Clinical trial results:
Randomised Controlled Trial of the efficacy and safety of an ICS/LABA reliever therapy regimen in asthma.

Summary

EudraCT number	2015-002384-42
Trial protocol	GB
Global end of trial date	30 August 2018

Results information

Result version number	v1 (current)
This version publication date	23 April 2021
First version publication date	23 April 2021

Trial information

Trial identification

Sponsor protocol code	MRINZ/15/A1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1170-2118
Other trial identifiers	Global Sponsor: MRINZ/15/A1, ANZCTR: ACTRN12615000999538

Notes:

Sponsors

Sponsor organisation name	(1) THE CHANCELLOR MASTERS AND SCHOLARS OF THE OXFORD OF OXFORD
Sponsor organisation address	Oxford Offices, Wellington Square, Oxford, United Kingdom, OX1 2JD
Public contact	Magda Laskawiec-Szkonter, Oxford Respiratory Trials Unit (ORTU), 44 01865225205, magda.laskawiec@ouh.nhs.uk
Scientific contact	Magda Laskawiec-Szkonter, Oxford Respiratory Trials Unit (ORTU), 44 01865225205, magda.laskawiec@ouh.nhs.uk
Sponsor organisation name	Medical Research Institute of New Zealand
Sponsor organisation address	Level 7 CSB Building, Wellington Hospital, Riddiford Street, Newtown, Wellington, New Zealand, 6021
Public contact	Richard Beasley, Medical Research Institute of New Zealand, 64 43890147, mark.holliday@mrinz.ac.nz
Scientific contact	Richard Beasley, Medical Research Institute of New Zealand, 64 43890147, mark.holliday@mrinz.ac.nz

Notes:

Paediatric regulatory details

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

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2018
Global end of trial reached?	Yes
Global end of trial date	30 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ICS/LABA reliever therapy with SABA reliever therapy and with maintenance ICS and SABA reliever therapy in adult patients using SABA monotherapy (i.e. without any other asthma medication).

Protection of trial subjects:

The Data Safety Monitoring Committee was established to ensure independent safety review during the study. Participants were withdrawn from the study after experiencing 3 asthma exacerbations or 1 severe asthma exacerbation for the purpose of safety, to ensure they were able to receive the appropriate treatment outside of the randomised regimens.

Background therapy:

n/a

Evidence for comparator:

Comparators were selected based on their use in clinical practice driven by international guidelines (the Global Initiative for Asthma). Short acting beta agonist (SABA) taken as required for relief of symptoms was recommended step 1 and maintenance inhaled corticosteroids plus SABA as required recommended as step 2 treatment at the time the trial was initiated.

Actual start date of recruitment	01 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	New Zealand: 553
Country: Number of subjects enrolled	Italy: 44
Worldwide total number of subjects	675
EEA total number of subjects	96

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	641
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from sites in New Zealand, Australia, Italy and the United Kingdom. The recruitment period ran from first patient first visit (FPFV) on 17/03/2016 to last patient first visit (LPFV) on 29/08/2017 worldwide.

Pre-assignment

Screening details:

Participants were screened according to the protocol inclusion/ exclusion criteria. Participants that were randomised but subsequently were found to be ineligible (incorrectly randomised) are not included as part of the baseline or analysis sets (n=7), based on a modified intention to treat approach.

Pre-assignment period milestones

Number of subjects started	675
Number of subjects completed	668

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 7

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	SABA reliever therapy

Arm description:

salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required.

Arm type	Active comparator
Investigational medicinal product name	salbutamol
Investigational medicinal product code	
Other name	Ventolin
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

salbutamol metered dose inhaler 100µg, 2 inhalations for relief of symptoms as required.

Arm title	ICS/LABA reliever therapy

Arm description:

budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.

Arm type	Experimental
Investigational medicinal product name	budesonide/formoterol
Investigational medicinal product code	
Other name	Symbicort
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.

Arm title	Maintenance ICS and SABA reliever therapy

Arm description:

budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.

Arm type	Active comparator
Investigational medicinal product name	budesonide Turbuhaler 200µg, 1 inhalation twice daily
Investigational medicinal product code	
Other name	Pulmicort
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

budesonide Turbuhaler 200µg, 1 inhalation twice daily

Investigational medicinal product name	salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.
Investigational medicinal product code	
Other name	Ventolin
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.

Number of subjects in period 1[1]	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy
Started	223	220	225
Completed	151	163	153
Not completed	72	57	72
Adverse event, serious fatal	-	1	1
incorrectly withdrawn in error	-	1	2
Physician decision	1	1	-
Consent withdrawn by subject	24	32	33
randomised in error, ineligible	3	2	1
Adverse event, non-fatal	-	2	10
Pregnancy	2	5	1
Lost to follow-up	5	1	2
Lack of efficacy	37	12	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 675 participants were randomised however 7 were found to have not met the eligibility criteria after they had been randomised (randomised in error). 668 participants were therefore included

in the analysis dataset, including within the baseline reporting datataset, as part of a modified intention to treat approach.

Baseline characteristics

Reporting groups	
Reporting group title	SABA reliever therapy
Reporting group description:	
salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required.	
Reporting group title	ICS/LABA reliever therapy
Reporting group description:	
budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.	
Reporting group title	Maintenance ICS and SABA reliever therapy
Reporting group description:	
budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.	

Reporting group values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy
Number of subjects	223	220	225
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	214	210	215
From 65-84 years	9	10	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	35.8	36	34.9
standard deviation	± 14	± 14.1	± 14.3
Gender categorical Units: Subjects			
Female	113	122	129
Male	110	98	96
Current Smoker Units: Subjects			
Smoker	24	18	22
Non-smoker	199	202	203
No. of severe exacerbations in the previous 12 months Units: Subjects			
Zero	203	208	208
One	20	12	15
Two	0	0	2

Patient-reported SABA use in the 4 weeks before enrollment			
Units: No. occasions per week			
arithmetic mean	3.4	3.8	3.2
standard deviation	± 3.3	± 3.5	± 3.0
No. of hospital admissions for asthma at any time before enrollment			
Units: Mean per participant			
arithmetic mean	0.3	0.3	0.3
standard deviation	± 0.9	± 1.3	± 0.9
Asthma Control Questionnaire-5 score			
Units: Score			
arithmetic mean	1.1	1.1	1.1
standard deviation	± 0.7	± 0.7	± 0.7
On-treatment Forced Expired Volume in 1 Second			
Units: % of predicted value			
arithmetic mean	89.2	89.8	90.3
standard deviation	± 13.7	± 14.1	± 13.6
Fractional Exhaled Nitric Oxide			
Units: parts per billion			
median	40	37	38
full range (min-max)	5 to 235	3 to 300	5 to 200
Periostin			
Units: ng/ml			
arithmetic mean	69.3	70.8	70.6
standard deviation	± 28.9	± 27	± 27.8
Blood eosinophil count			
Units: x10^9 per litre			
arithmetic mean	0.3	0.3	0.3
standard deviation	± 0.2	± 0.2	± 0.2

Reporting group values	Total		
Number of subjects	668		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	639		
From 65-84 years	29		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	364		
Male	304		
Current Smoker Units: Subjects			
Smoker	64		
Non-smoker	604		
No. of severe exacerbations in the previous 12 months Units: Subjects			
Zero	619		
One	47		
Two	2		
Patient-reported SABA use in the 4 weeks before enrollment Units: No. occasions per week			
arithmetic mean			
standard deviation	-		
No. of hospital admissions for asthma at any time before enrollment Units: Mean per participant			
arithmetic mean			
standard deviation	-		
Asthma Control Questionnaire-5 score Units: Score			
arithmetic mean			
standard deviation	-		
On-treatment Forced Expired Volume in 1 Second Units: % of predicted value			
arithmetic mean			
standard deviation	-		
Fractional Exhaled Nitric Oxide Units: parts per billion			
median			
full range (min-max)	-		
Periostin Units: ng/ml			
arithmetic mean			
standard deviation	-		
Blood eosinophil count Units: x10^9 per litre			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	SABA reliever therapy
Reporting group description:	
salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required.	
Reporting group title	ICS/LABA reliever therapy
Reporting group description:	
budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.	
Reporting group title	Maintenance ICS and SABA reliever therapy
Reporting group description:	
budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.	

Primary: Annualized rate of asthma exacerbations per patient

End point title	Annualized rate of asthma exacerbations per patient
End point description:	

End point type	Primary
End point timeframe:	
Overall study period	

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: Rate of exacerbations				
number (not applicable)	0.40	0.195	0.175	

Statistical analyses

Statistical analysis title	Relative rate exacerbations ICS/LABA vs SABA
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Poisson regression
Parameter estimate	Relative Rate
Point estimate	0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.72

Notes:

[1] - Overall test for a difference in rates by treatment: Chi-square 21.1 on 2 DF; P<0.001

Statistical analysis title	Relative rate exacerbations ICS/LABA vs ICS+SABA
Comparison groups	Maintenance ICS and SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Poisson regression
Parameter estimate	Relative rate
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.79

Secondary: Time to first exacerbation

End point title	Time to first exacerbation

End point description:

End point type	Secondary

End point timeframe:

Overall study period

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: Exacerbations	74	37	32	

Statistical analyses

Statistical analysis title	Time to first exacerbation ICS/LABA vs SABA only
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.73

Statistical analysis title	Time to first exacerbation ICS/LABA vs ICS+SABA
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.57

Secondary: Time to first severe exacerbation

End point title	Time to first severe exacerbation
End point description:	
End point type	Secondary
End point timeframe:	
Overall study period	

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: exacerbtions	23	9	21	

Statistical analyses

Statistical analysis title	Time to severe exacerbation ICS/LABA vs SABA only
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.82

Statistical analysis title	Time to severe exacerbation ICS/LABA vs ICS+SABA
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.9

Secondary: Number of severe exacerbations	
End point title	Number of severe exacerbations
End point description:	

End point type	Secondary
End point timeframe:	
Overall study period	

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: Severe Exacerbations	23	9	21	

Statistical analyses

Statistical analysis title	Relative risk sev. exacerbations ICS/LABA vs SABA
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.86

Statistical analysis title	Relative risk sev. exac ICS/LABA vs ICS+SABA
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.96

Secondary: Asthma Control Questionnaire-5 Score

End point title	Asthma Control Questionnaire-5 Score

End point description:

End point type	Secondary

End point timeframe:

Overall study period

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	220	225	
Units: Score				
arithmetic mean (standard deviation)				
Visit 1	1.1 (± 0.7)	1.1 (± 0.7)	1.1 (± 0.7)	
Visit 2	1.0 (± 0.7)	0.9 (± 0.6)	0.8 (± 0.7)	
Visit 3	1.0 (± 0.8)	0.8 (± 0.6)	0.7 (± 0.6)	
Visit 4	0.9 (± 0.7)	0.8 (± 0.6)	0.7 (± 0.7)	
Visit 5	0.9 (± 0.9)	0.8 (± 0.7)	0.6 (± 0.7)	
Visit 6	0.8 (± 0.8)	0.8 (± 0.7)	0.6 (± 0.8)	
Visit 7	0.9 (± 0.9)	0.8 (± 0.7)	0.7 (± 0.8)	

Statistical analyses

Statistical analysis title	Mean difference in ACQ-5 ICS/LABA vs SABA only

Statistical analysis description:

main effects averaged over all visits

Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.06

Notes:

[2] - Overall P<0.001 for treatment effect

Statistical analysis title	Mean difference in ACQ-5 ICS/LABA vs ICS+SABA

Statistical analysis description:	
Main effects analysis averaged over all visits	
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.23

Notes:

[3] - Overall P<0.001 for treatment effect

Secondary: Forced Expired Volume in 1 second (FEV1)

End point title	Forced Expired Volume in 1 second (FEV1)
End point description:	
End point type	Secondary
End point timeframe:	
Overall study period	

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	218	225	
Units: Litres				
arithmetic mean (standard deviation)				
Visit 1	3.30 (± 0.76)	3.30 (± 0.87)	3.30 (± 0.87)	
Visit 2	3.33 (± 0.77)	3.37 (± 0.85)	3.36 (± 0.88)	
Visit 3	3.35 (± 0.78)	3.36 (± 0.89)	3.38 (± 0.88)	
Visit 4	3.33 (± 0.78)	3.32 (± 0.84)	3.35 (± 0.88)	
Visit 5	3.32 (± 0.74)	3.30 (± 0.85)	3.33 (± 0.88)	
Visit 6	3.30 (± 0.72)	3.30 (± 0.87)	3.34 (± 0.91)	
Visit 7	3.23 (± 0.71)	3.28 (± 0.84)	3.31 (± 0.89)	

Statistical analyses

Statistical analysis title	Mean difference in FEV1 (L) ICS/LABA vs SABA only

Statistical analysis description:	
Main effects analysis averaged over all visits	
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.07

Notes:

[4] - Overall P=0.20 for treatment effect

Statistical analysis title	Mean difference in FEV1 (L) ICS/LABA vs ICS+SABA
Statistical analysis description:	
Main effects analysis averaged over all visits	
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.04

Secondary: Fraction of exhaled nitric oxide (FeNO)

End point title	Fraction of exhaled nitric oxide (FeNO)
End point description:	
End point type	Secondary
End point timeframe:	
Overall study period	

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: parts per billion				
log mean (standard deviation)				
Visit 1	3.69 (± 0.83)	3.56 (± 0.88)	3.66 (± 0.84)	
Visit 3	3.7 (± 0.8)	3.36 (± 0.78)	3.2 (± 0.65)	
Visit 7	3.61 (± 0.77)	3.32 (± 0.78)	3.29 (± 0.74)	

Statistical analyses

Statistical analysis title	Difference in log FeNO ICS/LABA vs SABA only V3
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	ratio of geometric means
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.87

Statistical analysis title	Difference in log FeNO ICS/LABA vs ICS+SABA V3
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	ratio of geometric means
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.4

Statistical analysis title	Difference in log FeNO ICS/LABA vs SABA only V7
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	ratio of geometric means
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.91

Statistical analysis title	Difference in log FeNO ICS/LABA vs ICS+SABA V7
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed models analysis
Parameter estimate	ratio of geometric means
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.25

Secondary: Mean inhaled corticosteroid dose per day

End point title	Mean inhaled corticosteroid dose per day[5]

End point description:

End point type	Secondary

End point timeframe:

overall study period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The SABA only arm did not take regular maintenance inhaled corticosteroid therefore no data is available for this outcome for that group.

End point values	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	225		
Units: microgram(s)				
arithmetic mean (standard deviation)	1.07 (± 109)	222 (± 113)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total systemic corticosteroid exposure use per year

End point title	Total systemic corticosteroid exposure use per year

End point description:

End point type	Secondary

End point timeframe:

overall study period

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: milligram(s)				
arithmetic mean (standard deviation)	17.4 (± 59.8)	71.4 (± 72.1)	152.3 (± 97.1)	

Statistical analyses

Statistical analysis title	Total systemic steroid exposure ICS/LABA vs SABA
Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimator
Point estimate	41.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.4
upper limit	48.4

Statistical analysis title	Total systemic steroid exp. ICS/LABA vs ICS+SABA
Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimator
Point estimate	-84.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-104
upper limit	-64.8

Secondary: Proportion of participants withdrawn due to treatment failure

End point title	Proportion of participants withdrawn due to treatment failure

End point description:

End point type	Secondary

End point timeframe:

Overall study period

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: Participants				
One Severe Exacerbation	23	9	21	
Three Exacerbations	3	3	1	
Randomised treatment modified by healthcare provid	11	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Global Initiative for Asthma Question Category

End point title	Global Initiative for Asthma Question Category

End point description:

End point type	Secondary

End point timeframe:

Overall study period

End point values	SABA reliever therapy	ICS/LABA reliever therapy	Maintenance ICS and SABA reliever therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	225	
Units: GINA Category				
Visit 1 Well controlled	54	44	54	
Visit 1 Partly controlled	121	123	108	
Visit 1 Uncontrolled	48	53	63	
Visit 2 Well controlled	60	38	79	
Visit 2 Partly controlled	95	127	101	
Visit 2 Uncontrolled	50	43	26	
Visit 3 Well controlled	57	53	95	
Visit 3 Partly controlled	95	109	82	
Visit 3 Uncontrolled	49	25	26	
Visit 4 Well controlled	53	58	85	
Visit 4 Partly controlled	90	95	78	
Visit 4 Uncontrolled	39	30	19	
Visit 5 Well controlled	71	56	82	
Visit 5 Partly controlled	68	87	69	
Visit 5 Uncontrolled	35	31	20	
Visit 6 Well controlled	58	62	74	
Visit 6 Partly controlled	77	78	56	
Visit 6 Uncontrolled	28	30	25	
Visit 7 Well controlled	72	69	87	
Visit 7 Partly controlled	77	97	74	
Visit 7 Uncontrolled	48	31	36	

Statistical analyses

Statistical analysis title	GINA level of control ICS/LABA vs SABA Visit 2

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 2

Comparison groups	ICS/LABA reliever therapy v SABA reliever therapy

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42 [6]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.32

Notes:

[6] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs SABA Visit 3

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 3

Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 [7]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.78

Notes:

[7] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs SABA Visit 4

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 4

Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [8]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.2

Notes:

[8] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs SABA Visit 5

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 5

Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [9]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.39

Notes:

[9] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs SABA Visit 6

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 6

Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68 [10]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.86

Notes:

[10] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs SABA Visit 7

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 7

Comparison groups	SABA reliever therapy v ICS/LABA reliever therapy
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 [11]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.05

Notes:

[11] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs ICS+SABA Visit 2

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 2

Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.65

Notes:

[12] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs ICS+SABA Visit 3

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 3

Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.64

Notes:

[13] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs ICS+SABA Visit 4

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 4

Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [14]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.79

Notes:

[14] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs ICS+SABA Visit 5

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 5

Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [15]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.77

Notes:

[15] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs ICS+SABA Visit 6

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 6

Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [16]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.09

Notes:

[16] - Time by treatment interaction not statistically significant, P=0.23

Statistical analysis title	GINA level of control ICS/LABA vs ICS+SABA Visit 7

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 7

Comparison groups	ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 [17]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.24

Notes:

[17] - Time by treatment interaction not statistically significant, P=0.23

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study period

Adverse event reporting additional description:

Adverse events were collected at each visit via participant self-report, investigator assessment and investigator review of the participant completed asthma management plans/ logbooks containing healthcare utilisation and asthma related events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Safety Analysis Dataset

Reporting group description:

Dataset includes all participants that were randomised, including those who were randomised incorrectly (those who were randomised and subsequently found to not meet the eligibility criteria).

Serious adverse events	Safety Analysis Dataset		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 675 (3.41%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic malignant melanoma			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			

subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery dissection			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	2 / 675 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eating disorder			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic sinusitis			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			

subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 675 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	2 / 675 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety Analysis Dataset		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	549 / 675 (81.33%)		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	21 / 675 (3.11%)		
occurrences (all)	23		
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 675 (5.63%)		
occurrences (all)	49		
Migraine			
subjects affected / exposed	14 / 675 (2.07%)		
occurrences (all)	14		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	27 / 675 (4.00%)		
occurrences (all)	28		
Gastrointestinal disorders			

Toothache			
subjects affected / exposed	14 / 675 (2.07%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	89 / 675 (13.19%)		
occurrences (all)	99		
Cough			
subjects affected / exposed	36 / 675 (5.33%)		
occurrences (all)	37		
Oropharyngeal pain			
subjects affected / exposed	22 / 675 (3.26%)		
occurrences (all)	23		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 675 (2.81%)		
occurrences (all)	19		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	23 / 675 (3.41%)		
occurrences (all)	24		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	221 / 675 (32.74%)		
occurrences (all)	305		
Nasopharyngitis			
subjects affected / exposed	128 / 675 (18.96%)		
occurrences (all)	163		
Influenza			
subjects affected / exposed	62 / 675 (9.19%)		
occurrences (all)	72		
Lower respiratory tract infection			
subjects affected / exposed	52 / 675 (7.70%)		
occurrences (all)	57		
Respiratory tract infection			

subjects affected / exposed	28 / 675 (4.15%)		
occurrences (all)	33		
Sinusitis			
subjects affected / exposed	26 / 675 (3.85%)		
occurrences (all)	35		
Gastroenteritis			
subjects affected / exposed	20 / 675 (2.96%)		
occurrences (all)	25		
Viral upper respiratory tract infection			
subjects affected / exposed	19 / 675 (2.81%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2016	Protocol Amendment v3.0 to v4.0 due to request by MHRA: Addition of exclusion criterion 14; 14. Any known or suspected contraindications to the Investigational Medicinal Products or excipients Update to wording in 7.2.3.; 7.2.3. In the case of safety concerns arising during the study, the Sponsor and Investigators may deviate from the protocol only in cases where appropriate urgent safety measures are warranted to protect the trial participants against any immediate hazard to their health or safety. The Global Sponsor must be informed of any cases where the protocol is not adhered to and the reasons for non-adherence, as soon as possible. Non-adherence will be reported to the appropriate ethics committees and regulatory authorities in line with local requirements.
30 August 2018	Protocol Amendment v4.0 to v5.0. The MHRA approval date for this amendment was 13/09/2018 however this cannot be entered into the system as it prevents form validation due to approval date being subsequent to global end date. Change of definition for exacerbation of asthma (removal of "use" and replacement with "prescription"): Exacerbation of Asthma: Worsening asthma resulting in the prescription of systemic corticosteroids, such as a course of oral prednisone for any duration and/or… Severe Asthma Exacerbation: a. The prescription of systemic corticosteroids for at least 3 days because of asthma, or… Addition of sensitivity analysis: Severe exacerbation sensitivity analysis Wherever severe exacerbations are analysed a separate sensitivity analysis will be performed using the interpretation of the definition of a severe exacerbation that has been used in the PRACTICAL41 study; i.e.: self-reported use of corticosteroids for 3 or more days because of asthma, rather than prescription of systemic corticosteroid for at least 3 days because of asthma. Addition of reference to the PRACTICAL trial: 41. Fingleton J, et al. Description of the protocol for the PRACTICAL study: a randomised controlled trial of the efficacy and safety of ICS/LABA reliever therapy in asthma. BMJ Open Respiratory Research 2017;4:e000217. DOI: 10.1136 /bmjresp-2017-000217

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31112386