Clinical trial results:
A two part, double blind, placebo controlled, study to assess the safety, tolerability, pharmacokinetics and pharmacodynamic effects of multiple doses of QBM076 in patients with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2012-005615-92
Trial protocol	DE GB BE NL HU
Global end of trial date	12 June 2015

Results information

Result version number	v1 (current)
This version publication date	29 May 2016
First version publication date	29 May 2016

Trial information

Trial identification

Sponsor protocol code	CQBM076X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01972776
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	12 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part 1: To evaluate the safety and tolerability of multiple ascending doses of QBM076 in current or ex-smoking patients with stable chronic bronchitis COPD with spirometry grades I-III (according to the current GOLD strategy(GOLD 2013)) for 14 consecutive days of treatment
Part 2: To evaluate the preliminary efficacy of 8 consecutive weeks of QBM076 in current or ex-smoking patients with stable chronic bronchitis COPD with spirometry grades I-III (according to the current GOLD strategy (GOLD 2013)): Lung Clearance Index (LCI); absolute neutrophil count in sputum ; spirometry FEV1; TDI.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2013
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	Germany: 37
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Romania: 4
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	26
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In part 1, participants were randomly assigned to one of two treatment arms in a ratio of 3:1 for each cohort. In part 2, participants were stratified by smoking status (current versus ex-smoker) and randomized in a ratio of 2:1 into one of two treatments.

Period 1

Period 1 title	Part 1 and Part 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	QBM076 Part 1 Cohort 1

Arm description:

Participants received QBM076 25 mg bid for 14 days.

Arm type	Experimental
Investigational medicinal product name	QBM076
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg twice daily (bid) for 14 days.

Arm title	QBM076 Part 1 Cohort 2

Arm description:

Participants received QBM076 75 mg bid for 14 days.

Arm type	Experimental
Investigational medicinal product name	QBM076
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg bid for 14 days

Arm title	QBM076 Part 1 Cohort 3

Arm description:

Participants received QBM076 150 mg bid for 14 days.

Arm type	Experimental
Investigational medicinal product name	QBM076
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
150 mg bid for 14 days

Arm title	Placebo Part 1
Arm description:	
Participants in each cohort received matching placebo bid for 14 days.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Participants in each cohort received matching placebo bid for 14 days.	
Arm title	QBM076 Part 2
Arm description:	
Participants received QBM076 150 mg bid for 8 weeks.	
Arm type	Experimental
Investigational medicinal product name	QBM076
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Participants received QBM076 150 mg bid for 8 weeks.	
Arm title	Placebo Part 2
Arm description:	
Participants received matching placebo bid for 8 weeks.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Participants received matching placebo bid for 8 weeks.	

Number of subjects in period 1	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3
Started	6	6	8
Completed	6	6	6
Not completed	0	0	2
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	1
Administrative problems	-	-	-

Number of subjects in period 1	Placebo Part 1	QBM076 Part 2	Placebo Part 2
Started	7	14	7
Completed	6	1	0
Not completed	1	13	7
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	3	-
Administrative problems	-	10	7

Baseline characteristics

Reporting groups	
Reporting group title	QBM076 Part 1 Cohort 1
Reporting group description:	
Participants received QBM076 25 mg bid for 14 days.	
Reporting group title	QBM076 Part 1 Cohort 2
Reporting group description:	
Participants received QBM076 75 mg bid for 14 days.	
Reporting group title	QBM076 Part 1 Cohort 3
Reporting group description:	
Participants received QBM076 150 mg bid for 14 days.	
Reporting group title	Placebo Part 1
Reporting group description:	
Participants in each cohort received matching placebo bid for 14 days.	
Reporting group title	QBM076 Part 2
Reporting group description:	
Participants received QBM076 150 mg bid for 8 weeks.	
Reporting group title	Placebo Part 2
Reporting group description:	
Participants received matching placebo bid for 8 weeks.	

Reporting group values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3
Number of subjects	6	6	8
Age categorical Units: Subjects			
Adults (18-64 years)	4	3	3
From 65-84 years	2	3	5
Age Continuous Units: Years			
arithmetic mean	63	64	65
standard deviation	± 5.6	± 7.5	± 4.5
Gender, Male/Female Units: Participants			
Female	2	2	4
Male	4	4	4

Reporting group values	Placebo Part 1	QBM076 Part 2	Placebo Part 2
Number of subjects	7	14	7
Age categorical Units: Subjects			
Adults (18-64 years)	6	7	3
From 65-84 years	1	7	4
Age Continuous Units: Years			
arithmetic mean	61	64	66
standard deviation	± 2.9	± 5.5	± 5.6

Gender, Male/Female Units: Participants			
Female	4	7	5
Male	3	7	2

Reporting group values	Total		
Number of subjects	48		
Age categorical Units: Subjects			
Adults (18-64 years)	26		
From 65-84 years	22		
Age Continuous Units: Years arithmetic mean standard deviation	- -		
Gender, Male/Female Units: Participants			
Female	24		
Male	24		

End points

End points reporting groups

Reporting group title	QBM076 Part 1 Cohort 1
Reporting group description: Participants received QBM076 25 mg bid for 14 days.	
Reporting group title	QBM076 Part 1 Cohort 2
Reporting group description: Participants received QBM076 75 mg bid for 14 days.	
Reporting group title	QBM076 Part 1 Cohort 3
Reporting group description: Participants received QBM076 150 mg bid for 14 days.	
Reporting group title	Placebo Part 1
Reporting group description: Participants in each cohort received matching placebo bid for 14 days.	
Reporting group title	QBM076 Part 2
Reporting group description: Participants received QBM076 150 mg bid for 8 weeks.	
Reporting group title	Placebo Part 2
Reporting group description: Participants received matching placebo bid for 8 weeks.	

Primary: Percentage of participants with adverse events (Part 1)

End point title	Percentage of participants with adverse events (Part 1)[1][2]
End point description: Adverse events were counted and corresponding percentages were tabulated.	
End point type	Primary
End point timeframe: 14 days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[2] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	Placebo Part 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	8	7
Units: percentage of participants	33	50	63	71

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Lung Clearance Index (LCI) (Part 2)

End point title	Change from baseline in Lung Clearance Index (LCI) (Part

End point description:

End point type	Primary

End point timeframe:

Baseline, 8 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[4] - 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: End point pertains to Part 2 arms only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: units on a scale				

Notes:

[5] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[6] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in absolute number of sputum neutrophils (Part 2)

End point title	Change from baseline in absolute number of sputum neutrophils (Part 2)[7][8]

End point description:

End point type	Primary

End point timeframe:

Baseline, 8 weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[8] - 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: End point pertains to Part 2 arms only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: number of sputum neutrophils				

Notes:

[9] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[10] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Transition Dyspnea Index (TDI) (Part 2)

End point title	Change from baseline in Transition Dyspnea Index (TDI) (Part 2)[11][12]

End point description:

End point type	Primary

End point timeframe:

Baseline, 8 weeks

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[12] - 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: End point pertains to Part 2 arms only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: units on a scale				

Notes:

[13] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[14] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Primary: Change From baseline in Forced Expiratory Volume in 1 Second (FEV1) (Part 2)

End point title	Change From baseline in Forced Expiratory Volume in 1 Second (FEV1) (Part 2)[15][16]

End point description:

End point type	Primary

End point timeframe:

Baseline, 8 weeks

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[16] - 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: End point pertains to Part 2 only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: liters				

Notes:

[17] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[18] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time zero to the end of the dosing interval, tau (AUCtau) (Part 1)

End point title	Area under the plasma concentration-time curve from time zero to the end of the dosing interval, tau (AUCtau) (Part 1)[19]

End point description:

Venous blood samples were collected for concentration-time profiles.

End point type	Secondary

End point timeframe:

day 1 (from pre-dose to 12 hours post dose)

Notes:

[19] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	8	
Units: ng*h/mL				
arithmetic mean (standard deviation)	431 (± 158)	2060 (± 829)	7640 (± 6770)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau, steady state (AUCtau,ss) (Part 1)

End point title	AUCtau, steady state (AUCtau,ss) (Part 1)[20]

End point description:

Venous blood samples were collected for concentration-time profiles.

End point type	Secondary

End point timeframe:

day 14 (from pre-dose to 72 hours post dose)

Notes:

[20] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	8	
Units: ng*h/mL				
arithmetic mean (standard deviation)	601 (± 112)	2220 (± 787)	6660 (± 4320)	

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma concentration following drug administration (Cmax) (Part 1)

End point title	Observed maximum plasma concentration following drug administration (Cmax) (Part 1)[21]

End point description:

Venous blood samples were collected for concentration-time profiles.

End point type	Secondary

End point timeframe:

day 1 (from pre-dose to 12 hours post dose)

Notes:

[21] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	8	
Units: ng/mL				
arithmetic mean (standard deviation)	69.5 (± 28.8)	366 (± 192)	1810 (± 1790)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax,ss (Part 1)

End point title	Cmax,ss (Part 1)[22]

End point description:

Venous blood samples were collected for concentration-time profiles.

End point type	Secondary

End point timeframe:

day 14 (from pre-dose to 72 hours post dose)

Notes:

[22] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	8	
Units: ng/mL				
arithmetic mean (standard deviation)	91 (± 13.9)	338 (± 123)	2380 (± 2680)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach the maximum concentration after drug administration (Tmax) (Part 1)

End point title	Time to reach the maximum concentration after drug administration (Tmax) (Part 1)[23]

End point description:

Venous blood samples were collected for concentration-time profiles.

End point type	Secondary

End point timeframe:

day 1 (from pre-dose to 12 hours post dose)

Notes:

[23] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	8	
Units: hours				
median (full range (min-max))	3.05 (2 to 6)	3.01 (2 to 8)	3.04 (2.02 to 10.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax,ss (Part 1)

End point title	Tmax,ss (Part 1)[24]

End point description:

Venous blood samples were collected for concentration-time profiles.

End point type	Secondary

End point timeframe:

day 14 (from pre-dose to 72 hours post dose)

Notes:

[24] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	8	
Units: hours				
median (full range (min-max))	2 (2 to 4)	2 (2 to 6.02)	2.05 (0.5 to 6.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cluster of differentiation 11b (CD11b) (Part 1)

End point title	Change from baseline in cluster of differentiation 11b (CD11b) (Part 1)[25]

End point description:

Whole blood samples were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein in order to measure CD11b expression on neutrophils. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, day 14

Notes:

[25] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	Placebo Part 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	5
Units: percentage change				
number (not applicable)	-69	-89	-75	-37

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Chemokine (C-X-C motif) receptor 2 (CXCR2) receptor occupancy (Part 1)

End point title	Change from baseline in Chemokine (C-X-C motif) receptor 2 (CXCR2) receptor occupancy (Part 1)[26]

End point description:

Whole blood samples were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein in order to measure CXCR2 receptor occupancy on neutrophils. A positive change from

baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, day 14

Notes:

[26] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	Placebo Part 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent change	98	104	129	37

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Forced expiratory volume in one second (FEV1) (Part 1)

End point title	Change from baseline in Forced expiratory volume in one second (FEV1) (Part 1)[27]

End point description:

FEV1 is the amount of air that can be exhaled in one second. FEV1 will be measured by spirometry and performed at approximately the same time of day on each visit to avoid diurnal variation. All spirometry calibrations and evaluations followed the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability. A positive change from baseline in FEV1 indicates improvement in lung function.

End point type	Secondary

End point timeframe:

baseline, day 14 pre-dose

Notes:

[27] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	Placebo Part 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: mL				
arithmetic mean (standard error)	-0.116 (± 0.05)	-0.008 (± 0.05)	0.117 (± 0.05)	0.039 (± 0.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Lung Clearance Index 2.5 (LCI2.5) (Part 1)

End point title	Change from baseline in Lung Clearance Index 2.5 (LCI2.5) (Part 1)[28]

End point description:

Lung clearance index (LCI) is a measure of abnormal ventilation distribution derived from the multiple breath inert gas washout (MBW) technique. LCI is equal to the cumulative expired volume/functional residual capacity. LCI was measured at baseline and day 14. LCI was analyzed using a Bayesian model for repeated measurements. The model may investigate effects for pre-dose baseline, treatment, time, age, COPD class, treatment by time interaction, and baseline by time interaction. A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, day 14 pre-dose

Notes:

[28] - 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: Part 1 placebo arm and Part 2 arms do not apply to this analysis.

End point values	QBM076 Part 1 Cohort 1	QBM076 Part 1 Cohort 2	QBM076 Part 1 Cohort 3	Placebo Part 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: index score				
arithmetic mean (standard error)	1.145 (± 0.42)	0.136 (± 0.42)	0.66 (± 0.42)	0.063 (± 0.42)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in forced expirtory flow 25-75 (FEF25-75), forced expiratory volume 3 (FEV3)/forced vital capacity (FVC), 1-(FEV3/FVC), FEV6, FEV1/FEV6 and post-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) (Part 2)

End point title	Change from baseline in forced expirtory flow 25-75 (FEF25-75), forced expiratory volume 3 (FEV3)/forced vital capacity (FVC), 1-(FEV3/FVC), FEV6, FEV1/FEV6 and post-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) (Part 2)[29]

End point description:

End point type	Secondary

End point timeframe:

baseline, day 56

Notes:

[29] - 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: End point pertains to Part 2 arms only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[30]	0[31]		
Units: liters				

Notes:

[30] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[31] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24 (Part 2)

End point title	AUC0-24 (Part 2)[32]

End point description:

End point type	Secondary

End point timeframe:

day 1, day 56

Notes:

[32] - 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: End point pertains to Part 2 only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[33]	0[34]		
Units: ng*hours/mL				

Notes:

[33] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[34] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax between 0h and 24h (Part 2)

End point title	Cmax between 0h and 24h (Part 2)

End point description:

End point type	Secondary

End point timeframe:

day 1, day 56

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax between 0h and 24h (Part 2)

End point title	Tmax between 0h and 24h (Part 2)[35]

End point description:

End point type	Secondary

End point timeframe:

day 1, day 56

Notes:

[35] - 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: End point pertains to Part 2 only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[36]	0[37]		
Units: hours				

Notes:

[36] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[37] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage sputum neutrophils (Part 2)

End point title	Change from baseline in percentage sputum neutrophils (Part 2)[38]

End point description:

End point type	Secondary

End point timeframe:

baseline, day 56

Notes:

[38] - 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: End point pertains to Part 2 only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[39]	0[40]		
Units: percentage sputum neutrophils				

Notes:

[39] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[40] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in diffusing capacity of the lung for carbon monoxide (DLco) (Part 2)

End point title	Change from baseline in diffusing capacity of the lung for carbon monoxide (DLco) (Part 2)[41]

End point description:

End point type	Secondary

End point timeframe:

baseline, day 56

Notes:

[41] - 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: End point pertains to part 2 only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[42]	0[43]		
Units: liters				

Notes:

[42] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[43] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Scond/Sacin as measured by multiple breath nitrogen washout (MBNW) (Part 2)

End point title	Change from baseline in Scond/Sacin as measured by multiple breath nitrogen washout (MBNW) (Part 2)[44]

End point description:

End point type	Secondary

End point timeframe:

baseline, day 56

Notes:

[44] - 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: End point pertains to Part 2 only.

End point values	QBM076 Part 2	Placebo Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[45]	0[46]		
Units: liters				

Notes:

[45] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

[46] - Part 2 was terminated for safety reasons. The Part 2 efficacy outcomes were not assessed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Part 1 QBM076 25 mg bid
Reporting group description:	
Part 1 QBM076 25 mg bid	
Reporting group title	Part 1 QBM076 75 mg bid
Reporting group description:	
Part 1 QBM076 75 mg bid	
Reporting group title	Part 1 QBM076 150 mg bid
Reporting group description:	
Part 1 QBM076 150 mg bid	
Reporting group title	Part 1 Placebo
Reporting group description:	
Part 1 Placebo	
Reporting group title	Part 2 QBM076 150 mg bid
Reporting group description:	
Part 2 QBM076 150 mg bid	
Reporting group title	Part 2 Placebo
Reporting group description:	
Part 2 Placebo	

Serious adverse events	Part 1 QBM076 25 mg bid	Part 1 QBM076 75 mg bid	Part 1 QBM076 150 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Injury, poisoning and procedural complications			

Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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

Serious adverse events	Part 1 Placebo	Part 2 QBM076 150 mg bid	Part 2 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	2 / 14 (14.29%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 14 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	0 / 7 (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

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

Non-serious adverse events	Part 1 QBM076 25 mg bid	Part 1 QBM076 75 mg bid	Part 1 QBM076 150 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	5 / 8 (62.50%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eyelid injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Procedural complication			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter site eczema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Catheter site erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Therapeutic response unexpected			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site haematoma			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal tenderness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatotoxicity			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Increased upper airway secretion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 1 Placebo	Part 2 QBM076 150 mg bid	Part 2 Placebo
Total subjects affected by non-serious adverse events			

subjects affected / exposed	4 / 7 (57.14%)	8 / 14 (57.14%)	3 / 7 (42.86%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Eyelid injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Procedural complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 14 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site eczema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Catheter site erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			

subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Therapeutic response unexpected			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Vessel puncture site bruise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haematoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Abdominal tenderness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Increased upper airway secretion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 14 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2013	Amendment 1, issued before the first patient was screened, introduced the following changes: clarified that the dose chosen for Part 2 did not exceed the MTD determined from Part 1; male contraceptive requirements were revised; exclusion criteria for tuberculosis was added; clarified that repeated administration of a dose level was only permitted as long as no stopping criteria were met in the previous cohort; and clarified that for individual patient withdrawal, investigator discretion was no longer permitted.
20 November 2013	Amendment 2 issued before the first patient was screened, introduced the following change(s): Sample logs were removed from the protocol and were included in the study reference manual, this resulted in updates to the assessment schedule. The deviation window for the MRI scan at baseline was increased to within 14 days prior to baseline visit. Caffeine restrictions for 4 hours prior to the start of lung function testing were added in on days the patient attended the clinic. All meal time data were to be entered into the eCRF following collection on the patient diary. Clarified that waist and hip circumference was measured in centimeters. Clarified that glucose was fasted when performed as part of safety laboratory tests. Clarified that urine albumin was measured at screening as per exclusion criteria. Clarified that FEV1 and FVC did not need to be repeated by whole body plethysmography, because they were measured during spirometry. Clarified that a second set of spirometry measurements for reversibility was only applicable at the screening visit. Other minor corrections and correction of typographical errors.
05 March 2014	Amendment 3, issued when Cohort 1 had completed and 6 patients were ongoing in Cohort 2, introduced the following changes: Stopping criteria specific to COPD were added as requested by BfArM during review of the protocol. Inclusion of smokers into Part 2 to more closely reflect the population of patients that required treatment for COPD. Revisions were also made to the inclusion and exclusion criteria. Creatinine clearance was lowered because neither the drug nor the metabolites have shown evidence of renal clearance. Further, the target patient population is likely to have mild to moderate renal insufficiency. Hence we would like to examine the safety, tolerability and efficacy of the drug on in patients with creatinine clearance ≥ 30mL/min. The list of potentially excluded medications was revised to focus on strong inhibitors and inducers of cytochrome 3A4 (CYP3A4).
07 July 2014	Amendment 4 was issued after all patients had started Cohort 3. The main purpose of this amendment was to remove the use of hyperpolarized helium-3 MRI and to provide the maximum proposed QBM076 dose intended for Part 2. Following feedback from the FDA, it was recognized that there was insufficient justification to conduct this exploratory assessment (hyperpolarized helium-3 MRI) in the setting of an exploratory clinical trial. Revisions were also made to clarify the use of fed state vs. fasted state in earlier and ongoing clinical trials.
23 October 2014	Amendment 5 was issued after the completion of Part 1. The main purpose of this amendment was to include data from pivotal embryo-fetal toxicity studies which allowed women of child bearing potential to participate in the study as long as they used effective contraception methods (with the exception of hormonal contraceptives, due to the risk of drug-drug interaction with QBM076) as defined in the protocol. In addition, the dose QBM076 to be tested in Part 2 of the study was confirmed as 150 mg bid x 8 weeks. Revisions were also made to clarify the term “chronic bronchitis" based on investigator feedback that the term could be misleading since there are no criteria requiring a level of cough & sputum production. This was revised to require GOLD I-III based on spirometry criteria. Changes were also made to the PD and PK assessment based on results from Part 1; and to study assessments to reduce the overall protocol burden in Part 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Part 2 was terminated after 21 patients were enrolled. Three of the 21 patients experienced moderate to severe (up to 17-fold) asymptomatic and reversible elevation of liver transaminase levels after 3 weeks of treatment with QBM076 150 mg bid.

Notes: