Clinical trial results:
The effectiveness of single dose Ultibro Breezhaler (indacaterol/glycopyrronium) by sd-DPI versus ipratropium/salbutamol by nebulizer in improving FEV1 and dyspnea during stable state of COPD

Summary

EudraCT number	2015-000473-12
Trial protocol	NL
Global end of trial date	30 September 2017

Results information

Result version number	v1 (current)
This version publication date	04 September 2021
First version publication date	04 September 2021
Summary attachment (see zip file)	results (Geffen RCT 2020 RM.pdf)

Trial information

Trial identification

Sponsor protocol code	ULT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576626
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UMCG
Sponsor organisation address	hanzeplein, Groningen, Netherlands,
Public contact	Afdeling Longziekten, UMCG, h.a.m.kerstjens@umcg.nl
Scientific contact	Afdeling Longziekten, UMCG, h.a.m.kerstjens@umcg.nl

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2017
Global end of trial reached?	Yes
Global end of trial date	30 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test our hypothesis that:
The combination of the two long-acting bronchodilators indacaterol and glycopyrronium confers a superior improvement compared to nebulisation with ipratropium/salbutamol, as administered single dose in patients with stable state COPD.

Primary objective:
The combination of the two long-acting bronchodilators indacaterol and glycopyrronium once daily confers a superior improvement in FEV1 as compared to nebulisation with ipratropium/salbutamol, both administered single dose in patients with stable state COPD.

Protection of trial subjects:

Rescue medication as needed open label fenoterol/ipratropium was provided in the wasout period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	8
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The main inclusion criteria were an age of at least 40 years with a diagnosis of COPD and a post-bronchodilator FEV1 below 80% predicted. COPD was defined as a physician diagnosis and an FEV1/FVC ratio of less than 0.70 after bronchodilation. Main exclusion criteria were asthma, chronic hypoxaemia, and the occurrence of a COPD exacerbation

Pre-assignment

Screening details:

The main inclusion criteria were an age of at least 40 years with a diagnosis of COPD and a post-bronchodilator FEV1 below 80% predicted. COPD was defined as a physician diagnosis and an FEV1/FVC ratio of less than 0.70 after bronchodilation. Main exclusion criteria were asthma, chronic hypoxaemia, and the occurrence of a COPD exacerbation

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	indacaterol/glycopyrronium

Arm description:

indacaterol/glycopyrronium

Arm type	Crossover
Investigational medicinal product name	indacaterol/glycopyrronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

indacaterol/glycopyrronium 110/50 µg as Ultibro® via Breezhaler®

Arm title	short-acting salbutamol plus ipratropium via nebulizer

Arm description: -

Arm type	Nebulizer
Investigational medicinal product name	salbutamol/ipratropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

salbutamol/ipratropium 2,5/0,5 mg via air driven nebulization (SAL/IPR)

Number of subjects in period 1	indacaterol/glycopyrronium	short-acting salbutamol plus ipratropium via nebulizer
Started	33	33
Completed	33	33

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	33	33	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
geometric mean	69		
standard deviation	± 6	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	26	26	

Subject analysis sets

Subject analysis set title	Primairy endpoint
Subject analysis set type	Per protocol

Subject analysis set description:

Between September 2015 and August 2017 53 patients were screened of whom 39 were included in the trial. Of those included, 33 completed the trial and were deemed evaluable

Reporting group values	Primairy endpoint		
Number of subjects	33		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			

Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years geometric mean standard deviation	 69 ± 6		
Gender categorical Units: Subjects			
Female Male	7 26		

End points

End points reporting groups

Reporting group title	indacaterol/glycopyrronium
Reporting group description: indacaterol/glycopyrronium	
Reporting group title	short-acting salbutamol plus ipratropium via nebulizer
Reporting group description: -	
Subject analysis set title	Primairy endpoint
Subject analysis set type	Per protocol
Subject analysis set description: Between September 2015 and August 2017 53 patients were screened of whom 39 were included in the trial. Of those included, 33 completed the trial and were deemed evaluable	

Primary: FEV1

End point title	FEV1
End point description: The primary endpoint, FEV1 AUC 0–6, showed a non-significant difference in favour of the SAL/IPR regimen: 2965 mL +/-1544 (mean +/- SD) for IND/GLY versus 3513 mL +/-1762 for SAL/IPR respectively (P= 0.08)	
End point type	Primary
End point timeframe: 2015-2017	

End point values	indacaterol/glycopyrronium	short-acting salbutamol plus ipratropium via nebulizer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: ML				
geometric mean (standard deviation)	2965 (± 1544)	3513 (± 1762)		

Statistical analyses

Statistical analysis title	Stats
Statistical analysis description: power calculation was performed for both the area under the curve (AUC) of the FEV1 and the Borg score. We used an alpha of 0.05 and a power of 90%. The estimated difference was extrapolated based on the known MCID of FEV1 and BORG for one time point. In a cross-over study aiming at superiority, with a two-tailed test this required a total sample size of 34 evaluable patients for the AUC of the FEV 1 and for the Borg score 30 patients. Data was analysed with IBM SPSS 24. Differences between	
Comparison groups	indacaterol/glycopyrronium v short-acting salbutamol plus ipratropium via nebulizer

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2015-2017

Adverse event reporting additional description:

No serious adverse events were reported in this short running trial.
Six patients did not complete the trial due to mild and moderate adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	UMCG
Dictionary version	2017

Reporting groups

Reporting group title	Analysis

Reporting group description: -

Serious adverse events	Analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)		
Respiratory, thoracic and mediastinal disorders			
2017	Additional description: One patient reported coughing after inhalation of IND/GLY		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/32917359