 40.0	17.1, 43.7
Respiratory Rate, breaths/min	N	13	13	26
	Mean (SD)	16.2 (3.4)	15.7 (1.8)	15.9 (2.7)
	Median (IQR)	16.0 (14.0, 18.0)	16.0 (14.0, 17.0)	16.0 (14.0, 17.0)
	Min, Max	12.0, 24.0	12.0, 18.0	12.0, 24.0
Oxygen Saturation, %	N	13	13	26
	Mean (SD)	97.0 (1.0)	97.1 (1.9)	97.0 (1.5)
	Median (IQR)	97.0 (96.0, 98.0)	97.0 (96.0, 98.0)	97.0 (96.0, 98.0)
	Min, Max	96.0, 98.0	94.0, 100.0	94.0, 100.0
Systolic BP, mmHg	N	13	13	26
	Mean (SD)	137.2 (14.3)	135.8 (20.9)	136.5 (17.6)
	Median (IQR)	134.0 (127.0, 145.0)	137.0 (123.0, 144.0)	134.0 (124.0, 145.0)
	Min, Max	119.0, 166.0	105.0, 174.0	105.0, 174.0
Diastolic BP, mmHg	N	13	13	26
	Mean (SD)	80.8 (7.1)	84.4 (14.4)	82.6 (11.3)
	Median (IQR)	81.0 (79.0, 84.0)	82.0 (69.0, 96.0)	81.0 (76.0, 90.0)
	Min, Max	69.0, 97.0	66.0, 106.0	66.0, 106.0
Heart Rate, beats/min	N	13	13	26
	Mean (SD)	77.5 (10.3)	76.7 (10.5)	77.1 (10.2)
	Median (IQR)	78.0 (69.0, 87.0)	80.0 (68.0, 85.0)	78.0 (68.0, 85.0)
	Min, Max	64.0, 97.0	56.0, 91.0	56.0, 97.0

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Temperature, ^{0}C	N	13	13	26
	Mean (SD)	36.7 (0.3)	36.9 (0.3)	36.8 (0.3)
	Median (IQR)	36.6 (36.4, 37.0)	36.8 (36.7, 37.0)	36.7 (36.5, 37.0)
	Min, Max	36.2, 37.2	36.5, 37.4	36.2, 37.4
COVID-19				
Has the participant received a positive PCR COVID-19 test result since their previous visit?				
	Yes, n(%)	1 (7.7%)	1 (7.7%)	2 (7.7%)
Exacerbation History (since the previous Run-In visit)				
Treatment duration, days	N	2 [a]	0	2
	Mean (SD)	7.0 (0.0)	-	7.0 (0.0)
	Median (IQR)	7.0 (7.0, 7.0)	-	7.0 (7.0, 7.0)
	Min, Max	7.0, 7.0	-	7.0, 7.0
Treatment	Antibiotics, n(%)	1 (7.1%)	-	1 (3.7%)
	Steroids, n(%)	2 (14.3%)	-	2 (7.4%)
	Antibiotics and Steroids, n(%)	1 (50%)	-	1 (50%)
Dose, mg of prednisolone	N	2	-	2
	Mean (SD)	40.0 (0.0)	-	40.0 (0.0)
	Median (IQR)	40.0 (40.0, 40.0)	-	40.0 (40.0, 40.0)
	Min, Max	40.0, 40.0	-	40.0, 40.0
Admission	Hospital, n(%)	0 (0%)	-	0 (0%)
	Emergency Department, n(%)	0 (0%)	-	0 (0%)
	Hospital and Emergency Department, n(%)	0 (0%)	-	0 (0%)
Confirmation of Severe Asthma				
	Patient Confirmed, n(%)	2 (100%)	-	2 (100%)
	Patient confirmed and verified, n(%)	0 (0%)	-	0 (0%)
Physical Examination				
General appearance	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
	Normal, n(%)	13 (100%)	12 (92.3%)	25 (96.2%)
	Abnormal, n(%)	0 (0%)	1 (7.7%)	1 (3.8%)
	Clinically significant (if abnormal), n(%)	-	0 (0%)	0 (0%)
Skin	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
	Normal, n(%)	13 (100%)	10 (76.9%)	23 (88.5%)
	Abnormal, n(%)	0 (0%)	3 (23.1%)	3 (11.5%)
	Clinically significant (if abnormal), n(%)	-	0 (0%)	0 (0%)
Head (eyes, ears, nose, mouth and throat)	Not done, n(%)	0 (0%)	2 (15.4%)	2 (7.7%)
	Normal, n(%)	12 (92.3%)	10 (76.9%)	22 (84.6%)
	Abnormal, n(%)	1 (7.7%)	1 (7.7%)	2 (7.7%)
	Clinically significant (if abnormal), n(%)	0 (0%)	0 (0%)	0 (0%)

[a] Only one participant reported 2 exacerbations at the Baseline visit

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Lymph nodes	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
	Normal, n(%)	13 (100%)	13 (100%)	26 (100%)
	Abnormal, n(%)	0 (0%)	0 (0%)	0 (0%)
	Clinically significant (if abnormal), n(%)	-	-	-
Musculoskeletal	Not done, n(%)	0 (0%)	1 (7.7%)	1 (3.8%)
	Normal, n(%)	10 (76.9%)	10 (76.9%)	20 (76.9%)
	Abnormal, n(%)	3 (23.1%)	2 (15.4%)	5 (19.2%)
	Clinically significant (if abnormal), n(%)	0 (0%)	0 (0%)	0 (0%)
Cardiovascular	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
	Normal, n(%)	13 (100%)	13 (100%)	26 (100%)
	Abnormal, n(%)	0 (0%)	0 (0%)	0 (0%)
	Clinically significant (if abnormal), n(%)	-	-	-
Respiratory	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
	Normal, n(%)	12 (92.3%)	13 (100%)	25 (96.2%)
	Abnormal, n(%)	1 (7.7%)	0 (0%)	1 (3.8%)
	Clinically significant (if abnormal), n(%)	0 (0%)	-	0 (0%)
Gastrointestinal	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
	Normal, n(%)	10 (76.9%)	12 (92.3%)	22 (84.6%)
	Abnormal, n(%)	3 (23.1%)	1 (7.7%)	4 (15.4%)
	Clinically significant (if abnormal), n(%)	0 (0%)	0 (0%)	0 (0%)
Neurological	Not done, n(%)	0 (0.0%)	1 (7.7%)	1 (3.8%)
	Normal, n(%)	12 (92.3%)	11 (84.6%)	23 (88.5%)
	Abnormal, n(%)	1 (7.7%)	1 (7.7%)	2 (7.7%)
	Clinically significant (if abnormal), n(%)	0 (0%)	0 (0%)	0 (0%)
Other	Not done, n(%)	1 (7.7%)	2 (15.4%)	3 (11.5%)
	Normal, n(%)	1 (7.7%)	0 (0%)	1 (3.8%)
	Abnormal, n(%)	0 (0%)	2 (15.4%)	2 (7.7%)
	Not applicable, n(%)	11 (84.6%)	9 (69.2%)	20 (76.9%)
	Clinically significant (if abnormal), n(%)	-	0 (0%)	0 (0%)
FeNO				
Assessment performed?	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Result 1, ppb	N	13	13	26
	Mean (SD)	27.1 (26.9)	21.2 (20.4)	24.2 (23.6)
	Median (IQR)	24.0 (11.0, 28.0)	16.0 (9.0, 19.0)	16.5 (9.0, 26.0)
	Min, Max	7.0, 107.0	6.0, 83.0	6.0, 107.0
Result 2, ppb	N	13	13	26
	Mean (SD)	28.5 (27.0)	21.0 (18.9)	24.8 (23.2)
	Median (IQR)	21.0 (12.0, 34.0)	16.0 (14.0, 17.0)	16.5 (12.0, 27.0)
	Min, Max	7.0, 109.0	6.0, 78.0	6.0, 109.0

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Average Result (only recorded if participant was unable to produce two measurements)	N	6	6	12
	Mean (SD)	16.5 (7.3)	14.0 (4.4)	15.2 (5.9)
	Median (IQR)	17.0 (9.0, 22.0)	15.5 (12.0, 17.0)	15.5 (10.5, 20.0)
	Min, Max	9.0, 25.0	6.0, 18.0	6.0, 25.0
Number of duplicate measurements not within 10% of one another	N	5	7	12
	Mean (SD)	1.4 (0.9)	0.6 (1.0)	0.9 (1.0)
	Median (IQR)	2.0 (1.0, 2.0)	0.0 (0.0, 2.0)	0.5 (0.0, 2.0)
	Min, Max	0.0, 2.0	0.0, 2.0	0.0, 2.0
Best Post-Bronchodilator Spirometry (if assessment done)				
FEV_1, L	N	12	12	24
	Mean (SD)	2.2 (0.8)	2.4 (0.8)	2.3 (0.8)
	Median (IQR)	2.5 (1.5, 2.7)	2.7 (2.3, 3.0)	2.5 (1.8, 2.8)
	Min, Max	0.9, 3.8	0.6, 3.2	0.6, 3.8
% Predicted FEV_1	N	11	12	23
	Mean (SD)	79.6 (20.9)	83.9 (29.7)	81.8 (25.4)
	Median (IQR)	83.0 (59.0, 97.0)	92.0 (80.1, 102.5)	90.0 (63.0, 99.0)
	Min, Max	46.0, 113.0	17.0, 113.0	17.0, 113.0
	Not available, N	1	0	1
FVC, L	N	12	12	24
	Mean (SD)	3.3 (1.0)	3.3 (0.6)	3.3 (0.8)
	Median (IQR)	3.0 (2.7, 3.6)	3.5 (2.9, 3.7)	3.4 (2.7, 3.7)
	Min, Max	2.3, 6.1	2.2, 4.2	2.2, 6.1
% Predicted FVC	N	11	12	23
	Mean (SD)	99.6 (14.6)	90.3 (22.2)	94.8 (19.1)
	Median (IQR)	101.0 (82.7, 112.0)	95.8 (81.5, 108.5)	98.0 (82.7, 110.0)
	Min, Max	80.0, 123.0	48.0, 111.0	48.0, 123.0
	Not available, N	1	0	1
PEF, L/min	N	11	11	22
	Mean (SD)	377.2 (138.2)	330.6 (195.2)	353.9 (166.8)
	Median (IQR)	386.0 (273.0, 458.0)	403.0 (161.0, 495.0)	394.5 (273.0, 458.0)
	Min, Max	165.0, 599.0	4.6, 569.0	4.6, 599.0
	Not available, N	1	1	2
% Predicted PEF	N	9	9	18
	Mean (SD)	84.7 (23.0)	90.6 (42.5)	87.6 (33.3)
	Median (IQR)	79.0 (72.0, 107.0)	96.0 (59.0, 123.0)	87.5 (60.0, 108.0)
	Min, Max	49.0, 111.0	30.0, 147.0	30.0, 147.0
	Not available, N	3	2	5
	Missing, N	0	1	1

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
% FEV_1/FVC	N	12	12	24
	Mean (SD)	67.5 (17.0)	71.3 (18.0)	69.4 (17.2)
	Median (IQR)	69.0 (56.2, 81.6)	74.2 (68.0, 85.0)	74.2 (59.7, 83.0)
	Min, Max	32.0, 88.7	26.0, 89.0	26.0, 89.0
% Predicted FEV_1/FVC	N	11	12	23
	Mean (SD)	82.7 (22.7)	88.8 (21.5)	85.9 (21.8)
	Median (IQR)	81.0 (66.0, 102.0)	91.5 (83.2, 105.0)	91.0 (73.0, 102.0)
	Min, Max	42.0, 110.0	35.0, 110.0	35.0, 110.0
	Not available, N	1	0	1
Bronchodilator Reversibility FEV_1, %	N	4	5	9
	Mean (SD)	13.7 (9.5)	5.6 (8.0)	9.2 (9.2)
	Median (IQR)	12.9 (7.4, 20.0)	2.0 (0.0, 7.1)	7.1 (2.0, 14.0)
	Min, Max	3.0, 26.0	0.0, 19.0	0.0, 26.0
	Not available, N	8	6	14
	Missing, N	0	1	1
Bronchodilator Reversibility FEV_1, mls	N	4	6	10
	Mean (SD)	269.6 (237.4)	143.3 (244.8)	193.8 (237.4)
	Median (IQR)	254.0 (100.2, 439.0)	25.0 (0.0, 190.0)	120.0 (0.0, 308.0)
	Min, Max	0.3, 570.0	0.0, 620.0	0.0, 620.0
	Not available, N	8	4	12
	Missing, N	0	2	2
Sputum Induction				
Sputum induction performed?	Yes, n(%)	4 (30.8%)	2 (15.4%)	6 (23.1%)
Sputum production spontaneous (S) or induced (I)?				
	Spontaneous, n(%)	4 (100%)	2 (100%)	6 (100%)
	Induced, n(%)	0 (0%)	0 (0%)	0 (0%)
Sample collected?	Yes, n(%)	3 (23.1%)	2 (15.4%)	5 (19.2%)
Sample taken for differential cell count?				
	Yes, n(%)	3 (23.1%)	2 (15.4%)	5 (19.2%)
Sample taken for qPCR?	Yes, n(%)	3 (23.1%)	2 (15.4%)	5 (19.2%)
Sample taken for routine NHS microbiological culture?				
	No, n(%)	3 (23.1%)	2 (15.4%)	5 (19.2%)
Biochemistry				
Sodium (mmol/L)	N	13	13	26
	Mean (SD)	139.3 (2.6)	139.7 (2.1)	139.5 (2.3)
	Median (IQR)	140.0 (138.0, 141.0)	141.0 (138.0, 141.0)	140.0 (138.0, 141.0)
	Min, Max	133.0, 143.0	135.0, 142.0	133.0, 143.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Potassium (mmol/L)	N	13	13	26
	Mean (SD)	4.3 (0.4)	4.3 (0.3)	4.3 (0.4)
	Median (IQR)	4.4 (4.0, 4.5)	4.3 (4.2, 4.4)	4.3 (4.1, 4.5)
	Min, Max	3.8, 5.2	3.7, 5.0	3.7, 5.2
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Urea (mmol/L)	N	13	13	26
	Mean (SD)	4.7 (0.9)	4.1 (0.9)	4.4 (1.0)
	Median (IQR)	4.8 (4.0, 5.3)	4.2 (3.6, 4.8)	4.6 (3.7, 5.0)
	Min, Max	3.2, 6.5	2.4, 5.5	2.4, 6.5
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Creatinine (mmol/L)	N	13	13	26
	Mean (SD)	65.9 (16.0)	64.3 (24.9)	65.1 (20.6)
	Median (IQR)	62.0 (59.0, 68.0)	68.0 (56.0, 72.0)	65.0 (59.0, 70.0)
	Min, Max	43.0, 102.0	0.0, 106.0	0.0, 106.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
eGFR (mL/min)	N	13	13	26
	Mean (SD)	81.5 (13.2)	86.1 (7.4)	83.8 (10.7)
	Median (IQR)	90.0 (77.0, 90.0)	90.0 (89.0, 90.0)	90.0 (77.0, 90.0)
	Min, Max	54.0, 90.0	70.0, 90.0	54.0, 90.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
C-Reactive Protein (mg/L)	N	13	13	26
	Mean (SD)	5.4 (6.8)	3.8 (3.4)	4.6 (5.3)
	Median (IQR)	2.0 (2.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)
	Min, Max	1.0, 26.0	1.0, 12.0	1.0, 26.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Alanine Transaminase (U/L)	N	12	13	25
	Mean (SD)	29.2 (14.7)	32.6 (22.1)	31.0 (18.6)
	Median (IQR)	22.5 (19.5, 38.0)	28.0 (23.0, 32.0)	24.0 (21.0, 36.0)
	Min, Max	18.0, 68.0	12.0, 97.0	12.0, 97.0
	Not done, n(%)	1 (7.7%)	0 (0%)	1 (3.8%)
Total Bilirubin (µmol/L)	N	13	13	26
	Mean (SD)	9.5 (4.6)	10.1 (5.1)	9.8 (4.8)
	Median (IQR)	10.0 (6.0, 11.0)	9.0 (7.0, 14.0)	9.5 (6.0, 14.0)
	Min, Max	4.0, 20.0	3.0, 21.0	3.0, 21.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Albumin (g/L)	N	13	13	26
	Mean (SD)	41.3 (3.9)	41.4 (4.4)	41.3 (4.1)
	Median (IQR)	41.0 (39.0, 45.0)	40.0 (38.0, 45.0)	40.5 (38.0, 45.0)
	Min, Max	35.0, 49.0	35.0, 48.0	35.0, 49.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Adjusted Calcium (mmol/L)	N	13	13	26
	Mean (SD)	2.4 (0.1)	2.3 (0.1)	2.4 (0.1)
	Median (IQR)	2.4 (2.3, 2.4)	2.3 (2.3, 2.4)	2.4 (2.3, 2.4)
	Min, Max	2.2, 2.5	2.2, 2.5	2.2, 2.5
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Inorganic Phosphate [a] (mmol/L)	N	11	13	24
	Mean (SD)	1.01 (0.34)	0.87 (0.33)	0.94 (0.34)
	Median (IQR)	1.09 (0.97, 1.18)	0.88 (0.81, 1.04)	1.00 (0.85, 1.10)
	Min, Max	0.07, 1.33	0.05, 1.40	0.05, 1.40
	Not done, n(%)	2 (15.4%)	0 (0.0%)	2 (7.7%)
Alkaline Phosphatase (lμ/L)	N	13	13	26
	Mean (SD)	89.3 (27.9)	81.3 (22.1)	85.3 (25.0)
	Median (IQR)	80.0 (75.0, 99.0)	71.0 (70.0, 97.0)	78.5 (70.0, 99.0)
	Min, Max	45.0, 148.0	52.0, 121.0	45.0, 148.0
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Cholesterol (mmol/L)	N	13	13	26
	Mean (SD)	5.0 (1.1)	5.1 (1.4)	5.1 (1.3)
	Median (IQR)	5.0 (4.6, 5.4)	4.8 (4.5, 5.5)	4.9 (4.5, 5.4)
	Min, Max	3.2, 8.0	3.5, 8.6	3.2, 8.6
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
Triglycerides (mmol/L)	N	13	13	26
	Mean (SD)	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)
	Median (IQR)	1.2 (1.1, 2.0)	1.6 (0.8, 1.9)	1.4 (1.0, 2.0)
	Min, Max	0.6, 2.8	0.6, 2.6	0.6, 2.8
	Not done, n(%)	0 (0%)	0 (0%)	0 (0%)
HDL Cholesterol (mmol/L)	N	9	11	20
	Mean (SD)	1.6 (0.5)	1.5 (0.4)	1.6 (0.4)
	Median (IQR)	1.5 (1.4, 1.8)	1.4 (1.2, 1.8)	1.5 (1.2, 1.8)
	Min, Max	1.0, 2.7	1.0, 2.3	1.0, 2.7
	Not done, n(%)	4 (30.8%)	2 (15.4%)	6 (23.1%)
Total Cholesterol: HDL Ratio (mmol/L)	N	9	11	20
	Mean (SD)	3.1 (1.2)	3.7 (1.2)	3.4 (1.2)
	Median (IQR)	2.8 (2.7, 3.8)	3.4 (2.8, 4.3)	3.2 (2.7, 4.1)
	Min, Max	1.1, 5.1	2.2, 6.4	1.1, 6.4
	Not done, n(%)	4 (30.8%)	2 (15.4%)	6 (23.1%)
LDL Cholesterol (mmol/L)	N	8	9	17
	Mean (SD)	2.9 (1.3)	3.0 (1.3)	2.9 (1.3)
	Median (IQR)	2.5 (2.1, 3.0)	2.5 (2.0, 3.2)	2.5 (2.1, 3.2)
	Min, Max	2.0, 5.8	1.9, 5.7	1.9, 5.8
	Not done, n(%)	5 (38.5%)	3 (23.1%)	8 (30.8%)
	Missing, N	0 (0%)	1 (7.7%)	1 (3.8%)

[a] Inorganic Phosphate data reported in this section was provided by sites in an Excel document as data captured in the MACRO database was not measured in mmol/L

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
Related Case Report				
Has the participant experienced any adverse events or serious adverse events since their last visit?				
	Yes, n(%)	4 (30.8%)	2 (15.4%)	6 (23.1%)
Has the participant reported any changes/additions/cessations in concomitant medications?				
	Yes, n(%)	1 (7.7%)	2 (15.4%)	3 (11.5%)
Informed Consent for Samples				
Has the participant provided their informed consent to allow their samples to be used for ethically approved research?				
	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Micro Diary				
Is the participant using a Micro Diary during the trial?				
	Yes, n(%)	12 (92.3%)	12 (92.3%)	24 (92.3%)
Participant declined to use the Micro Diary during the trial, it was due to:				
	High technical demand/load, n(%)	0 (0%)	1 (7.7%)	1 (3.8%)
	High level of inconvenience to recording data, n(%)	1 (7.7%)	0 (0%)	1 (3.8%)
	Did not want to undertake the Micro Diary component, n(%)	0 (0%)	0 (0%)	0 (0%)
	Manual dexterity, n(%)	0 (0%)	0 (0%)	0 (0%)
	Other, n(%)	0 (0%)	0 (0%)	0 (0%)
If the participant is not using the Micro Diary, have they have been provided with paper copies of the BEAT-SA Participant Asthma Diary and a PEF meter?				
	Yes, n(%)	1 (7.7%)	1 (7.7%)	2 (7.7%)
FEV_1 via Micro Diary (if used)				
FEV1	Not done, n(%)	5 (38.5%)	3 (23.1%)	8 (30.8%)
FEV_1 (L)	N	8	10	18
	Mean (SD)	2.3 (0.6)	2.5 (0.9)	2.4 (0.8)
	Median (IQR)	2.2 (2.0, 2.5)	2.6 (2.2, 3.1)	2.3 (2.0, 3.0)
	Min, Max	1.3, 3.3	0.6, 3.8	0.6, 3.8
FEV_1 (L)	N	8	8	16
	Mean (SD)	2.5 (0.8)	2.3 (0.8)	2.4 (0.8)
	Median (IQR)	2.3 (2.0, 3.0)	2.3 (2.0, 2.9)	2.3 (2.0, 2.9)
	Min, Max	1.4, 3.7	0.6, 3.2	0.6, 3.7
FEV_1 (L)	N	8	8	16
	Mean (SD)	2.4 (0.8)	2.2 (0.8)	2.3 (0.8)
	Median (IQR)	2.3 (2.1, 2.8)	2.2 (1.9, 2.9)	2.3 (2.0, 2.9)
	Min, Max	1.3, 3.7	0.6, 3.2	0.6, 3.7
Pregnancy Test (Urine) – WOCBP Only				
Pregnancy test performed	Yes, n(%)	4 (40%)	7 (87.5%)	11 (61.1%)
Result	Negative, n(%)	4 (40%)	7 (87.5%)	11 (61.1%)
	Positive, n(%)	0 (0%)	0 (0%)	0 (0%)

		Placebo (n=13)	Doxycycline (n=13)	Total (n=26)
12-Lead ECG				
12-Lead ECG performed?	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Rhythm	Normal, n(%)	11 (84.6%)	11 (84.6%)	22 (84.6%)
	Abnormal, n(%)	2 (15.4%)	2 (15.4%)	4 (15.4%)
If abnormal, is this clinically significant?	No, n(%)	2 (15.4%)	2 (15.4%)	4 (15.4%)
Heart Rate (beats/min)	N	12	12	24
	Mean (SD)	71.5 (10.8)	67.8 (10.9)	69.7 (10.8)
	Median (IQR)	75.0 (64.0, 77.0)	68.0 (60.5, 75.5)	68.5 (61.0, 77.0)
	Min, Max	53.0, 91.0	49.0, 84.0	49.0, 91.0
	Not Available, N	1	1	2
PR Interval (seconds)	N	12	12	24
	Mean (SD)	0.2 (0.0)	0.3 (0.4)	0.2 (0.3)
	Median (IQR)	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)
	Min, Max	0.1, 0.2	0.1, 1.6	0.1, 1.6
	Not Available, N	1	1	2
QRS Complex Width (seconds)	N	12	12	24
	Mean (SD)	0.1 (0.0)	0.2 (0.3)	0.1 (0.2)
	Median (IQR)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
	Min, Max	0.1, 0.1	0.0, 1.0	0.0, 1.0
	Not Available, N	1	1	2
QT Interval (corrected) Friedericia's correction (QTcF) (milliseconds)	N	12	12	24
	Mean (SD)	423.2 (23.5)	415.5 (27.6)	419.3 (25.4)
	Median (IQR)	418.5 (404.5, 432.5)	417.0 (400.0, 432.5)	417.0 (404.5, 432.5)
	Min, Max	399.0, 467.0	362.0, 466.0	362.0, 467.0
	Not Available, N	1	1	2
12-Lead ECG reviewed by treating clinician?	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Blood and Bio-banking samples taken				
Full Blood Count	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Plasma	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Serum	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
DNA	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Urine	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Nasosorption	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)
Nasopharyngeal swab	Yes, n(%)	13 (100%)	13 (100%)	26 (100%)

6 Primary Outcome Analysis – Annual Rate of Severe Exacerbations

Descriptive statistics of the primary outcome defined as the annual rate of severe exacerbations were produced using the Intention-to-treat population. The primary outcome was calculated as the sum of severe asthma exacerbations reported by each participant divided by the sum of follow-up time (measured in years). The number of severe exacerbations reported at visits 3, 4, 5 and 6 (and 7, where visit 6 and others were missed due to early discontinuation) was calculated using the following variables from the Exacerbation History: date started, treatment duration (days), antibiotics treatment (yes), steroid treatment (yes), hospital admission (yes) or emergency department attendance (yes). Data was capped at 372 days, if a severe exacerbation occurred after 372 days following randomisation it wasn't included in the summary below. The summary presented below assumes that missing primary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised primary outcome data up until the last known point for each participant prior to 372 days.

6.1 Summary of the Primary Outcome

Table 8. Descriptive Statistics | Primary Outcome: Annual Rate of Severe Exacerbations

		Placebo	Doxycycline	Total
Total number of severe exacerbations	N	13	13	26
	Median (IQR)	1 (0, 4)	1 (0, 3)	1 (0, 3)
	Min, Max	0, 8	0, 7	0, 8
Follow-up time (years)	N	13	13	26
	Median (IQR)	0.40 (0.24, 0.61)	0.44 (0.30, 0.99)	0.42 (0.24, 0.75)
	Min, Max	0, 1.01	0, 1.02	0, 1.02
Annual Rate of Severe Exacerbations	N	12	12	24
	Median (IQR)	2.51 (0, 7.47)	2.34 (0, 4.58)	2.44 (0, 6.31)
	Min, Max	0, 10.70	0, 10.15	0, 10.70

7 Secondary Outcomes Analysis

7.1 Time to first Severe Exacerbation

Descriptive statistics of the time to first severe exacerbation defined as the time (measured in days) from randomisation to the first severe asthma exacerbation were produced using the Intention-to-treat population. The date of randomisation as well as the date of the first severe exacerbation were used to calculate the time to event. The first severe exacerbation reported at 90, 180, 270, 365 days follow-up or Safety Follow-up was derived using the following criteria: date started, date of treatment duration (days), antibiotics treatment (yes), steroid treatment (yes), hospital admission (yes) or emergency department attendance (yes). The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 9. Descriptive Statistics | Secondary Outcome: Time to first Severe Exacerbation (days)

		Placebo	Doxycycline	Total
Time to first Severe Exacerbation (days)	N	13	13	26
	Median (IQR)	86 (54, 131)	80 (47, 155)	83 (47, 155)
	Min, Max	1, 188	1, 277	1, 277

NB: no severe exacerbations were reported for 10 participants (5 Placebo, 5 Doxycycline), therefore their time to first severe exacerbation was replaced with their follow-up time.

7.2 Annual Rate of Severe Exacerbations defined as the use of systemic steroid only

Descriptive statistics of this secondary outcome defined as the annual rate of severe exacerbations treated with systemic steroid only were produced using the Intention-to-treat population. The secondary outcome was calculated as the sum of severe asthma exacerbations reported by each participant divided by the sum of follow-up time (measured in years). The number of severe exacerbations reported at 90, 180, 270, 365 days follow-up and Safety Follow-up was calculated using the following variables from the Exacerbation History: date started, treatment duration (days), steroid treatment (yes) and antibiotic treatment (no). Data was capped at 372 days, if a severe exacerbation occurred after 372 days following randomisation it wasn't included in the summary below. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised primary outcome data up until the last known point for each participant.

Table 10. Descriptive Statistics | Secondary Outcome: Annual Rate of Severe Exacerbations

		Placebo	Doxycycline	Total
Total number of severe exacerbations	N	13	13	26
	Median (IQR)	0 (0, 3)	0 (0, 1)	0 (0, 2)
	Min, Max	0, 3	0, 8	0, 8
Follow-up time (years)	N	13	13	26
	Median (IQR)	0.40 (0.24, 0.61)	0.44 (0.30, 0.99)	0.42 (0.24, 0.75)
	Min, Max	0, 1.01	0, 1.02	0, 1.02
Annual Rate of Severe Exacerbations	N	12	12	24
	Median (IQR)	1.26 (0, 3.98)	0.82 (0, 4.19)	0.82 (0, 3.98)
	Min, Max	0, 8.36	0, 7.85	0, 8.36

7.3 Annual Rate of Severe Exacerbations defined as the use of antibiotic only

Descriptive statistics of this secondary outcome defined as the annual rate of severe exacerbations treated with antibiotic only were produced using the Intention-to-treat population. The secondary outcome was calculated as the sum of severe asthma exacerbations reported by each participant divided by the sum of follow-up time (measured in years). The number of severe exacerbations reported at 90, 180, 270, 365 days follow-up and Safety Follow-up was calculated using the following variables from the Exacerbation History: date started, treatment duration (days), steroid treatment (no) and antibiotics treatment (yes). Data was capped at 372 days, if a severe exacerbation occurred after 372 days following randomisation it wasn't included in the summary below. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised primary outcome data up until the last known point for each participant.

Table 11. Descriptive Statistics | Secondary Outcome: Annual Rate of Severe Exacerbations

		Placebo	Doxycycline	Total
Total number of severe exacerbations	N	13	13	26
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Min, Max	0, 3	0, 1	0, 3
Follow-up time (years)	N	13	13	26
	Median (IQR)	0.40 (0.24, 0.61)	0.44 (0.30, 0.99)	0.42 (0.24, 0.75)
	Min, Max	0, 1.01	0, 1.02	0, 1.02
Annual Rate of Severe Exacerbations	N	12	12	24
	Median (IQR)	0 (0, 1.19)	0 (0, 0)	0 (0, 0)
	Min, Max	0, 4.01	0, 1	0, 4.01

7.4 Annual Rate of Severe Exacerbations defined as the use of systemic steroid and antibiotic only

Descriptive statistics of this secondary outcome defined as the annual rate of severe exacerbations treated with systemic steroid and antibiotic only were produced using the Intention-to-treat population. The secondary outcome was calculated as the sum of severe asthma exacerbations reported by each participant divided by the sum of follow-up time (measured in years). The number of severe exacerbations reported at 90, 180, 270, 365 days follow-up and Safety Follow-up was calculated using the following variables from the Exacerbation History: date started, treatment duration (days), antibiotics treatment (yes) and steroid treatment (yes). Data was capped at 372 days, if a severe exacerbation occurred after 372 days following randomisation it wasn't included in the summary below. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised primary outcome data up until the last known point for each participant.

Table 12. Descriptive Statistics | Secondary Outcome: Annual Rate of Severe Exacerbations

		Placebo	Doxycycline	Total
Total number of severe exacerbations	N	13	13	26
	Median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 1)
	Min, Max	0, 3	0, 3	0, 3
Follow-up time (years)	N	13	13	26
	Median (IQR)	0.40 (0.24, 0.61)	0.44 (0.30, 0.99)	0.42 (0.24, 0.75)
	Min, Max	0, 1.01	0, 1.02	0, 1.02
Annual Rate of Severe Exacerbations	N	12	12	24
	Median (IQR)	0 (0, 0.83)	0 (0, 1.32)	0 (0, 1.32)
	Min, Max	0, 4.01	0, 3.38	0, 4.01

7.5 Annual Rate of Severe Exacerbations defined as admission to Hospital or Emergency Department

Descriptive statistics of this secondary outcome defined as the annual rate of severe exacerbations defined by admission to Hospital or Emergency Department were produced using the Intention-to-treat population. The secondary outcome was calculated as the sum of severe asthma exacerbations reported by each participant divided by the sum of follow-up time (measured in years). The number of severe exacerbations reported at 90, 180, 270, 365 days follow-up and Safety Follow-up was calculated using the following variables from the Exacerbation History: date started, treatment duration (days), hospital admission (yes) or emergency department admission (yes). Data was capped at 372 days, if a severe exacerbation occurred after 372 days following randomisation it wasn't included in the summary below. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised primary outcome data up until the last known point for each participant.

Table 13. Descriptive Statistics | Secondary Outcome: Annual Rate of Severe Exacerbations

		Placebo	Doxycycline	Total
Total number of severe exacerbations	N	13	13	26
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Min, Max	0, 2	0, 3	0, 3
Follow-up time (years)	N	13	13	26
	Median (IQR)	0.40 (0.24, 0.61)	0.44 (0.30, 0.99)	0.42 (0.24, 0.75)
	Min, Max	0, 1.01	0, 1.02	0, 1.02

		Placebo	Doxycycline	Total
Annual Rate of Severe Exacerbations	N	12	12	24
	Median (IQR)	0 (0, 0)	0 (0, 0.50)	0 (0, 0)
	Min, Max	0, 2.01	0, 10.15	0, 10.15

7.6 Change in Juniper Asthma Control Questionnaire 6 – Interviewer Administered (ACQ 6-IA) Score from Baseline to 90, 180, 270 and 365 days follow-up

The ACQ 6-IA score at each individual time point was calculated as the mean of the 7 questions of the questionnaire, with each question being scored on a 7-point scale (0=no impairment, 6=maximum impairment) and the total ACQ 6-ia score ranging between 0 (totally controlled asthma) and 6 (severely uncontrolled asthma). Descriptive statistics of this secondary outcome defined as the change in ACQ 6-IA score from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the score recorded at each of the follow-up visits and the score reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 14. Descriptive Statistics | ACQ 6-IA score

ACQ 6-IA score		Placebo	Doxycycline	Total
Baseline ACQ 6-IA score	N	13	13	26
	Median (IQR)	2.6 (2.3, 3.3)	2.5 (1.7, 3.0)	2.5 (2.2, 3.3)
	Min, Max	0.8, 4.5	1.2, 4.5	0.8, 4.5
90 days ACQ 6-IA score	N	8	8	16
	Median (IQR)	3.0 (1.2, 4.5)	2.0 (1.2, 3.0)	2.4 (1.2, 3.9)
	Min, Max	1.2, 5.5	0.3, 4.5	0.3, 5.5
180 days ACQ 6-IA score	N	4	5	9
	Median (IQR)	3.5 (2.4, 3.7)	3.0 (1.5, 4.2)	3.5 (1.5, 3.8)
	Min, Max	1.3, 3.8	1.3, 4.3	1.3, 4.3
270 days ACQ 6-IA score	N	2	4	6
	Median (IQR)	1.8 (0.3, 3.3)	3.2 (1.9, 3.8)	3.0 (1.0, 3.6)
	Min, Max	0.3, 3.3	1.0, 4.0	0.3, 4.0
365 days ACQ 6-IA score	N	0	2	2
	Median (IQR)	-	2.3 (1.2, 3.5)	2.3 (1.2, 3.5)
	Min, Max	-	1.2, 3.5	1.2, 3.5

Table 15. Descriptive Statistics | Secondary Outcome: Change in ACQ 6-IA score

Change in ACQ 6-IA score		Placebo	Doxycycline	Total
Change in ACQ 6-IA score from Baseline to 90 days follow-up	N	8	8	16
	Median (IQR)	0.4 (-0.5, 1.0)	-0.4 (-1.0, 0.5)	0.3 (-1.0, 0.5)
	Min, Max	-1.9, 4.0	-1.9, 0.5	-1.9, 4.0
Change in ACQ 6-IA score from Baseline to 180 days follow-up	N	4	5	9
	Median (IQR)	0.6 (0.3, 1.1)	0.2 (0.0, 0.3)	0.3 (0.2, 0.8)
	Min, Max	0.2, 1.5	-0.9, 1.3	-0.9, 1.5

Change in ACQ 6-IA score		Placebo	Doxycycline	Total
Change in ACQ 6-IA score from Baseline to 270 days follow-up	N	2	4	6
	Median (IQR)	0.2 (-0.5, 1.0)	-0.1 (-0.2, 0.3)	-0.1 (-0.3, 0.6)
	Min, Max	-0.5, 1.0	-0.3, 0.6	-0.5, 1.0
Change in ACQ 6-IA score from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	-0.2 (-0.5, 0.0)	-0.2 (-0.5, 0.0)
	Min, Max	-	-0.5, 0.0	-0.5, 0.0

7.7 Change in Juniper Asthma Quality of Life Questionnaire – Interviewer Administered (AQLQ S-IA) Score from Baseline to 90, 180, 270 and 365-days follow-up

The AQLQ S-IA score at each individual time point was calculated as the mean of the 32 questions of the questionnaire, with each question being scored on a 7-point scale (1=maximal impairment, 7=no impairment) and the total AQLQ S-IA score ranging between 1 (severely impaired) and 7 (not impaired at all). Descriptive statistics of this secondary outcome defined as the change in AQLQ S-IA score from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the score recorded at each of the follow-up visits and the score reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 16. Descriptive statistics | AQLQ S-IA score

AQLQ S-IA score		Placebo	Doxycycline	Total
Baseline AQLQ S-IA score	N	13	13	26
	Median (IQR)	4.3 (3.7, 4.9)	4.4 (3.8, 5.5)	4.4 (3.7, 5.3)
	Min, Max	2.8, 6.5	2.4, 6.3	2.4, 6.5
90 days AQLQ S-IA score	N	8	8	16
	Median (IQR)	5.3 (2.7, 5.7)	4.9 (4.3, 5.1)	5.0 (3.7, 5.4)
	Min, Max	2.3, 6.8	3.2, 6.1	2.3, 6.8
180 days AQLQ S-IA score	N	4	5	9
	Median (IQR)	4.1 (3.4, 4.9)	4.7 (4.5, 4.9)	4.5 (3.8, 4.9)
	Min, Max	3.1, 5.4	3.7, 5.5	3.1, 5.5
270 days AQLQ S-IA score	N	2	4	6
	Median (IQR)	5.0 (4.2, 5.8)	4.5 (4.0, 5.3)	4.6 (4.0, 5.7)
	Min, Max	4.2, 5.8	4.0, 5.7	4.0, 5.8
365 days AQLQ S-IA score	N	0	2	2
	Median (IQR)	-	5.4 (4.9, 5.8)	5.4 (4.9, 5.8)
	Min, Max	-	4.9, 5.8	4.9, 5.8

Table 17. Descriptive Statistics | Secondary Outcome: Change in AQLQ S-IA score

Change in AQLQ S-IA score		Placebo	Doxycycline	Total
Change in AQLQ S-IA score from Baseline to 90 days follow-up	N	8	8	16
	Median (IQR)	0.2 (-0.2, 0.6)	0.2 (-0.5, 0.8)	0.2 (-0.4, 0.6)
	Min, Max	-2.5, 2.0	-0.7, 1.3	-2.5, 2.0
Change in AQLQ S-IA score from Baseline to 180 days follow-up	N	4	5	9
	Median (IQR)	-0.7 (-1.1, 0.0)	0.2 (0.0, 0.3)	0.0 (-0.8, 0.3)
	Min, Max	-1.1, 0.3	-0.8, 0.5	-1.1, 0.5
Change in AQLQ S-IA score from Baseline to 270 days follow-up	N	2	4	6
	Median (IQR)	-0.6 (-0.7, -0.5)	0.4 (-0.5, 0.7)	-0.2 (-0.7, 0.6)
	Min, Max	-0.7, -0.5	-1.3, 0.8	-1.3, 0.8
Change in AQLQ S-IA score from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)
	Min, Max	-	0.3, 0.5	0.3, 0.5

7.8 Change in Post-Bronchodilator FEV_1 measured via remote digital asthma spirometry (and post-bronchodilator FEV_1/FVC at Baseline and week 52 only, subject to feasibility of testing at trial sites during COVID-19)

Descriptive statistics of this secondary outcome defined as the change in Post-Bronchodilator FEV_1 from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the FEV_1 value recorded at each of the follow-up visits and the FEV_1 value reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 18. Descriptive statistics | Post-Bronchodilator FEV_1

Post-Bronchodilator FEV_1		Placebo	Doxycycline	Total
Baseline Post-Bronchodilator FEV_1 (L)	N	12	12	24
	Median (IQR)	2.5 (1.5, 2.7)	2.7 (2.3, 3.0)	2.5 (1.8, 2.8)
	Min, Max	0.9, 3.8	0.6, 3.2	0.6, 3.8
365 days Post-Bronchodilator FEV_1 (L)	N	0	2	2
	Median (IQR)	-	2.2 (1.4, 3.1)	2.2 (1.4, 3.1)
	Min, Max	-	1.4, 3.1	1.4, 3.1

Table 19. Descriptive Statistics | Secondary Outcome: Change in post bronchodilator FEV_1

Change in Post-Bronchodilator FEV_1		Placebo	Doxycycline	Total
Change in Post-Bronchodilator FEV_1 (L) from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)
	Min, Max	-	-0.1, 0.1	-0.1, 0.1

Table 20. Post-Bronchodilator FEV_1/FVC

Post-Bronchodilator FEV_1/FC		Placebo	Doxycycline	Total
Baseline Post-Bronchodilator FEV_1/FVC (L)	N	12	12	24
	Median (IQR)	69.0 (56.2, 81.6)	74.2 (68.0, 85.0)	74.2 (59.7, 83.0)
	Min, Max	32.0, 88.7	26.0, 89.0	26.0, 89.0
365 days Post-Bronchodilator FEV_1/FVC (L)	N	0	2	2
	Median (IQR)	-	71.0 (52.0, 90.0)	71.0 (52.0, 90.0)
	Min, Max	-	52.0, 90.0	52.0, 90.0

Table 21. Descriptive Statistics | Secondary Outcome: Change in post bronchodilator FEV_1/FVC

Change in Post-Bronchodilator FEV_1/FC		Placebo	Doxycycline	Total
Change in Post-Bronchodilator FEV_1/FVC from Baseline to 365 days follow-up (L)	N	0	2	2
	Median (IQR)	-	1.5 (1.0, 2.1)	1.5 (1.0, 2.1)
	Min, Max	-	1.0, 2.1	1.0, 2.1

7.9 Change in Absolute Blood Eosinophil and Neutrophil levels from Baseline to 90, 180, 270 and 365 days follow-up

Descriptive statistics of this secondary outcome defined as the change in absolute blood eosinophil and neutrophil levels from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the absolute blood eosinophil and neutrophil levels recorded at each of the follow-up visits and the absolute levels reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 22. Descriptive statistics | Absolute blood eosinophil levels

Absolute blood eosinophil levels		Placebo	Doxycycline	Total
Baseline absolute blood eosinophil levels ($x10^9/L$)	N	12	12	24
	Median (IQR)	0.10 (0.07, 0.16)	0.09 (0.06, 0.16)	0.09 (0.06, 0.16)
	Min, Max	0.05, 0.35	0.03, 0.26	0.03, 0.35
90 days absolute blood eosinophil levels ($x10^9/L$)	N	7	8	15
	Median (IQR)	0.09 (0.03, 0.16)	0.09 (0.08, 0.16)	0.09 (0.06, 0.16)
	Min, Max	0.00, 0.19	0.06, 0.33	0.00, 0.33
180 days absolute blood eosinophil levels ($x10^9/L$)	N	3	5	8
	Median (IQR)	0.07 (0.02, 0.11)	0.07 (0.06, 0.20)	0.07 (0.05, 0.16)
	Min, Max	0.02, 0.11	0.05, 0.20	0.02, 0.20
270 days absolute blood eosinophil levels ($x10^9/L$)	N	1	4	5
	Median (IQR)	0.08 (0.08, 0.08)	0.09 (0.05, 0.18)	0.08 (0.07, 0.12)
	Min, Max	0.08, 0.08	0.04, 0.24	0.04, 0.24
365 days absolute blood eosinophil levels ($x10^9/L$)	N	0	1	1
	Median (IQR)	-	0.06 (0.06, 0.06)	0.06 (0.06, 0.06)
	Min, Max	-	0.06, 0.06	0.06, 0.06

Table 23. Descriptive Statistics | Secondary Outcome: Change in Absolute Blood Eosinophil levels

Change in absolute blood eosinophil levels		Placebo	Doxycycline	Total
Change in absolute blood eosinophil levels from Baseline to 90 days follow-up (x10^9/L)	N	6	8	14
	Median (IQR)	-0.05 (-0.09, 0.02)	0.02 (-0.00, 0.05)	0.01 (-0.03, 0.04)
	Min, Max	-0.14, 0.02	-0.03, 0.17	-0.14, 0.17
Change in absolute blood eosinophil levels from Baseline to 180 days follow-up (x10^9/L)	N	3	5	8
	Median (IQR)	-0.06 (-0.08, 0.02)	0.03 (0.02, 0.05)	0.02 (-0.04, 0.04)
	Min, Max	-0.08, 0.02	-0.02, 0.06	-0.08, 0.06
Change in absolute blood eosinophil levels from Baseline to 270 days follow-up (x10^9/L)	N	1	4	5
	Median (IQR)	-0.11 (-0.11, -0.11)	0.00 (-0.01, 0.05)	0.00 (-0.03, 0.01)
	Min, Max	-0.11, -0.11	-0.03, 0.10	-0.11, 0.10
Change in absolute blood eosinophil levels from Baseline to 365 days follow-up (x10^9/L)	N	0	1	1
	Median (IQR)	-	0.03 (0.03, 0.03)	0.03 (0.03, 0.03)
	Min, Max	-	0.03, 0.03	0.03, 0.03

Table 24. Descriptive statistics | Absolute blood neutrophil levels

Absolute blood neutrophil levels		Placebo	Doxycycline	Total
Baseline absolute blood neutrophil levels (x10^9/L)	N	12	12	24
	Median (IQR)	4.32 (3.49, 5.03)	4.93 (3.16, 6.05)	4.65 (3.22, 5.61)
	Min, Max	2.97, 12.95	2.89, 11.95	2.89, 12.95
90 days absolute blood neutrophil levels (x10^9/L)	N	7	8	15
	Median (IQR)	5.83 (2.96, 7.85)	4.79 (4.03, 5.99)	5.04 (3.59, 6.62)
	Min, Max	2.87, 11.53	2.58, 9.30	2.58, 11.53
180 days absolute blood neutrophil levels (x10^9/L)	N	3	5	8
	Median (IQR)	6.11 (4.68, 10.20)	4.46 (3.75, 4.88)	4.78 (4.11, 7.72)
	Min, Max	4.68, 10.20	2.95, 9.32	2.95, 10.20
270 days absolute blood neutrophil levels (x10^9/L)	N	1	4	5
	Median (IQR)	5.05 (5.05, 5.05)	4.60 (4.01, 6.60)	5.05 (4.13, 5.06)
	Min, Max	5.05, 5.05	3.89, 8.13	3.89, 8.13
365 days absolute blood neutrophil levels (x10^9/L)	N	0	1	1
	Median (IQR)	-	4.77 (4.77, 4.77)	4.77 (4.77, 4.77)
	Min, Max	-	4.77, 4.77	4.77, 4.77

Table 25. Descriptive Statistics | Secondary Outcome: Change in Absolute Blood Neutrophil levels

Change in absolute blood neutrophil levels		Placebo	Doxycycline	Total
Change in absolute blood neutrophil levels from Baseline to 90 days follow-up ($x10^9$/L)	N	6	8	14
	Median (IQR)	0.97 (-0.10, 2.59)	-0.67 (-0.90, 0.50)	0.06 (-0.80, 1.10)
	Min, Max	-0.26, 2.91	-2.65, 1.83	-2.65, 2.91
Change in absolute blood neutrophil levels from Baseline to 180 days follow-up ($x10^9$/L)	N	3	5	8
	Median (IQR)	1.11 (-0.26, 6.39)	-0.17 (-0.39, 0.07)	-0.05 (-0.32, 0.83)
	Min, Max	-0.26, 6.39	-2.63, 0.54	-2.63, 6.39
Change in absolute blood neutrophil levels from Baseline to 270 days follow-up ($x10^9$/L)	N	1	4	5
	Median (IQR)	0.05 (0.05, 0.05)	-0.23 (-2.48, 0.68)	0.05 (-1.14, 0.67)
	Min, Max	0.05, 0.05	-3.82, 0.68	-3.82, 0.68
Change in absolute blood neutrophil levels from Baseline to 365 days follow-up ($x10^9$/L)	N	0	2	2
	Median (IQR)	-	-6.45 (-12.39, -0.50)	-6.45 (-12.39, -0.50)
	Min, Max	-	-12.39, -0.50	-12.39, -0.50

7.10 Change in Fractional Exhaled Nitric Oxide Levels (FeNO) from Baseline to 90, 180, 270 and 365 days follow-up

The FeNO measured at each individual time point was calculated as the average of the 1st and 2nd FeNO result. Descriptive statistics of this secondary outcome defined as the change in FeNO from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the FeNO value recorded at each of the follow-up visits and the FeNO value reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 26. Descriptive statistics | FeNO

FeNO		Placebo	Doxycycline	Total
Baseline FeNO (ppb)	N	13	13	26
	Median (IQR)	22.5 (11.5, 27.0)	15.5 (11.5, 18.0)	17.0 (11.5, 26.5)
	Min, Max	7.0, 108.0	6.0, 80.5	6.0, 108.0
90 days FeNO (ppb)	N	8	8	16
	Median (IQR)	21.2 (11.8, 39.5)	20.2 (13.2, 35.2)	21.2 (12.8, 35.2)
	Min, Max	7.5, 57.5	6.5, 137.0	6.5, 137.0
180 days FeNO (ppb)	N	4	5	9
	Median (IQR)	10.8 (7.2, 15.5)	14.5 (12.5, 23.5)	12.5 (9.5, 19.0)
	Min, Max	5.0, 19.0	7.5, 24.5	5.0, 24.5
270 days FeNO (ppb)	N	2	4	6
	Median (IQR)	22.2 (14.0, 30.5)	17.0 (11.5, 23.5)	18.0 (12.0, 25.0)
	Min, Max	14.0, 30.5	11.0, 25.0	11.0, 30.5

FeNO		Placebo	Doxycycline	Total
	N	0	2	2
365 days FeNO (ppb)	Median (IQR)	-	15.5 (11.5, 19.5)	15.5 (11.5, 19.5)
	Min, Max	-	11.5, 19.5	11.5, 19.5

Table 27. Descriptive Statistics | Secondary Outcome: Change in FeNO levels

Change in FeNO		Placebo	Doxycycline	Total
Change in FeNO from	N	8	8	16
Baseline to 90 days	Median (IQR)	-0.5 (-2.2, 7.5)	-0.8 (-3.0, 14.2)	-0.8 (-3.0, 9.5)
follow-up (ppb)	Min, Max	-5.0, 20.0	-5.0, 56.5	-5.0, 56.5
Change in FeNO from	N	4	5	9
Baseline to 180 days	Median (IQR)	-0.2 (-4.8, 3.0)	-0.5 (-0.5, 6.0)	-0.5 (-3.0, 3.5)
follow-up (ppb)	Min, Max	-6.5, 3.5	-5.5, 8.0	-6.5, 8.0
Change in FeNO from	N	2	4	6
Baseline to 270 days	Median (IQR)	7.0 (5.5, 8.5)	0.2 (-5.0, 6.5)	5.0 (-4.0, 8.5)
follow-up (ppb)	Min, Max	5.5, 8.5	-6.0, 8.5	-6.0, 8.5
Change in FeNO from	N	0	2	2
Baseline to 365 days	Median (IQR)	-	-0.8 (-3.5, 2.0)	-0.8 (-3.5, 2.0)
follow-up (ppb)	Min, Max	-	-3.5, 2.0	-3.5, 2.0

7.11 Change in Sino-nasal Outcome Test (SNOT-22) Score from Baseline to 90, 180, 270 and 365 days follow-up

The SNOT-22 score at each individual time point was calculated as the sum of the score for all items of the questionnaire, with the total score ranging between 0 and 110 noting that higher scores indicate greater rhinosinusitis-related health burden. Descriptive statistics of this secondary outcome defined as the change in SNOT-22 score from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the SNOT-22 score recorded at each of the follow-up visits and the SNOT-22 score reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 28. Descriptive statistics | SNOT-22 score

SNOT-22 score		Placebo	Doxycycline	Total
	N	13	12	25
Baseline SNOT-22 score	Median (IQR)	30.0 (18.0, 49.0)	28.5 (12.5, 42.0)	30.0 (18.0, 44.0)
	Min, Max	0.0, 61.0	0.0, 57.0	0.0, 61.0
	N	7	7	14
90 days SNOT-22 score	Median (IQR)	45.0 (10.0, 53.0)	37.0 (19.0, 46.0)	41.0 (13.0, 47.0)
	Min, Max	4.0, 54.0	8.0, 54.0	4.0, 54.0
	N	4	5	9
180 days SNOT-22 score	Median (IQR)	28.5 (10.5, 42.0)	21.0 (20.0, 27.0)	21.0 (17.0, 34.0)
	Min, Max	4.0, 44.0	3.0, 34.0	3.0, 44.0

SNOT-22 score		Placebo	Doxycycline	Total
270 days SNOT-22 score	N	2	4	6
	Median (IQR)	17.5 (13.0, 22.0)	32.0 (10.5, 53.5)	21.5 (13.0, 43.0)
	Min, Max	13.0, 22.0	0.0, 64.0	0.0, 64.0
365 days SNOT-22 score	N	0	2	2
	Median (IQR)	-	5.0 (0.0, 10.0)	5.0 (0.0, 10.0)
	Min, Max	-	0.0, 10.0	0.0, 10.0

Table 29. Descriptive Statistics | Secondary Outcome: Change in SNOT-22 score

Change in SNOT-22 score		Placebo	Doxycycline	Total
Change in SNOT-22 score from Baseline to 90 days follow-up	N	7	7	14
	Median (IQR)	9.0 (-6.0, 13.0)	-2.0 (-9.0, 6.0)	4.0 (-6.0, 10.0)
	Min, Max	-15.0, 15.0	-11.0, 18.0	-15.0, 18.0
Change in SNOT-22 score from Baseline to 180 days follow-up	N	4	5	9
	Median (IQR)	5.0 (1.0, 10.0)	2.0 (1.0, 3.0)	3.0 (1.0, 6.0)
	Min, Max	-2.0, 14.0	-23.0, 14.0	-23.0, 14.0
Change in SNOT-22 score from Baseline to 270 days follow-up	N	2	4	6
	Median (IQR)	2.5 (-8.0, 13.0)	-2.5 (-8.5, 21.5)	-2.5 (-8.0, 13.0)
	Min, Max	-8.0, 13.0	-14.0, 45.0	-14.0, 45.0
Change in SNOT-22 score from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	-8.0 (-14.0, -2.0)	-8.0 (-14.0, -2.0)
	Min, Max	-	-14.0, -2.0	-14.0, -2.0

7.12 Change in Visual Analogue Scale (VAS) Score for cough, shortness of breath and wheeze from Baseline to 90, 180, 270 and 365 days follow-up

The VAS score at each individual time point was calculated as the sum of the score recorded for each of the 4 items, with each item being scored on a 0-100mm scale noting that higher scores indicate greater severity of breathlessness. Descriptive statistics of this secondary outcome defined as the change in VAS score from Baseline to 90, 180, 270 and 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the VAS score recorded at each of the follow-up visits and the VAS score reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 30. Descriptive statistics | VAS score

VAS score		Placebo	Doxycycline	Total
Baseline VAS score	N	13	13	26
	Median (IQR)	81.0 (18.0, 150.0)	14.0 (13.0, 127.0)	51.5 (13.0, 139.0)
	Min, Max	7.0, 261.0	2.0, 290.0	2.0, 290.0
90 days VAS score	N	8	8	16
	Median (IQR)	43.0 (14.0, 177.5)	20.0 (6.0, 48.5)	25.0 (10.0, 74.5)
	Min, Max	5.0, 272.0	1.0, 237.0	1.0, 272.0

VAS score		Placebo	Doxycycline	Total
180 days VAS score	N	4	5	9
	Median (IQR)	99.0 (13.0, 210.0)	21.0 (15.0, 142.0)	21.0 (15.0, 165.0)
	Min, Max	9.0, 239.0	2.0, 165.0	2.0, 239.0
270 days VAS score	N	2	4	6
	Median (IQR)	13.5 (7.0, 20.0)	70.0 (9.5, 168.0)	19.0 (7.0, 122.0)
	Min, Max	7.0, 20.0	1.0, 214.0	1.0, 214.0
365 days VAS score	N	0	2	2
	Median (IQR)	-	51.5 (2.0, 101.0)	51.5 (2.0, 101.0)
	Min, Max	-	2.0, 101.0	2.0, 101.0

Table 31. Descriptive Statistics | Secondary Outcome: Change in VAS score

Change in VAS score		Placebo	Doxycycline	Total
Change in VAS score from Baseline to 90 days follow-up	N	8	8	16
	Median (IQR)	3.5 (-20.0, 7.5)	-3.0 (-40.5, 7.0)	-0.5 (-23.5, 7.5)
	Min, Max	-142.0, 120.0	-78.0, 98.0	-142.0, 120.0
Change in VAS score from Baseline to 180 days follow-up	N	4	5	9
	Median (IQR)	-17.5 (-57.5, 79.0)	3.0 (0.0, 3.0)	0.0 (-35.0, 3.0)
	Min, Max	-80.0, 158.0	-100.0, 38.0	-100.0, 158.0
Change in VAS score from Baseline to 270 days follow-up	N	2	4	6
	Median (IQR)	-17.0 (-37.0, 3.0)	2.5 (-9.0, 46.5)	1.0 (-17.0, 6.0)
	Min, Max	-37.0, 3.0	-17.0, 87.0	-37.0, 87.0
Change in VAS score from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	-19.0 (-38.0, 0.0)	-19.0 (-38.0, 0.0)
	Min, Max	-	-38.0, 0.0	-38.0, 0.0

7.13 Change in EuroQol-5D-5L (EQ-5D-5L) Quality of Life Questionnaire from Baseline to Visit 6 (365 days follow-up)

Descriptive statistics of this secondary outcome defined as the change in EQ-5D-5L values (VAS and utility score) from Baseline to 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the EQ-5D-5L values recorded at 365 days follow-up and the EQ-5D-5L values reported at Baseline. The summaries presented below assume that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 32. Descriptive statistics | EQ-5D-5L VAS score

EQ-5D-5L VAS score		Placebo	Doxycycline	Total
Baseline EQ-5D-5L VAS score	N	13	13	26
	Median (IQR)	65.0 (60.0, 65.0)	60.0 (50.0, 80.0)	65.0 (50.0, 75.0)
	Min, Max	40.0, 100.0	15.0, 95.0	15.0, 100.0
365 days EQ-5D-5L VAS score	N	0	2	2
	Median (IQR)	-	67.5 (45.0, 90.0)	67.5 (45.0, 90.0)
	Min, Max	-	45.0, 90.0	45.0, 90.0

Table 33. Descriptive Statistics | Secondary Outcome: Change in EQ-5D-5L VAS score

Change in EQ-5D-5L VAS score		Placebo	Doxycycline	Total
Change in EQ-5D-5L VAS score from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	-17.5 (-30.0, -5.0)	-17.5 (-30.0, -5.0)
	Min, Max	-	-30.0, -5.0	-30.0, -5.0

Responses recorded for the EuroQol-5D-5L domains at Baseline and at 365 days follow-up time using the EuroQol-5D-5L questionnaire were used to map (or cross-walk) the 5L descriptive system data onto the 3L value set in accordance with new guidance published by NICE in January 2022 (Hernández-Alava et al, 2022).

Table 34. Descriptive statistics | EQ-5D-5L utility score

EQ-5D-5L utility score		Placebo	Doxycycline	Total
Baseline EQ-5D-5L utility score	N	13	13	26
	Median (IQR)	0.7 (0.6, 0.8)	0.8 (0.7, 0.9)	0.7 (0.6, 0.9)
	Min, Max	0.2, 1.0	0.3, 1.0	0.2, 1.0
365 days EQ-5D-5L utility score	N	0	2	2
	Median (IQR)	-	0.8 (0.5, 1.0)	0.8 (0.5, 1.0)
	Min, Max	-	0.5, 1.0	0.5, 1.0

Table 35. Descriptive Statistics | Secondary Outcome: Change in EQ-5D-5L Utility score

Change in EQ-5D-5L utility score		Placebo	Doxycycline	Total
Change in EQ-5D-5L utility score from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	-0.1 (-0.2, 0.0)	-0.1 (-0.2, 0.0)
	Min, Max	-	-0.2, 0.0	-0.2, 0.0

7.14 Change in Work Productivity & Activity Impairment (WPAI) questionnaire Score from Baseline to Visit 6 (365 days follow-up)

The WPAI comprises four main outcomes: work time missed, impairment at work, overall work impairment and activity impairment, with each of these outcomes due to asthma being expressed as percentages. Descriptive statistics of this secondary outcome defined as the change in WPAI score from Baseline to 365 days follow-up were produced using the Intention-to-treat population. The secondary outcome was calculated as the difference between the WPAI score recorded at 365 days follow-up and the WPAI score reported at Baseline. The summary presented below assumes that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

Table 36. Descriptive statistics | WPAI

WPAI		Placebo	Doxycycline	Total
Baseline % of work time missed due to asthma	N	10	6	16
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
365 days % of work time missed due to asthma	N	0	1	1
	Median (IQR)	-	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	-	0.0, 0.0	0.0, 0.0
Baseline % of impairment while working due to asthma	N	10	6	16
	Median (IQR)	45.0 (10.0, 60.0)	25.0 (10.0, 30.0)	30.0 (10.0, 55.0)
	Min, Max	0.0, 90.0	0.0, 60.0	0.0, 90.0
365 days % of impairment while working due to asthma	N	0	1	1
	Median (IQR)	-	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	Min, Max	-	10.0, 10.0	10.0, 10.0
Baseline % of overall work impairment due to asthma	N	10	6	16
	Median (IQR)	45.0 (10.0, 60.0)	25.0 (10.0, 30.0)	30.0 (10.0, 55.0)
	Min, Max	0.0, 90.0	0.0, 60.0	0.0, 90.0
365 days % of overall work impairment due to asthma	N	0	1	1
	Median (IQR)	-	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	Min, Max	-	10.0, 10.0	10.0, 10.0
Baseline % of activity impairment due to asthma	N	13	13	26
	Median (IQR)	60.0 (20.0, 60.0)	60.0 (40.0, 60.0)	60.0 (20.0, 60.0)
	Min, Max	10.0, 90.0	0.0, 80.0	0.0, 90.0
365 days % of activity impairment due to asthma	N	0	2	2
	Median (IQR)	-	10.0 (0.0, 20.0)	10.0 (0.0, 20.0)
	Min, Max	-	0.0, 20.0	0.0, 20.0

Table 37. Descriptive Statistics | Secondary Outcome: Change in WPAI

Change in WPAI		Placebo	Doxycycline	Total
Change in % of work time missed due to asthma from Baseline to 365 days follow-up	N	0	1	1
	Median (IQR)	-	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	-	0.0, 0.0	0.0, 0.0
Change in % of impairment while working due to asthma from Baseline to 365 days follow-up	N	0	1	1
	Median (IQR)	-	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	Min, Max	-	10.0, 10.0	10.0, 10.0
Change in % of overall work impairment due to asthma from Baseline to 365 days follow-up	N	0	1	1
	Median (IQR)	-	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	Min, Max	-	10.0, 10.0	10.0, 10.0
Change in % of activity impairment due to asthma from Baseline to 365 days follow-up	N	0	2	2
	Median (IQR)	-	-10.0 (-20.0, 0.0)	-10.0 (-20.0, 0.0)
	Min, Max	-	-20.0, 0.0	-20.0, 0.0

7.15 Adverse Events

The summary of safety data presented in this section was produced using the Safety population.

A total of 34 adverse events were reported in 15 (57.7%) participants who were randomised into the T2-LOW trial and included in the Safety population. None of the adverse events were reported as serious.

7.15.1 Number of participants with Adverse Events

Table 38. Number of participants with Adverse Events | Secondary Outcome: Adverse Events

	Placebo	Doxycycline	Total
Randomised participants, n	13	13	26
Participants with Adverse Events, n(%)	8 (61.5%)	7 (53.9%)	15 (57.7%)
Participants with no Adverse Events, n(%)	5 (38.5%)	6 (46.1%)	11 (42.3%)
Participants with 1 Adverse Events, n(%)	4 (30.8%)	1 (7.7%)	5 (19.2%)
Participants with 2 Adverse Events, n(%)	3 (23.1%)	3 (23.1%)	6 (23.1%)
Participants with 3 Adverse Events, n(%)	0 (0%)	1 (7.7%)	1 (3.9%)
Participants with 4 Adverse Events, n(%)	1 (7.6%)	1 (7.7%)	2 (7.6%)
Participants with 6 Adverse Events, n(%)	0 (0%)	1 (7.7%)	1 (3.9%)

7.15.2 Characteristics of Adverse Events

Table 39. Characteristics of Adverse Events | Secondary Outcome: Adverse Events

	Placebo	Doxycycline	Total
Overall number of Adverse Events, n	14	20	34
Severity			
Mild, n(%)	5 (35.7%)	4 (20%)	9 (26.5%)
Moderate, n(%)	8 (57.1%)	12 (60%)	20 (58.8%)
Severe, n(%)	1 (7.1%)	4 (20%)	5 (14.7%)
Fatal, n(%)	0 (0%)	0 (0%)	0 (0%)
Outcome			
Resolved, n(%)	12 (85.7%)	18 (90%)	30 (88.2%)
Resolved with sequelae, n(%)	0 (0%)	0 (0%)	0 (0%)
Continuing, n(%)	1 (7.1%)	2 (10%)	3 (8.8%)
Fatal, n(%)	0 (0%)	0 (0%)	0 (0%)
Unknown, n(%)	1 (7.1%)	0 (0%)	1 (2.9%)
Treatment			
None, n(%)	5 (35.7%)	8 (40.0%)	13 (38.2%)
Concomitant Medication, n(%)	8 (57.1%)	11 (55.0%)	19 (55.9%)
Non-drug therapy, n(%)	1 (7.1%)	1 (5.0%)	2 (5.9%)
Concomitant Medication and Non-drug therapy, n(%)	0 (0%)	0 (0%)	0 (0%)
Action taken			
None, n(%)	9 (64.3%)	15 (75.0%)	24 (70.6%)
Study interrupted, n(%)	3 (21.4%)	4 (20.0%)	7 (20.6%)
Study discontinued, n(%)	2 (14.3%)	1 (5.0%)	3 (8.8%)
Relatedness			
Not related, n(%)	12 (85.7%)	14 (70%)	26 (76.5%)
Unlikely, n(%)	0 (0%)	3 (15%)	3 (8.8%)
Possible, n(%)	2 (14.3%)	1 (5%)	3 (8.8%)
Probable, n(%)	0 (0%)	2 (10%)	2 (5.9%)
Definite, n(%)	0 (0%)	0 (0%)	0 (0%)
Serious Adverse Event			
Yes, n(%)	0 (0%)	0 (0%)	0 (0%)
No, n(%)	14 (100%)	20 (100%)	34 (100%)
Expectedness			
Yes, n(%)	1 (7.1%)	3 (15.0%)	4 (11.8%)
No, n(%)	13 (92.9%)	17 (85.0%)	30 (88.2%)

7.16 Treatment Adherence and Compliance (patient level drug accountability) reported at 90, 180, 270 and 365 days follow-up

Numbers (with percentages) for binary variables and descriptive statistics of the proportion of missed tablets reported at 90, 180, 270 and 365 days follow-up were produced for this secondary outcome using the Intention-to-treat population. The number of missed tablets reported at each of the aforementioned study visits and the follow-up time (measured in days) were used to calculate the proportion of missed tablets. The summaries presented below assume that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

7.16.1 Treatment Adherence and Compliance at 90 days follow-up

Table 40. Descriptive Statistics | Secondary Outcome: Treatment Adherence at 90 days follow-up

	Placebo	Doxycycline	Total
Has the participant missed >21 days of treatment?			
Yes, n(%)	2 (25%)	0 (0%)	2 (12.5%)
Proportion of missed tablets since their previous visit			
N	8	8	16
Median (IQR)	0.1 (0.0, 0.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)
Min, Max	0.0, 0.7	0.0, 0.1	0.0, 0.7
Has the participant taken less than 75% of their trial medication since their previous visit?			
Yes, n(%)	1 (12.5%)	1 (12.5%)	2 (12.5%)

7.16.2 Treatment Adherence and Compliance at 180 days follow-up

Table 41. Descriptive Statistics | Secondary Outcome: Treatment Adherence at 180 days follow-up

	Placebo	Doxycycline	Total
Has the participant missed >21 days of treatment?			
Yes, n(%)	0 (0%)	1 (20%)	1 (11.1%)
Proportion of missed tablets since their previous visit			
N	4	5	9
Median (IQR)	0.1 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Min, Max	0.0, 0.3	0.0, 0.0	0.0, 0.3
Has the participant taken less than 75% of their trial medication since their previous visit?			
No, n(%)	4 (100%)	5 (100%)	9 (100%)

7.16.3 Treatment Adherence and Compliance at 270 days follow-up

Table 42. Descriptive Statistics | Secondary Outcome: Treatment Adherence at 270 days follow-up

	Placebo	Doxycycline	Total
Has the participant missed >21 days of treatment?			
Yes, n(%)	1 (50%)	1 (25%)	2 (33.3%)
Proportion of missed tablets since their previous visit			
N	2	4	6
Median (IQR)	0.2 (0.1, 0.4)	0.1 (0.0, 0.2)	0.1 (0.1, 0.3)
Min, Max	0.1, 0.4	0.0, 0.3	0.0, 0.4
Has the participant taken less than 75% of their trial medication since their previous visit?			
Yes, n(%)	1 (50%)	0 (0%)	1 (16.7%)

7.16.4 Treatment Adherence and Compliance at 365 days follow-up

Table 43. Descriptive Statistics | Secondary Outcome: Treatment Adherence at 365 days follow-up

	Placebo	Doxycycline	Total
Has the participant missed >21 days of treatment?			
No, n(%)	0 (0%)	2 (100%)	2 (100%)
Proportion of missed tablets since their previous visit			
N	0	2	2
Median (IQR)	-	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)
Min, Max	-	0.0, 0.1	0.0, 0.1
Has the participant taken less than 75% of their trial medication since their previous visit?			
No, n(%)	0 (0%)	2 (100%)	2 (100%)

8 Mechanistic Outcomes Analysis

Descriptive statistics of the γ-proteobacteria:firmicutes ratio and the Neutrophil Elastase reported at Baseline, 90, 180 and 365 days follow-up were produced using nasal swabs and nasosorption data corresponding to participants included in the Intention-to-treat population. The laboratory data reported in this section were provided to the LCTU in an Excel document by the Central Laboratory. The number of missed tablets reported at each of the aforementioned study visits were used to calculate the proportion of missed tablets. The summaries presented below assume that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

8.1 γ-proteobacteria:firmicutes ratio

Table 44. Descriptive Statistics | Mechanistic Outcome: γ-proteobacteria:firmicutes ratio

		Placebo	Doxycycline	Total
γ-proteobacteria:firmicutes ratio at Baseline	N	8	10	18
	Median (IQR)	0.5 (0.0, 2.9)	1.4 (0.0, 21.2)	0.5 (0.0, 7.3)
	Min, Max	0.0, 20.7	0.0, 271.0	0.0, 271.0
γ-proteobacteria:firmicutes ratio at 90 days follow-up	N	4	5	9
	Median (IQR)	0.5 (0.0, 8.6)	0.0 (0.0, 2.5)	0.0 (0.0, 2.5)
	Min, Max	0.0, 16.3	0.0, 3.1	0.0, 16.3
γ-proteobacteria:firmicutes ratio at 180 days follow-up	N	1	5	6
	Median (IQR)	1.2 (1.2, 1.2)	0.8 (0.0, 1.6)	1.0 (0.0, 1.6)
	Min, Max	1.2, 1.2	0.0, 50.7	0.0, 50.7
γ-proteobacteria:firmicutes ratio at 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.2 (0.0, 0.4)	0.2 (0.0, 0.4)
	Min, Max	-	0.0, 0.4	0.0, 0.4

8.2 Neutrophil Elastase

Table 45. Descriptive Statistics | Mechanistic Outcome: Neutrophil Elastase

		Placebo	Doxycycline	Total
Neutrophil Elastase (ng/mL) at Baseline	N	13	13	26
	Median (IQR)	84.1 (28.9, 160.7)	184.7 (84.3, 564.8)	104.0 (65.3, 285.5)
	Min, Max	8.1, 526.4	25.6, 1002.6	8.1, 1002.6
Neutrophil Elastase (ng/mL) at 90 days follow-up	N	8	8	16
	Median (IQR)	84.5 (36.1, 93.4)	147.4 (79.1, 371.2)	92.3 (57.1, 147.4)
	Min, Max	10.8, 94.8	6.1, 924.0	6.1, 924.0
Neutrophil Elastase (ng/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	394.2 (110.0, 650.5)	87.8 (80.1, 113.8)	113.8 (80.1, 155.5)
	Min, Max	64.5, 668.0	51.4, 144.1	51.4, 668.0
Neutrophil Elastase (ng/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	210.4 (162.1, 258.7)	210.4 (162.1, 258.7)
	Min, Max	-	162.1, 258.7	162.1, 258.7

9 Exploratory Outcomes Analysis

Correlations between Exploratory Outcomes were not calculated in line with the SAP v2.2. This is because the laboratory data provided to the LCTU was collected only from nasosorption and nasal swabs samples. The data reported in this section were provided to the LCTU in an Excel document by the Central Laboratory. Participants in the study did not produce sputum either via induction or spontaneously. As a result, descriptive statistics of the Exploratory Outcomes reported at Baseline, 90, 180 and 365 days follow-up were produced using the nasal sample data corresponding to participants included in the Intention-to-treat population. The summaries presented below assume that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. This approach utilised secondary outcome data up until the last known point for each participant.

9.1 Total 16s RNA

Table 46. Descriptive Statistics | Exploratory Outcome: Total 16s RNA

		Placebo	Doxycycline	Total
Total 16s RNA (copies/mL) at Baseline	N	13	13	26
	Median (IQR)	88293.1 (21222.2, 228787.4)	42654.1 (0.0, 113265.4)	46584.0 (10967.9, 228787.4)
	Min, Max	0.0, 6563830.2	0.0, 8267823.9	0.0, 8267823.9
Total 16s RNA (copies/mL) at 90 days follow-up	N	8	6	14
	Median (IQR)	90648.4 (0.0, 244724.1)	43894.5 (11508.8, 63571.6)	43894.5 (0.0, 199826.8)
	Min, Max	0.0, 5084551.0	0.0, 9888507.5	0.0, 9888507.5
Total 16s RNA (copies/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	29709.9 (19985.6, 549252.0)	37702.2 (18872.5, 385699.3)	37702.2 (19903.3, 385699.3)
	Min, Max	19903.3, 1059152.0	11121.3, 1.7e+07	11121.3, 1.7e+07
Total 16s RNA (copies/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	350346.0 (32631.4, 668060.6)	350346.0 (32631.4, 668060.6)
	Min, Max	-	32631.4, 668060.6	32631.4, 668060.6

9.2 Streptococcus pneumonia

Table 47. Descriptive Statistics | Exploratory Outcome: Streptococcus pneumonia

		Placebo	Doxycycline	Total
Streptococcus pneumonia (copies/mL) at Baseline	N	13	13	26
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Streptococcus pneumonia (copies/mL) at 90 days follow-up	N	8	6	14
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Streptococcus pneumonia (copies/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 15801.2	0.0, 15801.2
Streptococcus pneumonia (copies/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	-	0.0, 0.0	0.0, 0.0

9.3 Haemophilus influenza

Table 48. Descriptive Statistics | Exploratory Outcome: Haemophilus influenza

		Placebo	Doxycycline	Total
Haemophilus influenza (copies/mL) at Baseline	N	13	13	26
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Haemophilus influenza (copies/mL) at 90 days follow-up	N	8	6	14
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 28652.0	0.0, 28652.0
Haemophilus influenza (copies/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	0.0 (0.0, 76722.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 153444.6	0.0, 0.0	0.0, 153444.6
Haemophilus influenza (copies/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	-	0.0, 0.0	0.0, 0.0

9.4 Moraxella catarrhalis

Table 49. Descriptive Statistics | Exploratory Outcome: Moraxella catarrhalis

		Placebo	Doxycycline	Total
Moraxella catarrhalis (copies/mL) at Baseline	N	13	13	26
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Moraxella catarrhalis (copies/mL) at 90 days follow-up	N	8	6	14
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Moraxella catarrhalis (copies/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Moraxella catarrhalis (copies/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	-	0.0, 0.0	0.0, 0.0

9.5 γ-proteobacteria:firmicutes ratio

Table 50. Descriptive Statistics | Exploratory Outcome: γ-proteobacteria:firmicutes ratio

		Placebo	Doxycycline	Total
γ-proteobacteria:firmicutes ratio at Baseline	N	8	10	18
	Median (IQR)	0.5 (0.0, 2.9)	1.4 (0.0, 21.2)	0.5 (0.0, 7.3)
	Min, Max	0.0, 20.7	0.0, 271.0	0.0, 271.0
γ-proteobacteria:firmicutes ratio at 90 days follow-up	N	4	5	9
	Median (IQR)	0.5 (0.0, 8.6)	0.0 (0.0, 2.5)	0.0 (0.0, 2.5)
	Min, Max	0.0, 16.3	0.0, 3.1	0.0, 16.3
γ-proteobacteria:firmicutes ratio at 180 days follow-up	N	1	5	6
	Median (IQR)	1.2 (1.2, 1.2)	0.8 (0.0, 1.6)	1.0 (0.0, 1.6)
	Min, Max	1.2, 1.2	0.0, 50.7	0.0, 50.7
γ-proteobacteria:firmicutes ratio at 365 days follow-up	N	0	2	2
	Median (IQR)	-	0.2 (0.0, 0.4)	0.2 (0.0, 0.4)
	Min, Max	-	0.0, 0.4	0.0, 0.4

9.6 Neutrophil Elastase (NE)

Table 51. Descriptive Statistics | Exploratory Outcome: Neutrophil Elastase

		Placebo	Doxycycline	Total
Neutrophil Elastase (ng/mL) at Baseline	N	13	13	26
	Median (IQR)	84.1 (28.9, 160.7)	184.7 (84.3, 564.8)	104.0 (65.3, 285.5)
	Min, Max	8.1, 526.4	25.6, 1002.6	8.1, 1002.6
Neutrophil Elastase (ng/mL) at 90 days follow-up	N	8	8	16
	Median (IQR)	84.5 (36.1, 93.4)	147.4 (79.1, 371.2)	92.3 (57.1, 147.4)
	Min, Max	10.8, 94.8	6.1, 924.0	6.1, 924.0
Neutrophil Elastase (ng/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	394.2 (110.0, 650.5)	87.8 (80.1, 113.8)	113.8 (80.1, 155.5)
	Min, Max	64.5, 668.0	51.4, 144.1	51.4, 668.0
Neutrophil Elastase (ng/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	210.4 (162.1, 258.7)	210.4 (162.1, 258.7)
	Min, Max	-	162.1, 258.7	162.1, 258.7

9.7 Eosinophil Derived Neurotoxin (EDN)

Table 52. Descriptive Statistics | Exploratory Outcome: Eosinophil Derived Neurotoxin

		Placebo	Doxycycline	Total
Eosinophil Derived Neurotoxin (ng/mL) at Baseline	N	13	13	26
	Median (IQR)	16.4 (10.9, 47.5)	35.5 (22.3, 125.8)	33.9 (13.1, 85.5)
	Min, Max	3.8, 308.7	7.8, 190.2	3.8, 308.7
Eosinophil Derived Neurotoxin (ng/mL) at 90 days follow-up	N	8	8	16
	Median (IQR)	37.1 (19.0, 56.1)	57.3 (5.1, 118.5)	37.1 (6.8, 94.5)
	Min, Max	3.1, 87.4	3.2, 166.5	3.1, 166.5
Eosinophil Derived Neurotoxin (ng/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	124.8 (71.9, 140.3)	15.7 (9.4, 108.6)	108.6 (15.7, 134.5)
	Min, Max	28.6, 146.0	4.0, 143.1	4.0, 146.0
Eosinophil Derived Neurotoxin (ng/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	-	100.6 (89.8, 111.4)	100.6 (89.8, 111.4)
	Min, Max	-	89.8, 111.4	89.8, 111.4

9.8 Eosinophil Peroxidase (EPX)

Table 53. Descriptive Statistics | Exploratory Outcome: Eosinophil Peroxidase

		Placebo	Doxycycline	Total
Eosinophil Peroxidase (ng/mL) at Baseline	N	13	13	26
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Eosinophil Peroxidase (ng/mL) at 90 days follow-up	N	8	8	16
	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
Eosinophil Peroxidase (ng/mL) at 180 days follow-up	N	4	5	9
	Median (IQR)	0.0 (0.0, 1.4)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	0.0, 2.7	0.0, 0.0	0.0, 2.7
Eosinophil Peroxidase (ng/mL) at 365 days follow-up	N	0	2	2
	Median (IQR)	. (., .)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Min, Max	., .	0.0, 0.0	0.0, 0.0

10 Protocol Deviations

A total of 41 Protocol Deviations were reported for 25 (96.2%) participants who were randomised into the T2-LOW trial.

10.1 Number of participants with Protocol Deviations

Table 54. Number of participants with Protocol Deviations

	Placebo	Doxycycline	Total
Randomised participants, n	13	13	26
Participants with at least one Protocol Deviation, n(%)	13 (100%)	12 (92.3%)	25 (96.2%)
Participants with no Protocol Deviations, n(%)	0 (0%)	1 (7.7%)	1 (3.8%)
Participants with 1 Protocol Deviation, n(%)	7 (53.8%)	5 (38.5%)	12 (46.2%)
Participants with 2 Protocol Deviations, n(%)	3 (23.1%)	7 (53.8%)	10 (38.5%)
Participants with 3 Protocol Deviations, n(%)	3 (23.1%)	0 (0%)	3 (11.5%)

10.2 Major Protocol Deviations

Table 55. Reasons for Major Protocol Deviation and number of participants affected by deviation type

Major Protocol Deviation Reason	Placebo		Doxycycline		Total	
	P	N	P	N	P	N
Participant discovered to be ineligible for entry into trial post-randomisation, n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-compliance with randomised treatment:						
Participant did not take greater than 75% of trial treatment within the last 3 months [a], n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Participant received incorrect trial treatment, n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Participant received prohibited medications, n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total, n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[a] There are 3 deviations (2 participants in the Placebo group, 1 participant in the Doxycycline group) that were not recorded by sites in the Protocol Deviations CRF and/or MACRO.

P: number of protocol deviations by deviation type, **N:** number participants affected per deviation type Please note the percentage corresponding to the proportion of participants affected per minor deviation type (including the total for each treatment arm and Total) was calculated out of the total number of participants randomised.

10.3 Minor Protocol Deviations

Table 56. Reasons for Minor Protocol Deviations and number of participants affected by deviation type

Minor Protocol Deviation Reason	Placebo		Doxycycline		Total	
	P	N	P	N	P	N
Time Window or Assessment deviations for any of the dispensing visits listed below [a]:						
Baseline [b] , n(%)	11 (91.7%)	11 (91.7%)	12 (85.7%)	12 (85.7%)	23 (88.5%)	23 (88.5%)
Visit 3 (90 days follow-up) [b] , n(%)	1 (8.3%)	1 (8.3%)	2 (14.3%)	2 (14.3%)	3 (11.5%)	3 (11.5%)
Visit 4 (180 days follow-up), n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Visit 5 (270 days follow-up) [b], n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total, n(%)	12 (100%)	11 (84.6%)	14 (100%)	12 (92.3%)	26 (100%)	23 (88.5%)

P: number of protocol deviations by deviation type, **N:** number participants affected per deviation type Please note the percentage corresponding to the proportion of participants affected per minor deviation type (including the total for each treatment arm and Total) was calculated out of the total number of participants randomised.

[a] Each one of the visits had a ± 7 day time window. The number of deviations corresponding to each visit was calculated out of participants who attended their visit.
[b] Please note that figures corresponding to one time window deviation are not reported here as the deviation was recorded under the category of "Other deviation".

Please refer to section 7.13 Treatment Adherence and Compliance for the reporting of taking less than 25% of the intended number of tablets also constitutes a minor deviation in accordance with the SAP v2.2.

10.4 Additional Protocol Deviations

A summary of protocol deviations that were not classed as either major or minor is presented in the table below:

Table 57. Reasons for Additional Protocol Deviations and number of participants affected by deviation type

Protocol Deviation Reason	Placebo		Doxycycline		Total	
	P	N	P	N	P	N
Participant did not attend the scheduled drug dispensing visit at 3, 6 or 9 months, n(%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other deviations, n(%)	10 (100%)	6 (46.2%)	5 (100%)	5 (38.5%)	15 (100%)	11 (42.3%)
Total, n(%)	10 (100%)	6 (46.2%)	5 (100%)	5 (38.5%)	15 (100%)	11 (42.3%)

P: number of protocol deviations by deviation type, **N:** number participants affected per deviation type Please note the percentage corresponding to the proportion of participants affected per minor deviation type (including the total for each treatment arm and Total) was calculated out of the total number of participants randomised.

11 Appendix

11.1 Medical History reported at Screening visit: Listing of Other medical conditions

Table 58. Listing of Other medical conditions

Screening ID	Description of Other medical condition(s)
BSA010-001	Ibuprofen
BSA013-002	Cerebral Palsy
	Achilles Tendon Shortening (Bilateral)
BSA013-004	Opiates - causes nausea
	Pineapple and Kiwi fruit
BSA013-003	ulcerative colitis
	hysterectomy fibroids
BSA014-001	Previous nephrectomy and hysterectomy, now bladder dysfunction, self-catheterises
	Previous spinal fixation with spinal impact
BSA015-001	Borderline personality disorder
	Migraine
BSA005-001	Hypothyroidism
	total abdominal hysterectomy
BSA006-002	Intermittent headaches
	occasional migraines
BSA006-003	insomnia
	sleep apnoea
BSA006-004	psoriasis
	diverticulitis
BSA006-005	Diverticular disease
	Lower back pain
BSA006-009	Tramadol allergy
	Trimethoprim allergy
BSA008-001	Latex
	Nikel
BSA008-004	Azithromycin
BSA008-002	Doxazosin
BSA008-005	Aminophylline
BSA009-008	Mustard

11.2 Listing of Protocol Deviations

11.2.1 Other

Table 59. Protocol Deviation: Other

Trial ID	Treatment	Deviation date	Deviation reason details
T2L006-001	Doxycycline	20/12/2021	Screening pregnancy test was urine instead of serum
T2L009-007	Doxycycline	13/04/2022	Blood sample form did not get sent with samples. Bloods not analysed in Leicester labs.
T2L009-005	Placebo	29/06/2022	Blood pregnancy test form not send to local lab along with sample. Sample not processed.
T2L009-004	Placebo	23/08/2022	Participant informed they couldn't attend the site for safety washout follow up visit on 10/08/2022. So had to reschedule it for 2 weeks later. Visit completed 1 week out of window.
T2L003-017	Placebo	05/01/2023	Visit 1 and 2 were completed on the same day on the 05/01/2023
T2L003-017	Placebo	05/01/2023	lab sample returned by DHL, box labelled correctly with un3373 but waybill incorrect so shipping returned
T2L011-013	Placebo	11/01/2023	Issue with accountability check at V3
T2L009-025	Placebo	15/02/2023	Further exacerbation during screening period- to enable 2 weeks washout period following OCS, further delay to randomisation visit (now extended by 4 weeks).
T2L009-009	Doxycycline	22/02/2023	Visit 5 completed 3 days out of the visit window because of a mistake in calculation of visit due date.
T2L014-018	Placebo	05/04/2023	FBC sample was not sent to Leicester but sent to the local lab instead for analysis
T2L003-017	Placebo	17/04/2023	visit 3 out of the visit window due to beat easter holiday and national doctor strike
T2L014-018	Placebo	16/05/2023	Patient attended end-of-study safety visit early as unable to attend within planned date range.
T2L011-013	Placebo	22/05/2023	Visit schedule. SFU visit after early closure of study completed early. Participant stopped medication 19/04/2023 due to exacerbation. Telephoned 20/04/2023 to inform of study closure. SFU visits completed 3 days out of 6week (+/-day) window in protocol. Participant unable to attend at any other time
T2L011-029	Doxycycline	02/06/2023	9 capsules of imp unaccountable for. Participant has on first day recorded in his diary (2 capsules). however, has verbally confirmed he took one tablet per day as Pxop until he was contacted on 20th April 2023 (i.e. closure of study).
T2L012-022	Doxycycline	06/06/2023	Patient feeling unwell and did not come to his visit. It was re-scheduled for the following week, but patient exacerbated and was admitted to hospital. Follow-up visit completed on 23/06/2023

11.3 Listing of Adverse Events reported for participants in the Placebo group

Table 60. Listing of Adverse Events reported in the Placebo group

Trial ID	Adverse Event description	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
T2L003-017	Covid 19	-	Moderate	Resolved	None	Not related	No	No
T2L006-002	Extraction of two teeth	0	Moderate	Resolved	None	Not related	No	No
T2L006-002	Gum infection	-	Moderate	Unknown	Concomitant Medication	Not related	No	No
T2L006-002	Gastritis	365	Severe	Resolved	Concomitant Medication	Not related	No	No
T2L006-002	Covid-19 infection	12	Moderate	Resolved	None	Not related	No	No
T2L008-015	Prickly, burning sensation in skin	13	Mild	Resolved	None	Possibly related	No	No
T2L009-004	Deterioration in anxiety and depression	-	Moderate	Continuing	Concomitant Medication	Not related	No	No
T2L009-004	Covid 19	6	Mild	Resolved	Concomitant Medication	Not related	No	No
T2L009-020	Urinary Tract Infection	13	Mild	Resolved	Concomitant Medication	Not related	No	No
T2L011-013	Asthma Exacerbation	13	Moderate	Resolved	Concomitant Medication	Not related	No	No
T2L011-013	Chest infection	4	Mild	Resolved	Concomitant Medication	Not related	No	No
T2L014-018	UTI (exacerbation of recurrent urinary tract infections)	14	Moderate	Resolved	Concomitant Medication	Not related	No	Yes
T2L014-018	Surgical repair of fractured 3rd metatarsal left foot	47	Moderate	Resolved	Non-drug therapy	Not related	No	No
T2L015-027	Abdominal Pain	9	Mild	Resolved	None	Possibly related	No	No

11.4 Listing of Adverse Events in the Doxycycline group

Table 61. Listing of Adverse Events reported in the Doxycycline group

Trial ID	Adverse Event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
T2L006-001	asthma exacerbation	11	Severe	Resolved	Concomitant Medication	Not related	No	No
T2L006-001	Viral LRTI	11	Severe	Resolved	Concomitant Medication	Not related	No	No
T2L006-001	asthma exacerbation	30	Severe	Resolved	Concomitant Medication	Not related	No	No
T2L006-001	Itchy rash on both arms	7	Moderate	Resolved	Concomitant Medication	Possibly related	No	Yes
T2L006-001	covid-19 infection	5	Moderate	Resolved	None	Not related	No	No
T2L006-001	Increased asthma symptoms	4	Severe	Resolved	Concomitant Medication	Not related	No	No
T2L006-016	sore and swollen tongue	2	Moderate	Resolved	Concomitant Medication	Not related	No	No
T2L006-016	nausea	5	Mild	Resolved	None	Probably related	No	Yes
T2L006-016	asthma exacerbation	8	Moderate	Resolved	Concomitant Medication	Not related	No	No
T2L006-016	Low serum ferritin	-	Moderate	Continuing	Concomitant Medication	Not related	No	No
T2L008-006	Ingrowing toenail	-	Moderate	Continuing	Non-drug therapy	Not related	No	No
T2L008-006	Cellulitis	27	Moderate	Resolved	Concomitant Medication	Not related	No	No
T2L009-007	Diarrhoea	150	Mild	Resolved	None	Probably related	No	Yes
T2L009-007	Dermatitis to right fifth toe	43	Mild	Resolved	None	Not related	No	No
T2L009-009	Campylobacter infection	6	Moderate	Resolved	Concomitant Medication	Not related	No	No
T2L009-009	Right breast lump	17	Mild	Resolved	None	Not related	No	No

Trial ID	Adverse Event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
T2L011-014	asthma flare up following a viral infection	7	Moderate	Resolved	Concomitant Medication	Not related	No	No
T2L012-022	Asthma exacerbation	10	Moderate	Resolved	None	Unlikely to be related	No	No
T2L012-022	Asthma exacerbation	3	Moderate	Resolved	None	Unlikely to be related	No	No
T2L012-022	Asthma exacerbation	8	Moderate	Resolved	None	Unlikely to be related	No	No

11.5 Post-hoc analysis of the Primary, Secondary, Mechanistic and Exploratory Outcomes

The analyses reported in this section were not specified in the SAP. They were carried out post-hoc at the request of the co-Chief Investigators to placate reviewers of the paper submission. It is important to note that none of the analyses were adjusted for the minimisation factors due to the low number of participants recruited into the T2-LOW trial.

11.5.1 Post-hoc analysis of the Primary Outcome

A negative binomial regression model comparing the treatment arms (Doxycycline vs Placebo) was fitted with the number of severe exacerbations per participant as the outcome and the log-follow-up time (in weeks) as an offset variable. The offset allows for different lengths of time on treatment for each participant. The model was adjusted for a categorical variable of treatment arm (Placebo as reference). The analysis was conducted on the Intention-to-treat population and it assumes that missing primary outcome data are missing at random (MAR) with no deletion or imputation being implemented. The results are presented as IRR, 95% CI and a p-value.

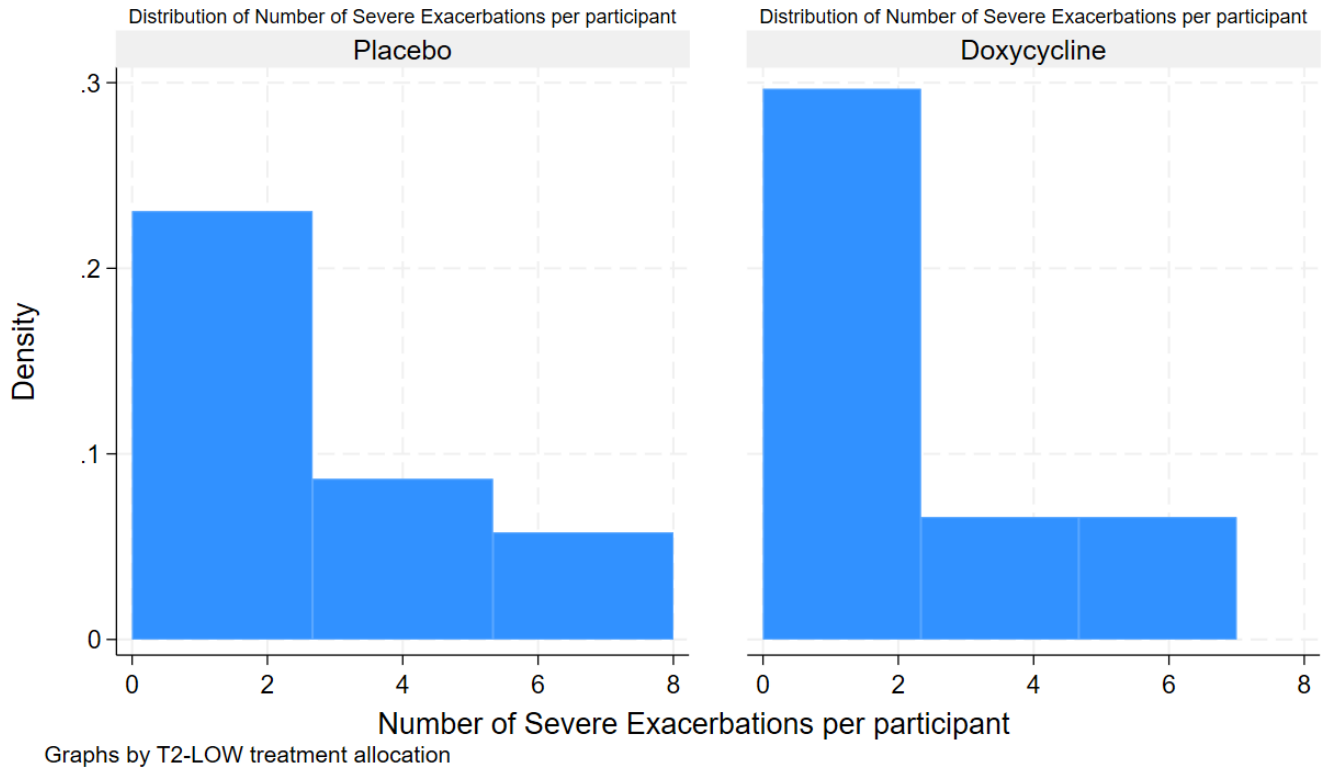

Figure 2. Distribution of Number of Severe Exacerbations per participant

Table 62. Post-Hoc Analysis | Outcome: Total Number of Severe Exacerbations per participant

Primary Outcome		IRR (95% CI)	P-value
Total number of severe exacerbations per participant	Doxycycline vs Placebo	0.74 (0.33, 1.65)	0.459

Placebo: Participants=12
Doxycycline: Participants=12
Overall: Participants=24

11.5.2 Post-hoc analysis of Secondary Outcomes

The Wilcoxon rank-sum test, also known as the Mann-Whitney two-sample statistic, was conducted to compare the treatment arms (Doxycycline vs Placebo) using the Intention-to-treat population. The test was conducted for each secondary outcome using data collected at 90 days post-randomisation. The analyses assume that missing secondary outcome data are missing at random (MAR) with no deletion or imputation being implemented. The results are presented as a p-value.

Table 63. Post-Hoc Analysis | Outcome: FeNO

Secondary Outcome		P-value
Fractional Exhaled Nitric Oxide Levels (FeNO) (ppb)	Doxycycline vs Placebo	0.834

Placebo: Participants=8
Doxycycline: Participants=8
Overall: Participants=16

Table 64. Post-Hoc Analysis | Outcome: Absolute Blood Eosinophil levels

Secondary Outcome		P-value
Absolute Blood Eosinophil level ($x10^9$/L)	Doxycycline vs Placebo	0.417

Placebo: Participants=7
Doxycycline: Participants=8
Overall: Participants=15

Table 65. Post-Hoc Analysis | Outcome: Absolute Blood Neutrophil levels

Secondary Outcome		P-value
Absolute Blood Neutrophil level ($x10^9$/L)	Doxycycline vs Placebo	0.563

Placebo: Participants=7
Doxycycline: Participants=8
Overall: Participants=15

Table 66. Post-Hoc Analysis | Outcome: ACQ 6-IA score

Secondary Outcome		P-value
Juniper Asthma Control Questionnaire 6 – Interviewer Administered (ACQ 6-IA) Score	Doxycycline vs Placebo	0.344

Placebo: Participants=8
Doxycycline: Participants=8
Overall: Participants=16

Table 67. Post-Hoc Analysis | Outcome: AQLQ S-IA score

Secondary Outcome		P-value
Juniper Asthma Quality of Life Questionnaire – Interviewer Administered (AQLQ S-IA) Score	Doxycycline vs Placebo	0.713

Placebo: Participants=8
Doxycycline: Participants=8
Overall: Participants=16

Table 68. Post-Hoc Analysis | Outcome: SNOT-22 score

Secondary Outcome		P-value
Sino-nasal Outcome Test (SNOT-22) Score	Doxycycline vs Placebo	1.000

Placebo: Participants=7
Doxycycline: Participants=7
Overall: Participants=14

Table 69. Post-Hoc Analysis | Outcome: VAS score

Secondary Outcome		P-value
Visual Analogue Scale (VAS) Score	Doxycycline vs Placebo	0.227

Placebo: Participants=8
Doxycycline: Participants=8
Overall: Participants=16

11.5.3 Post-hoc analysis of Mechanistic Outcome

The Wilcoxon rank-sum test, also known as the Mann-Whitney two-sample statistic, was conducted to compare the treatment arms (Doxycycline vs Placebo) using the Intention-to-treat population. The test was conducted for the y-proteobacteria:firmicutes ratio (mechanistic outcome) using data collected at 90 days post-randomisation. The analysis assumes that missing outcome data are missing at random (MAR) with no deletion or imputation being implemented. The result is presented as a p-value.

Table 70. Post-Hoc Analysis | Outcome: y-proteobacteria:firmicutes ratio

Mechanistic Outcome		P-value
y-proteobacteria:firmicutes ratio	Doxycycline vs Placebo	0.788

Placebo: Participants=4
Doxycycline: Participants=5
Overall: Participants=9

11.5.4 Post-hoc analysis of Exploratory Outcome

The Wilcoxon rank-sum test, also known as the Mann-Whitney two-sample statistic, was conducted to compare the treatment arms (Doxycycline vs Placebo) using the Intention-to-treat population. The test was conducted for the Total 16s RNA (exploratory outcome) using data collected at 90 days post-randomisation. The analysis assumes that missing outcome data are missing at random (MAR) with no deletion or imputation being implemented. The result is presented as a p-value.

Table 71. Post-Hoc Analysis | Outcome: Total 16s RNA

Exploratory Outcome		P-value
Total 16s RNA (copies/mL)	Doxycycline vs Placebo	0.845

Placebo: Participants=8
Doxycycline: Participants=6
Overall: Participants=14