



Clinical trial results:

A randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two doses of nebulised budesonide delivered by the VR475 Inhalation System, with an open-label comparison to conventionally nebulised budesonide, in subjects with uncontrolled asthma despite treatment with high dose inhaled corticosteroid and at least a second controller (GINA Step 4) and those receiving oral corticosteroid (GINA Step 5).

Summary

EudraCT number	2015-000353-20
Trial protocol	DE HU BG PL Outside EU/EEA
Global end of trial date	27 September 2018

Results information

Result version number	v1 (current)
This version publication date	10 April 2019
First version publication date	10 April 2019

Trial information

Trial identification

Sponsor protocol code	VR475/3/001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Vectura Limited
Sponsor organisation address	1 Prospect West, Chippenham, United Kingdom, SN14 6FH
Public contact	Clinical Trials Information, Vectura Limited, +44 1249667700, clinical.enquiries@vectura.com
Scientific contact	Clinical Trials Information, Vectura Limited, +44 1249667700, clinical.enquiries@vectura.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001087-PIP02-12
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	27 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2018
Global end of trial reached?	Yes
Global end of trial date	27 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy, safety and tolerability of VR475 1 mg/2 ml twice daily given for 52 weeks compared to placebo.

Protection of trial subjects:

All subjects had the right to withdraw from the study at any time and for any reason, without having to give their reason and without any disadvantages for their subsequent care.

Background therapy:

For background therapy, subjects were required to be on high dose inhaled corticosteroids (ICS) plus at least a second asthma controller medication.

During the study, for any subject that was on oral corticosteroids (OCS) at randomisation, consideration was made to reduce the OCS dose, depending on clinical response and in line with the investigator's judgement; all other existing asthma therapy (including ICS) remained unchanged, with study medication provided as add-on therapy.

Evidence for comparator:

This Phase 3, randomised, double-blind, placebo-controlled, parallel group study evaluated the efficacy and safety of two doses of nebulised budesonide delivered by the VR475 Inhalation System, with an open-label comparison to conventionally nebulised budesonide, in subjects with severe uncontrolled asthma.

Actual start date of recruitment	28 October 2015
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	Philippines: 69
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Ukraine: 166
Country: Number of subjects enrolled	Poland: 86
Country: Number of subjects enrolled	Romania: 74
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Bulgaria: 129
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Hungary: 98

Worldwide total number of subjects	711
EEA total number of subjects	460

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)	75
Adults (18-64 years)	514
From 65 to 84 years	122
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 28 October 2015 (first subject, Screening visit) and 27 September 2018 (last subject, final study visit) at 96 sites (Bulgaria, Germany, Hungary, Poland, Romania, Serbia, Ukraine, United Kingdom and Philippines).

Pre-assignment

Screening details:

A total of 816 subjects were screened, of whom 103 were screen failures. Of the 713 subjects who were randomised, 711 subjects were treated. The 2 subjects (from Germany) who were not treated withdrew consent prior to treatment and have therefore been omitted from the analyses presented herein. Of the 711 treated subjects, 615 completed the study.

Period 1

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

Blinding implementation details:

Due to the unblinded nature of the conventionally nebulised budesonide group, subjects and site staff knew whether they were randomised to that group or to one of the three blinded groups (placebo or either of the two doses of VR475 Nebuliser Suspension via the VR475 Inhalation System). The foil pouches containing each of the two doses of VR475 Nebuliser Suspension and placebo were identical. Any in-clinic administration of VR475 Nebuliser Suspension/placebo was supervised by unblinded staff.

Arms

Are arms mutually exclusive?	Yes
Arm title	VR475 1 mg

Arm description:

VR475 1 mg delivered by the VR475 Inhalation System twice per day.

Arm type	Experimental
Investigational medicinal product name	VR475 (budesonide) 1 mg delivered by the VR475 Inhalation System
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

VR475 Nebuliser Suspension (budesonide) delivered by the VR475 Inhalation System (1 mg twice daily, at least 8 hours apart, for 52 weeks).

Arm title	VR475 0.5 mg
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Arm description:

VR475 0.5 mg delivered by the VR475 Inhalation System twice per day.

Arm type	Experimental
Investigational medicinal product name	VR475 (budesonide) 0.5 mg delivered by the VR475 Inhalation System
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

VR475 Nebuliser Suspension (budesonide) delivered by the VR475 Inhalation System (0.5 mg twice

daily, at least 8 hours apart, for 52 weeks).

Arm title	VR475 Placebo
Arm description: VR475 Placebo delivered by the VR475 Inhalation System twice per day.	
Arm type	Placebo
Investigational medicinal product name	VR475 Placebo delivered by the VR475 Inhalation System
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

VR475 Placebo (saline solution) delivered by the VR475 Inhalation System (twice daily, at least 8 hours apart, for 52 weeks).

Arm title	CN-BUD 1 mg
Arm description: Budesonide 1 mg delivered by conventional nebuliser twice per day.	
Arm type	Active comparator
Investigational medicinal product name	Budesonide 1 mg delivered by conventional nebuliser
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide nebuliser suspension delivered by conventional nebuliser (PARI BOY® SX Inhalation System; 1 mg twice daily, at least 8 hours apart, for 52 weeks).

Number of subjects in period 1	VR475 1 mg	VR475 0.5 mg	VR475 Placebo
Started	237	119	119
Completed	196	95	103
Not completed	41	24	16
Previous AE	1	-	-
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	30	18	14
Physician decision	-	-	-
Adverse event, non-fatal	7	1	1
Non-compliance with study medication	1	-	-
Decision of medical monitor	1	-	-
Change of residence	-	1	-
Lost to follow-up	1	-	-
Sponsor decision	-	2	1

Protocol deviation	-	-	-
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Number of subjects in period 1	CN-BUD 1 mg
Started	236
Completed	221
Not completed	15
Previous AE	-
Adverse event, serious fatal	-
Consent withdrawn by subject	8
Physician decision	1
Adverse event, non-fatal	3
Non-compliance with study medication	-
Decision of medical monitor	-
Change of residence	-
Lost to follow-up	2
Sponsor decision	-
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	VR475 1 mg
Reporting group description: VR475 1 mg delivered by the VR475 Inhalation System twice per day.	
Reporting group title	VR475 0.5 mg
Reporting group description: VR475 0.5 mg delivered by the VR475 Inhalation System twice per day.	
Reporting group title	VR475 Placebo
Reporting group description: VR475 Placebo delivered by the VR475 Inhalation System twice per day.	
Reporting group title	CN-BUD 1 mg
Reporting group description: Budesonide 1 mg delivered by conventional nebuliser twice per day.	

Reporting group values	VR475 1 mg	VR475 0.5 mg	VR475 Placebo
Number of subjects	237	119	119
Age categorical Units: Subjects			
Adolescents (12-17 years)	26	13	11
Adults (18-64 years)	179	84	86
From 65-84 years	32	22	22
Age continuous Units: years			
arithmetic mean	48.5	49.2	50.0
standard deviation	± 16.75	± 17.57	± 16.94
Gender categorical Units: Subjects			
Female	141	59	74
Male	96	60	45

Reporting group values	CN-BUD 1 mg	Total	
Number of subjects	236	711	
Age categorical Units: Subjects			
Adolescents (12-17 years)	25	75	
Adults (18-64 years)	165	514	
From 65-84 years	46	122	
Age continuous Units: years			
arithmetic mean	49.1	-	
standard deviation	± 16.81		
Gender categorical Units: Subjects			
Female	145	419	
Male	91	292	

End points

End points reporting groups

Reporting group title	VR475 1 mg
Reporting group description: VR475 1 mg delivered by the VR475 Inhalation System twice per day.	
Reporting group title	VR475 0.5 mg
Reporting group description: VR475 0.5 mg delivered by the VR475 Inhalation System twice per day.	
Reporting group title	VR475 Placebo
Reporting group description: VR475 Placebo delivered by the VR475 Inhalation System twice per day.	
Reporting group title	CN-BUD 1 mg
Reporting group description: Budesonide 1 mg delivered by conventional nebuliser twice per day.	

Primary: The annualised rate of clinically significant exacerbations (CSEs) during the 52-week treatment period

End point title	The annualised rate of clinically significant exacerbations (CSEs) during the 52-week treatment period
End point description:	
End point type	Primary
End point timeframe: During the 52-week treatment period.	

End point values	VR475 1 mg	VR475 0.5 mg	VR475 Placebo	CN-BUD 1 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	227	111	114	231
Units: Annualised CSE rate (adjusted)				
number (confidence interval 95%)	0.23 (0.13 to 0.41)	0.22 (0.12 to 0.43)	0.28 (0.15 to 0.52)	0.20 (0.11 to 0.36)

Statistical analyses

Statistical analysis title	Ratio of CSEs (VR475 1 mg versus Placebo)
Statistical analysis description: Primary analysis. The observed CSE rates were calculated based on the number of exacerbations during time on treatment. Ratios of CSEs (VR475 1 mg versus placebo) were calculated.	
Comparison groups	VR475 1 mg v VR475 Placebo

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3909
Method	Regression, Linear
Parameter estimate	Negative binomial regression
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.29

Statistical analysis title	Ratio of CSEs (VR475 0.5 mg versus Placebo)
Comparison groups	VR475 0.5 mg v VR475 Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.4028
Method	Regression, Linear
Parameter estimate	Negative binomial regression
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.35

Notes:

[1] - Secondary analysis.

Secondary: Change in in-clinic pre-bronchodilator forced expiratory volume in one second (FEV1) from baseline during the treatment period

End point title	Change in in-clinic pre-bronchodilator forced expiratory volume in one second (FEV1) from baseline during the treatment period
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End point description:

End point type	Secondary
End point timeframe:	
Change from baseline at Weeks 24 and 52.	

End point values	VR475 1 mg	VR475 0.5 mg	VR475 Placebo	CN-BUD 1 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	227 ^[2]	111 ^[3]	114 ^[4]	231 ^[5]
Units: litre(s)				
arithmetic mean (standard deviation)				
Change from baseline to Week 24	0.240 (± 0.508)	0.198 (± 0.455)	0.117 (± 0.393)	0.147 (± 0.380)
Change from baseline to Week 52	0.241 (± 0.515)	0.198 (± 0.460)	0.150 (± 0.439)	0.155 (± 0.421)

Notes:

[2] - N=210 at Week 24; N=195 at Week 52.

[3] - N=101 at Week 24; N=95 at Week 52.

[4] - N=108 at Week 24; N=102 at Week 52.

[5] - N=226 at Week 24; N=220 at Week 52.

Statistical analyses

Statistical analysis title	Mean difference at Wk 24 (VR475 1 mg vs Placebo)
Statistical analysis description:	
Mean difference in FEV1 from baseline to Week 24. N=318.	
Comparison groups	VR475 1 mg v VR475 Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.033
upper limit	0.222

Statistical analysis title	Mean difference at Wk 24 (VR475 0.5 mg vs Placebo)
Statistical analysis description:	
Mean difference in FEV1 from baseline to Week 24. N=209.	
Comparison groups	VR475 0.5 mg v VR475 Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2074
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.182

Statistical analysis title	Mean difference at Wk 52 (VR475 1 mg vs Placebo)
Statistical analysis description: Mean difference in FEV1 from baseline to Week 52. N=297.	
Comparison groups	VR475 1 mg v VR475 Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0641
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.195

Statistical analysis title	Mean difference at Wk 52 (VR475 0.5 mg vs Placebo)
Statistical analysis description: Mean difference in FEV1 from baseline to Week 52. N=197.	
Comparison groups	VR475 0.5 mg v VR475 Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	0.151

Secondary: Change in Asthma Control Questionnaire (ACQ-5) scores from baseline during the treatment period

End point title	Change in Asthma Control Questionnaire (ACQ-5) scores from baseline during the treatment period
End point description:	
End point type	Secondary
End point timeframe: Change from baseline to Weeks 24 and 52.	

End point values	VR475 1 mg	VR475 0.5 mg	VR475 Placebo	CN-BUD 1 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	227 ^[6]	111 ^[7]	114 ^[8]	231 ^[9]
Units: Change from baseline in ACQ-5 score				
arithmetic mean (standard deviation)				
Change from baseline to Week 24	-0.98 (± 1.067)	-1.04 (± 1.033)	-0.80 (± 0.936)	-0.92 (± 1.024)
Change from baseline to Week 52	-1.08 (± 1.085)	-0.94 (± 1.040)	-0.91 (± 0.996)	-0.98 (± 1.093)

Notes:

[6] - N=207 at Week 24; N=212 at Week 52.

[7] - N=97 at Week 24; N=100 at Week 52.

[8] - N=106 at Week 24; N=105 at Week 52.

[9] - N=221 at Week 24; N=226 at Week 52.

Statistical analyses

Statistical analysis title	Difference at Wk 24 (VR475 1 mg vs Placebo)
Statistical analysis description:	
Mean difference in ACQ-5 score from baseline to Week 24. N=313.	
Comparison groups	VR475 1 mg v VR475 Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1768
Method	Repeated measures mixed effect model
Parameter estimate	LS Mean
Point estimate	-0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.369
upper limit	0.068

Statistical analysis title	Difference at Wk 24 (VR475 0.5 mg vs Placebo)
Statistical analysis description:	
Mean difference in ACQ-5 score from baseline to Week 24. N=203.	
Comparison groups	VR475 0.5 mg v VR475 Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1657
Method	Repeated measures mixed effect model
Parameter estimate	LS Mean
Point estimate	-0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.436
upper limit	0.075

Statistical analysis title	Difference at Wk 52 (VR475 1 mg vs Placebo)
Statistical analysis description:	
Mean difference in ACQ-5 score from baseline to Week 52. N=317.	
Comparison groups	VR475 1 mg v VR475 Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.122
Method	Repeated measures mixed effects model
Parameter estimate	LS Mean
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.408
upper limit	0.048

Statistical analysis title	Difference at Wk 52 (VR475 0.5 mg vs Placebo)
Statistical analysis description:	
Mean difference in ACQ-5 score from baseline to Week 52. N=205.	
Comparison groups	VR475 0.5 mg v VR475 Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9481
Method	Repeated measures mixed effects model
Parameter estimate	LS Mean
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.258
upper limit	0.275

Secondary: Change in number of puffs of reliever medication use from baseline during the treatment period

End point title	Change in number of puffs of reliever medication use from baseline during the treatment period
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End point description:

End point type	Secondary
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End point timeframe:

Change from baseline in mean number of puffs per day of reliever medication at Weeks 24 and 52 .

End point values	VR475 1 mg	VR475 0.5 mg	VR475 Placebo	CN-BUD 1 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	227 ^[10]	111 ^[11]	114 ^[12]	231 ^[13]
Units: Puffs				
arithmetic mean (standard deviation)				
Change from baseline to Week 24	-0.93 (± 1.97)	-1.06 (± 1.97)	-0.73 (± 2.12)	-0.71 (± 1.83)
Change from baseline to Week 52	-1.09 (± 2.26)	-0.92 (± 1.88)	-0.84 (± 1.77)	-0.92 (± 1.98)

Notes:

[10] - N=209 at Week 24; N=189 at Week 52.

[11] - N=100 at Week 24; N=90 at Week 52.

[12] - N=104 at Week 24; N=94 at Week 52.

[13] - N=220 at Week 24; N=212 at Week 52.

Statistical analyses

Statistical analysis title	Mean difference at Wk 24 (VR475 1 mg vs Placebo)
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Statistical analysis description:

Mean difference in rescue medication use (number of puffs) from baseline to Week 24. N=313.

Comparison groups	VR475 1 mg v VR475 Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2522
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.633
upper limit	0.166

Statistical analysis title	Mean difference at Wk 24 (VR475 0.5 mg vs Placebo)
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Statistical analysis description:

Mean difference in rescue medication use (number of puffs) from baseline to Week 24. N=204.

Comparison groups	VR475 0.5 mg v VR475 Placebo
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Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1673
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.329
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.796
upper limit	0.138

Statistical analysis title	Mean difference at Wk 52 (VR475 1 mg vs Placebo)
Statistical analysis description:	
Mean difference in rescue medication use (number of puffs) from baseline to Week 52. N=283.	
Comparison groups	VR475 1 mg v VR475 Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4802
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.569
upper limit	0.268

Statistical analysis title	Mean difference at Wk 52 (VR475 0.5 mg vs Placebo)
Statistical analysis description:	
Mean difference in rescue medication use (number of puffs) from baseline to Week 52. N=184.	
Comparison groups	VR475 0.5 mg v VR475 Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9416
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.472
upper limit	0.509

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred during the study period, from the date of consent to the Follow-up Visit, were recorded.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	VR475 1 mg
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Reporting group description:

VR475 1 mg delivered by the VR475 Inhalation System twice per day.

Reporting group title	VR475 0.5 mg
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Reporting group description:

VR475 0.5 mg delivered by the VR475 Inhalation System twice per day.

Reporting group title	VR475 Placebo
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Reporting group description:

VR475 Placebo delivered by the VR475 Inhalation System twice per day.

Reporting group title	CN-BUD 1 mg
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Reporting group description:

Budesonide 1 mg delivered by conventional nebuliser twice per day.

Serious adverse events	VR475 1 mg	VR475 0.5 mg	VR475 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 237 (5.91%)	11 / 119 (9.24%)	7 / 119 (5.88%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism arterial			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	1 / 119 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 237 (2.95%)	2 / 119 (1.68%)	4 / 119 (3.36%)
occurrences causally related to treatment / all	0 / 8	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood cortisol decreased			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			

subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stab wound			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	1 / 119 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neurodegenerative disorder			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculitis cervical			

subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	1 / 119 (0.84%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal cyst			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 237 (0.42%)	1 / 119 (0.84%)	1 / 119 (0.84%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	1 / 119 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection bacterial			

subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 237 (0.00%)	1 / 119 (0.84%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CN-BUD 1 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 236 (3.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism arterial			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 236 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Asthma	subjects affected / exposed	4 / 236 (1.69%)		
	occurrences causally related to treatment / all	0 / 7		
	deaths causally related to treatment / all	0 / 0		
Haemoptysis	subjects affected / exposed	1 / 236 (0.42%)		
	occurrences causally related to treatment / all	0 / 1		
	deaths causally related to treatment / all	0 / 0		
Investigations				
Blood cortisol decreased	subjects affected / exposed	0 / 236 (0.00%)		
	occurrences causally related to treatment / all	0 / 0		
	deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications				
Femur fracture	subjects affected / exposed	0 / 236 (0.00%)		
	occurrences causally related to treatment / all	0 / 0		
	deaths causally related to treatment / all	0 / 0		
Foot fracture	subjects affected / exposed	0 / 236 (0.00%)		
	occurrences causally related to treatment / all	0 / 0		
	deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage	subjects affected / exposed	0 / 236 (0.00%)		
	occurrences causally related to treatment / all	0 / 0		
	deaths causally related to treatment / all	0 / 0		
Stab wound	subjects affected / exposed	0 / 236 (0.00%)		
	occurrences causally related to treatment / all	0 / 0		
	deaths causally related to treatment / all	0 / 0		
Tibia fracture	subjects affected / exposed	0 / 236 (0.00%)		
	occurrences causally related to treatment / all	0 / 0		
	deaths causally related to treatment / all	0 / 0		

Wound haemorrhage			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 236 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neurodegenerative disorder			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinsonism			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculitis cervical			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			

subjects affected / exposed	1 / 236 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal inflammation			
subjects affected / exposed	1 / 236 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			
subjects affected / exposed	1 / 236 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal cyst			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	0 / 236 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 236 (0.85%) 0 / 2 0 / 0		
Acute sinusitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 236 (0.00%) 0 / 0 0 / 0		
Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 236 (0.00%) 0 / 0 0 / 0		
Lobar pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 236 (0.00%) 0 / 0 0 / 0		
Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 236 (0.00%) 0 / 0 0 / 0		
Superinfection bacterial subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 236 (0.00%) 0 / 0 0 / 0		
Metabolism and nutrition disorders Type 2 diabetes mellitus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 236 (0.00%) 0 / 0 0 / 0		

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

Non-serious adverse events	VR475 1 mg	VR475 0.5 mg	VR475 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 237 (64.14%)	68 / 119 (57.14%)	76 / 119 (63.87%)
Investigations			
Blood cortisol decreased			
subjects affected / exposed	27 / 237 (11.39%)	5 / 119 (4.20%)	2 / 119 (1.68%)
occurrences (all)	28	5	2
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 237 (7.59%)	6 / 119 (5.04%)	7 / 119 (5.88%)
occurrences (all)	26	7	8
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	6 / 237 (2.53%)	6 / 119 (5.04%)	0 / 119 (0.00%)
occurrences (all)	7	7	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	64 / 237 (27.00%)	30 / 119 (25.21%)	39 / 119 (32.77%)
occurrences (all)	103	48	74
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 237 (5.06%)	10 / 119 (8.40%)	13 / 119 (10.92%)
occurrences (all)	17	15	17
Bronchitis			
subjects affected / exposed	12 / 237 (5.06%)	12 / 119 (10.08%)	9 / 119 (7.56%)
occurrences (all)	14	13	11
Respiratory tract infection			
subjects affected / exposed	13 / 237 (5.49%)	3 / 119 (2.52%)	5 / 119 (4.20%)
occurrences (all)	16	4	10
Upper respiratory tract infection			
subjects affected / exposed	10 / 237 (4.22%)	2 / 119 (1.68%)	8 / 119 (6.72%)
occurrences (all)	11	9	11
Pharyngitis			
subjects affected / exposed	9 / 237 (3.80%)	6 / 119 (5.04%)	2 / 119 (1.68%)
occurrences (all)	12	9	3

Non-serious adverse events	CN-BUD 1 mg		
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	149 / 236 (63.14%)		
Investigations			
Blood cortisol decreased			
subjects affected / exposed	14 / 236 (5.93%)		
occurrences (all)	14		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 236 (8.90%)		
occurrences (all)	24		
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	3 / 236 (1.27%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	64 / 236 (27.12%)		
occurrences (all)	108		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 236 (11.86%)		
occurrences (all)	37		
Bronchitis			
subjects affected / exposed	5 / 236 (2.12%)		
occurrences (all)	7		
Respiratory tract infection			
subjects affected / exposed	10 / 236 (4.24%)		
occurrences (all)	15		
Upper respiratory tract infection			
subjects affected / exposed	9 / 236 (3.81%)		
occurrences (all)	12		
Pharyngitis			
subjects affected / exposed	9 / 236 (3.81%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2016	<p>The following substantial amendments were made in protocol version 2 (dated 07 April 2016); however, as further minor updates were required, this version was not submitted. The submitted version of the protocol that contained these substantial amendments was therefore protocol version 3 (dated 15 April 2016).</p> <ul style="list-style-type: none">• 24-hour serum cortisol levels were no longer assessed. Morning cortisol or adrenocorticotrophic hormone (ACTH) stimulation testing was included.• The serum budesonide analysis in a sub-group of subjects was considered better suited to a specialist unit. An exploratory population pharmacokinetic analysis was incorporated.• The Week 54 Follow-up call was changed to a clinic visit at Week 56; the Treatment Period Follow-up was extended to 4 weeks.• Study visits were not limited to take place in the morning. Within-subject assessments were performed at approximately the same time of day.• An additional exploratory endpoint (CompEx) was added to inform future studies.• A Data Monitoring Committee (with access to both blinded and unblinded data) was set up to assess the quality of the study as well as ensure subject safety in the study.
22 March 2017	<ul style="list-style-type: none">• The sample size was increased to a total of 702 subjects due to continued overall low rate of CSEs and higher than projected early withdrawals.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported