Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient: ipratropium bromide and salbutamol		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

Title of trial:	A comparison of ipratropium bromide/salbutamol delivered by the Respimat® inhaler to Combivent® Inhalation Aerosol and ipratropium bromide delivered by the Respimat® in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicenter trial
Publication (reference):	None
Clinical phase:	III
Objectives:	The primary objective of this study was to compare the long-term (12-week) bronchodilator efficacy and safety of the COMBIVENT [ipratropium bromide 20 micrograms (mcg) and salbutamol 100 mcg] delivered by the RESPIMAT inhaler at one inhalation four times daily (q.i.d). to ipratropium bromide 20 mcg delivered by the RESPIMAT inhaler at one inhalation q.i.d. and to COMBIVENT (ipratropium bromide 36 mcg and salbutamol 206 mcg) delivered by the CFC-MDI inhaler at two inhalations q.i.d in patients with chronic obstructive pulmonary disease (COPD).
Methodology:	Three-treatment, 12-week, randomized, multinational, parallel group, double-blind, double dummy, active controlled design.
No. of subjects:	
planned:	enrolled (signed consent): 2462 entered (randomized): 1480 entered: 1480
actual:	COMBIVENT RESPIMAT plus placebo COMBIVENT CFC-MDI: entered: 493 treated: 486 analysed (for primary endpoint): AUC_{0-6} and AUC_{0-4}: 474, AUC_{4-6} 447. ipratropium bromide RESPIMAT plus placebo COMBIVENT CFC-MDI: entered: 489 treated: 483 analysed (for primary endpoint): AUC_{0-6} and AUC_{0-4}: 468, AUC_{4-6} 427. COMBIVENT CFC-MDI plus placebo COMBIVENT RESPIMAT:

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 2 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

	entered: 498 treated: 491 analysed (for primary endpoint): AUC_{0-6} and AUC_{0-4}: 482, AUC_{4-6} 449.
Diagnosis and main criteria for inclusion:	Outpatients of either sex, 40 years or older, with a diagnosis of COPD [Forced expiratory volume in 1 second (FEV_1) ≤65% predicted normal and FEV_1/Forced vital capacity (FVC) ≤70%].
Test product:	COMBIVENT RESPIMAT (ipratropium bromide/salbutamol) [plus placebo COMBIVENT CFC-MDI]
dose:	20 mcg/100 mcg, one inhalation q.i.d.
mode of admin.:	Inhalation spray by RESPIMAT inhaler
batch no.:	20 mcg/100 mcg Ipratropium Bromide/Salbutamol Inhalation Solution B06300048 with RESPIMAT inhaler B063000461
Test product:	ipratropium bromide (Atrovent®) RESPIMAT [plus placebo COMBIVENT CFC-MDI]
dose:	20 mcg, one inhalation q.i.d.
mode of admin.:	Inhalation spray by RESPIMAT inhaler
batch no.:	20 mcg Ipratropium Bromide Inhalation Solution B063000477 with RESPIMAT inhaler B063000461
Reference therapy:	COMBIVENT Inhalation Aerosol (CFC-MDI) [plus placebo COMBIVENT RESPIMAT]
dose:	36 mcg/206 mcg q.i.d. (two inhalations each of 18 mcg/103 mcg)
mode of admin.:	Inhalation aerosol by metered dose inhaler (MDI)
batch no.:	0.021/0.120 mg through the valve (TTV) Ipratropium Bromide/Salbutamol Sulfate Inhalation Aerosol B063000475
Duration of treatment:	12 weeks

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 3 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

Criteria for evaluation:

Efficacy / clinical pharmacology: Primary: Comparison of COMBIVENT RESPIMAT 20/100 mcg with COMBIVENT CFC-MDI 36/206 mcg (FEV_1 AUC_{0-6}) and comparison of COMBIVENT RESPIMAT 20/100 mcg with ipratropium RESPIMAT 20 mcg (FEV_1 AUC_{0-4} and FEV_1 AUC_{4-6}) at Day 85.

Key Secondary: FEV_1 (peak, peak response, onset, duration and time to peak response); FVC (AUC_{0-4}, AUC_{0-6}, AUC_{4-6}, peak response); rescue medication use; COPD symptom score; morning PEFR (see Section 8.3 for complete list).

Safety: Adverse events, vital signs, physical examinations, electrocardiogram (ECG) testing.

Statistical methods: Analysis of covariance with fixed effect for treatment and pooled centre, test-day-1 baseline used as a covariate; descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Efficacy

Overall, this 12-week phase III active controlled study demonstrated that COMBIVENT RESPIMAT 20/100 mcg had comparable efficacy to COMBIVENT CFC-MDI 36/206 mcg with respect to FEV_1 AUC_{0-6} (change from test-day baseline), and had superior efficacy to the mono-component ipratropium RESPIMAT 20 mcg with respect to FEV_1 AUC_{0-4} (change from test-day baseline) and had comparable efficacy to the mono-component ipratropium RESPIMAT 20 mcg with respect to FEV_1 AUC_{4-6} (change from test-day baseline).

FEV_1 3 Primary Endpoints

1) for mean FEV_1 AUC_{0-6} (change from test-day baseline) COMBIVENT RESPIMAT 20/100 mcg was non-inferior to COMBIVENT CFC-MDI 36/206 mcg after 12 weeks of treatment, with a difference of 0.003 liters [95% Confidence Interval (CI) -0.022, 0.015 liters] in favor of COMBIVENT CFC-MDI 36/206 mcg; 2) for mean FEV_1 AUC_{0-4} (change from test-day baseline), COMBIVENT RESPIMAT 20/100 mcg was superior to ipratropium RESPIMAT 20 mcg after 12 weeks of treatment with a difference of 0.047 litres in favour of COMBIVENT RESPIMAT 20/100 mcg ($P < 0.0001$).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 4 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

and 3) for mean FEV_1 AUC_{4-6} , COMBIVENT RESPIMAT 20/100 mcg was non-inferior to ipratropium RESPIMAT 20 mcg during the last two hours of the 6-hour treatment period after 12 weeks of treatment with a difference of 0.017 liters (95% CI -0.039, 0.005 liters) in favour of ipratropium RESPIMAT 20 mcg .

Secondary FEV_1 endpoints

1) for mean FEV_1 AUC_{0-6} (change from test-day baseline) , COMBIVENT RESPIMAT 20/100 mcg was non-inferior to COMBIVENT CFC-MDI 36/206 mcg on Test Days 1, 29, and 57, 2) for mean FEV_1 AUC_{0-4} (change from test-day baseline), COMBIVENT RESPIMAT 20/100 mcg was superior to the ipratropium RESPIMAT 20 mcg on Test Days 1, 29, and 57 ($P < 0.0001$), 3) for mean FEV_1 AUC_{4-6} (change from test-day baseline) , COMBIVENT RESPIMAT 20/100 mcg was non-inferior to ipratropium RESPIMAT 20 mcg on Test Days 1, 29, and 57, 4) for peak FEV_1 and the peak FEV_1 response within the first two hours after study drug administration, the COMBIVENT RESPIMAT 20/100 mcg group was superior to the ipratropium RESPIMAT 20 mcg group on all test days, and 5) the median time to onset of a therapeutic response was faster and the median duration of a therapeutic response (FEV_1 change from test day baseline ≥15%) was longer for the COMBIVENT RESPIMAT 20/100 mcg group as compared to the ipratropium RESPIMAT 20 mcg group on all test days.

Secondary FVC endpoints

Individual FVC measurement at each measurement time point, FVC AUC_{0-6}, AUC_{0-4}, AUC_{4-6} (change from test-day baseline) and peak FVC response on Test Days 1, 29, 57, and 85 were consistent with those observed in FEV_1 and supportive of the primary endpoints.

Morning PEFR

Morning peak flow was comparable between all three treatment groups throughout the study with a 12-week average of approximately 190 L/min.

Rescue salbutamol use

Night-time and daytime salbutamol rescue medication usage was low and comparable across all treatment groups. The average night-time rescue

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Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 5 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

medication use was approximately 1.0 actuations; the average daytime rescue medication use was approximately 2.3 actuations during the 12 weeks of treatment. This usage was comparable to the baseline rescue medication usage for both night-time (0.97 actuations per night) and daytime (2.62 actuations per day).

COPD symptoms

The night-time and daytime COPD symptom scores were low and comparable across treatment groups.

Physician Global Evaluation

The physician global evaluation score (PGE) improved and was comparable across treatment groups with an average score of approximately 5 (good) after 12 weeks of treatment that increased from baseline (4.8) (better than fair but not good).

COPD Exacerbations

The mean COPD exacerbation rate (per patient year) during this study was low across all three treatment groups, and within the historical range of what would be expected for a study involving moderate to severe COPD patients: the COMBIVENT RESPIMAT 20/100 mcg and COMBIVENT CFC-MDI 36/206 mcg groups had similar mean COPD exacerbation rate (per patient year) (0.76 and 0.69, respectively), and ipratropium RESPIMAT 20 mcg group was lower (0.53).

Pharmacokinetics

A total of 162 patients in U.S. sites were enrolled in the pharmacokinetic substudy distributed as COMBIVENT RESPIMAT 20/100 mcg (n=52), COMBIVENT CFC-MDI 36/206 mcg (n=56), and ipratropium RESPIMAT 20 mcg (n=54). Comparable systemic exposures were obtained for ipratropium following all three treatments. The ipratropium plasma and urine systemic exposure ratio for COMBIVENT RESPIMAT 20/100 mcg/ COMBIVENT CFC-MDI 36/206 mcg was 1.04 and 1.18. The ipratropium plasma and urine systemic exposure ratio for Ipratropium Bromide RESPIMAT 20 mcg / COMBIVENT CFC-MDI 36/206 mcg was 0.91 and 0.91.

The comparability of the systemic exposure with ipratropium between COMBIVENT RESPIMAT 20/100 mcg and the mono-component ipratropium

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 6 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

RESPIMAT 20 mcg indicated that salbutamol does not have an effect on the deposition, absorption and elimination of ipratropium bromide. The comparability of the systemic exposure for both active ingredients between COMBIVENT RESPIMAT 20/100 mcg and the market standard, COMBIVENT CFC-MDI 36/206 mcg demonstrated that the dose combination of 20/100 mcg chosen for COMBIVENT RESPIMAT should not pose any further systemic safety burden than the marketed product. The systemic exposure observed with the COMBIVENT RESPIMAT 20/100 mcg four-times daily in these 52 COPD patients was approximately half the systemic exposure observed in the previous study with the COMBIVENT RESPIMAT 40/200 mcg four-times daily in 48 COPD patients. Comparable systemic exposures, as measured by excretion of unchanged drug in the total urine over one dosing interval, were obtained for ipratropium following all three treatments consistent with the plasma data.

For the 108 patient pharmacokinetic sample of the U.S. population on a COMBIVENT treatment, the systemic exposure obtained for salbutamol following COMBIVENT RESPIMAT 20/100 mcg was less than the systemic exposure following the market standard, COMBIVENT CFC-MDI 36/206 mcg. The salbutamol plasma and urine systemic exposure ratio for COMBIVENT RESPIMAT 20/100 mcg/ COMBIVENT CFC-MDI 36/206 mcg was 0.74 and 0.86. Therefore, from a pharmacokinetic perspective, COMBIVENT RESPIMAT should not pose any further systemic safety burden than the marketed product. The salbutamol systemic exposure observed with the COMBIVENT RESPIMAT 20/100 mcg four-times daily in these 52 COPD patients was approximately half the systemic exposure observed in the previous study with the COMBIVENT RESPIMAT 40/200 mcg four-times daily in 48 COPD patients. Excretion of unchanged salbutamol in the total urine collected over one dosing interval of the COMBIVENT RESPIMAT 20/100 mcg dose to the market standard, COMBIVENT CFC-MDI 36/206 mcg, was consistent with the plasma salbutamol data.

The steady state pharmacokinetic data from the 52 patients treated with COMBIVENT RESPIMAT 20/100 mcg was sub-grouped by gender, age, and current smoking status to determine if any of these patient groups had differences in systemic exposure. Patients 65 years of age or older and ex-smokers had higher systemic exposures of ipratropium than their younger or currently smoking counterparts; whereas, for salbutamol, only the patient group of 65 years of age or older had higher systemic exposures than their

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 7 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

younger counterparts.

Device Assessments

End of use testing of the RESPIMAT COMBIVENT device established that the dosing behavior was accurate, precise, and remained unchanged from the results at batch release. The patient assessment questionnaire of the two device attributes demonstrated patient preference for the RESPIMAT over the MDI device for each of the 10 attributes assessed ($p<0.0001$). Approximately 70% of patients rated the action of turning the RESPIMAT base as very easy, and 70% of patients preferred the RESPIMAT over the MDI device.

Safety results:

The overall adverse event rate was similar in the COMBIVENT RESPIMAT 20/100 mcg (45.7%) and the ipratropium RESPIMAT 20 mcg (44.5%) treatment groups and higher in the COMBIVENT CFC-MDI 36/206 mcg treatment group (51.7%).

The most frequently occurring adverse events in this study population were respiratory events. Overall, lower respiratory system events occurred in a total of 301 patients (20.6%). There were equal frequencies in both COMBIVENT treatment groups (21.6% for RESPIMAT and 21.8% for CFC-MDI), and slightly fewer events in the ipratropium RESPIMAT treatment group (18.4%). These lower respiratory system events were primarily COPD exacerbations, which occurred in similar frequencies in the COMBIVENT RESPIMAT 20/100 mcg (14.8%) and COMBIVENT CFC-MDI 36/206 mcg (13.0%) treatment groups and at a slightly lower frequency in the ipratropium RESPIMAT 20 mcg (10.4%) treatment group. Frequencies of bronchitis were 3.5% in the COMBIVENT CFC-MDI 36/206 mcg group, 2.9% in the COMBIVENT RESPIMAT 20/100 mcg group and 1.4% in the ipratropium RESPIMAT 20 mcg group. Upper respiratory system disorders were reported in 13.8% of the patients and were comparable across the treatment groups. In summary, common and drug related individual adverse events occurred at comparable rates in COMBIVENT RESPIMAT and COMBIVENT CFC-MDI groups, and also at comparable rates in the ipratropium RESPIMAT group, with the exception of a slightly lower frequency of COPD exacerbation which occurred in the ipratropium RESPIMAT-treated patients.

Serious adverse events occurred in a total of 64 patients (4.4%). There was a higher frequency of SAEs in the COMBIVENT CFC-MDI 36/206 mcg dose group (6.7%) compared to the COMBIVENT RESPIMAT 20/100 mcg (3.5%)

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Name of finished product: Combivent® Respimat®		**EudraCT No.:** 2006-002694-52	
Name of active ingredient:		**Page:** 8 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

and ipratropium RESPIMAT 20 mcg (2.5%) treatment groups. Lower respiratory system disorders accounted for the highest frequency of SAEs (2.9%). Across treatment groups, the frequencies of lower respiratory system events were 2.7%, 3.7% and 2.3% for the COMBIVENT RESPIMAT 20/100 mcg, COMBIVENT CFC-MDI 36/206 mcg and ipratropium RESPIMAT 20 mcg treatment groups, respectively. Most of the lower respiratory system SAEs were COPD exacerbation, which were distributed across treatment groups as 2.6% in the COMBIVENT CFC-MDI 36/206 mcg dose group, followed by 2.3% in the COMBIVENT RESPIMAT 20/100 mcg group and 1.7% in the ipratropium RESPIMAT 20 mcg group.

There were 6 patient deaths that occurred during the study; 3 in the COMBIVENT RESPIMAT 20/100 mcg group, 1 in the COMBIVENT CFC-MDI 36/206 mcg group and 2 in the ipratropium RESPIMAT 20 mcg group. None was considered related to the study treatment.

In total, 85 patients (5.8%) discontinued participation in the trial due to adverse events. The frequencies were similar for the COMBIVENT CFC-MDI and ipratropium RESPIMAT treatment groups (6.9% and 6.8%, respectively) and slightly lower for the COMBIVENT RESPIMAT treated patients (3.7%). Similar to the pattern of adverse events and SAEs, the majority of events leading to discontinuation in this trial were lower respiratory system disorders, with exacerbation of COPD contributing the highest frequency.

Overall, 72 patients (4.9%) had adverse events that were considered by the investigator to be related to study medication. The highest frequency (7.0%) in the ipratropium RESPIMAT group followed by the COMBIVENT CFC-MDI group (5.1%), and the COMBIVENT RESPIMAT group (2.7%).

There were no differences between the three treatment groups in the frequency of defined potential anticholinergic class adverse events (2.1%, 2.0% and 1.6%) for the ipratropium RESPIMAT, COMBIVENT CFC-MDI and COMBIVENT RESPIMAT treatment groups, respectively. The majority of these events were dry mouth (0.7%), followed by tremor (0.3%). The highest frequency of potential beta-agonist class adverse events occurred in the ipratropium RESPIMAT group (9.1%) while the two COMBIVENT treatment groups were similar (7.2% and 7.5% for the RESPIMAT and CFC-MDI, respectively). Across all treatment groups, the occurrences of headache, dizziness, nausea and hypertension were most frequent (ranging from 2.7 % to 1.0 %).

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Name of active ingredient:		**Page:** 9 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 Aug 2008	**Trial No. / U No.:** 1012.56 / U08-3368-01	**Date of trial:** 15 NOV 2006 – 04 APR 2008	**Date of revision** (if applicable)**:**

	Subgroup analyses for age, gender, corticosteroid use, American Thoracic Society (ATS) COPD disease severity (ECSC), FEV_1 reversibility to salbutamol and smoking history showed no clinically meaningful safety differences between the three treatment groups. Race and xanthine use were not analyzable because of imbalance of numbers across the racial sub-groups or infrequent xanthine use. There were no clinically significant differences in vital signs among the three treatment groups. Overall, COMBIVENT RESPIMAT 20/100 mcg was safe and well tolerated with a safety profile comparable to the COMBIVENT CFC-MDI 36/206 mcg and ipratropium RESPIMAT 20 mcg.
Conclusions:	This 12 week Phase III active controlled study demonstrated that COMBIVENT RESPIMAT 20/100 mcg had comparable efficacy and safety to COMBIVENT CFC-MDI 36/206 mcg, and has superior efficacy to the mono-component ipratropium RESPIMAT 20 mcg. This study supports that COMBIVENT RESPIMAT 20/100 mcg administered one inhalation q.i.d. is a safe and effective bronchodilator for the maintenance treatment of patients with airflow obstruction due to COPD.

Trial Synopsis - Appendix

The appended tables on the following page supplements the trial results presented in the Trial Synopsis. They complement disposition results and results for primary and secondary endpoints of the trial.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
FEV_1 $AUC_{0–6}$ change from test−day baseline on test day 85 (Primary endpoint) FEV_1 $AUC_{0–4}$ change from test−day baseline on test day 85 (Primary endpoint) FEV_1 $AUC_{0–6}$ change from test−day baseline on test days 1, 29, 57 (Secondary endpoint) FEV_1 $AUC_{0–4}$ change from test−day baseline on test days 1, 29, 57 (Secondary endpoint) FEV_1 peak response change from test−day baseline on test days 1, 29, 57, and 85 (Secondary endpoint)	Table 15.2.1: 6
FEV_1 $AUC_{4–6}$ change from test−day baseline on test day 85 (Primary endpoint) FEV_1 AUC_{4-6} change from test−day baseline on test days 1, 29, 57 (Secondary endpoint)	Table 15.2.1: 8
Median time to therapeutic response within the first 2 hrs on test days 1, 29, 57, and 85 (Secondary endpoint) Median duration of therapeutic response within the first 2 hrs on test days 1, 29, 57, and 85 (Secondary endpoint) Median time to peak response within the first 2 hrs on test days 1, 29, 57, and 85 (Secondary endpoint)	Table 15.2.1: 9
FVC $AUC_{0–6}$ change from test−day baseline in liters on test days 1, 29, 57, and 85 (Secondary endpoint)	Table 15.2.3: 4
Weekly mean morning pre−dose PEFR (liters/minute) per day by weeks on treatment (Secondary endpoint)	Table 15.2.7: 2
Daily night−time symptom scores per week for 12 weeks on treatment (Secondary endpoint)	Table 15.2.6: 3
Daily daytime symptom scores per week for 12 weeks on treatment (Secondary endpoint)	Table 15.2.6: 4

Table 15.1.1: 1 Conclusion of patient participation
for all enrolled patients

	CVT R 20/100 N (%)	CVTCFC36/206 N (%)	IB R 20 N (%)	Total N (%)
Enrolled				2462
Not entered/randomised				982
Entered	493	498	489	1480
Not treated	7	7	6	20
Treated	486(100.0)	491(100.0)	483(100.0)	1460(100.0)
Not prematurely discontinued from trial medication	438(90.1)	436(88.8)	422(87.4)	1296(88.8)
Prematurely discontinued from trial medication	48(9.9)	55(11.2)	61(12.6)	164(11.2)
AE study dis. worse	14(2.9)	19(3.9)	20(4.1)	53(3.6)
AE oth. dis. worse	2(0.4)	1(0.2)	0(0.0)	3(0.2)
AE other	3(0.6)	14(2.9)	15(3.1)	32(2.2)
Non compl. protocol	7(1.4)	4(0.8)	9(1.9)	20(1.4)
Lost to follow-up	2(0.4)	1(0.2)	4(0.8)	7(0.5)
Refused cont. medicat	12(2.5)	11(2.2)	10(2.1)	33(2.3)
Other	8(1.6)	5(1.0)	3(0.6)	16(1.1)

Twenty patients from French study site 3302 are excluded from Treated Set because accuracy of data could not be verified.

Source data: Appendix 16.2, Listing 1.1 disp1.sas 23JUL2008

Table 15.2.1: 6 Mean treatment differences in FEV1 AUC0-6, FEV1 AUC0-4, and peak FEV1 (change from test-day baseline) on test days 1, 29, 57, and 85 - FAS_PFT

Endpoint	Treatment comparison	Test Day	Mean (SE) (liters)	P-value	95% CI (liters)
AUC 0-4	CVT R 20/100 - CVTCFC36/206	1	-0.016 (0.011)	0.1265	(-0.037, 0.005)
		29	-0.001 (0.010)	0.8927	(-0.021, 0.019)
		57	-0.012 (0.010)	0.2371	(-0.031, 0.008)
		85	-0.001 (0.010)	0.9465	(-0.020, 0.018)
	CVT R 20/100 - IB R 20	1	0.061 (0.011)	<.0001	(0.040, 0.083)
		29	0.044 (0.010)	<.0001	(0.024, 0.065)
		57	0.047 (0.010)	<.0001	(0.027, 0.067)
		85	0.047 (0.010)	<.0001	(0.028, 0.066)
AUC 0-6	CVT R 20/100 - CVTCFC36/206	1	-0.016 (0.010)	0.1240	(-0.036, 0.004)
		29	-0.007 (0.010)	0.4888	(-0.026, 0.013)
		57	-0.014 (0.010)	0.1433	(-0.033, 0.005)
		85	-0.003 (0.010)	0.7135	(-0.022, 0.015)
	CVT R 20/100 - IB R 20	1	0.049 (0.010)	<.0001	(0.028, 0.069)
		29	0.026 (0.010)	0.0088	(0.007, 0.046)
		57	0.028 (0.010)	0.0044	(0.009, 0.047)
		85	0.026 (0.010)	0.0068	(0.007, 0.045)
Peak 0-2	CVT R 20/100 - CVTCFC36/206	1	-0.020 (0.011)	0.0743	(-0.042, 0.002)
		29	0.006 (0.011)	0.5711	(-0.015, 0.028)
		57	-0.013 (0.011)	0.2274	(-0.033, 0.008)
		85	0.003 (0.011)	0.8065	(-0.018, 0.024)
	CVT R 20/100 - IB R 20	1	0.065 (0.011)	<.0001	(0.043, 0.087)
		29	0.065 (0.011)	<.0001	(0.044, 0.087)
		57	0.060 (0.011)	<.0001	(0.040, 0.081)
		85	0.068 (0.011)	<.0001	(0.047, 0.089)

The treatment baseline is 1.114 (0.011) liters.
Means (SE) adjusted for treatment baseline and pooled centre (fixed).
A separate ANCOVA was fitted for each time point and test day.
Test days entirely missing were imputed by carrying the last test day forward.
Missing data within a test day were imputed by carrying either the lowest or last value forward depending on why the data were missing.
Analysis set: 1012.56 FAS_PFT (N= 1424)
Source data: Appendix 16.1.9.2, Statdoc 6.1.4, 6.1.5, 6.3.1 stat\fev1.sas 15JUL2008

Table 15.2.1: 8 Mean (SE) treatment differences in FEV1 AUC4-6 (change from test-day baseline) on test days 1, 29, 57, and 85 - FAS_PFT46

Endpoint	Treatment comparison	Test Day	Mean (SE) (liters)	P-value	95% CI (liters)
AUC 4-6	CVT R 20/100 - CVTCFC36/206	1	-0.015 (0.012)	0.1835	(-0.038, 0.007)
		29	-0.019 (0.011)	0.0917	(-0.041, 0.003)
		57	-0.021 (0.011)	0.0578	(-0.043, 0.001)
		85	-0.010 (0.011)	0.3562	(-0.032, 0.012)
	CVT R 20/100 - IB R 20	1	0.026 (0.012)	0.0258	(0.003, 0.049)
		29	-0.010 (0.011)	0.3749	(-0.032, 0.012)
		57	-0.011 (0.011)	0.3355	(-0.033, 0.011)
		85	-0.017 (0.011)	0.1389	(-0.039, 0.005)

The treatment baseline is 1.110 (0.011) liters.
Means (SE) adjusted for treatment baseline and pooled centre (fixed).
A separate ANCOVA was fitted for each time point and test day.
Test days entirely missing were imputed by carrying the last test day forward.
Missing data within a test day were imputed by carrying either the lowest or last value forward depending on why the data were missing.
Analysis set: 1012.56 FAS_PFT46 (N= 1323)
Source data: Appendix 16.1.9.2, Statdoc 6.1.6, Appendix 16.2, Listing 6.1.3 stat\fev1.sas 15JUL2008

Table 15.2.1: 9 Median time to therapeutic response, median time to peak response, median duration of therapeutic response, and number of patients achieving a therapeutic response withing the first 2 hrs on test days 1, 29, 57, and 85 - FAS_PFT

Test Day	Treatment	N	Time to onset of 15% increase above test-day baseline (minutes)	Time to peak Response (minutes)	Duration of 15% increase (minutes)	No. of patients with 15% increase above test-day baseline N(%)
1	CVT R 20/100	474	13	60	189	375 (79.1)
	CVTCFC36/206	482	12	60	219	385 (79.9)
	IB R 20	468	28	120	104	300 (64.1)
29	CVT R 20/100	474	12	60	170	374 (78.9)
	CVTCFC36/206	482	13	60	178	377 (78.2)
	IB R 20	468	27	120	122	311 (66.5)
57	CVT R 20/100	474	13	60	165	354 (74.7)
	CVTCFC36/206	482	12	60	194	374 (77.6)
	IB R 20	468	29	60	84	300 (64.1)
85	CVT R 20/100	474	12	60	168	358 (75.5)
	CVTCFC36/206	482	13	60	172	357 (74.1)
	IB R 20	468	27	60	70	295 (63.0)

15% increase had to occur within 2 hours of inhaling randomised treatment.
Censored values were used for patients who did not achieve a 15% increase above test day baseline.
Peak response could occur at any time during the 6 hour observation period.
Test days entirely missing were imputed by carrying the last test day forward.
Missing data within a test day were imputed by carrying either the lowest or last value forward depending on why the data were missing.
Analysis set: 1012.56 FAS_PFT (N= 1424)
Source data: Appendix 16.1.9.2, Statdoc 6.3.3, 6.3.4, 6.3.5, Appendix 16.2, Listing 6.1.5 stat\fev1.sas 15JUL2008

Table 15.2.3: 4 Mean treatment differences in FVC AUC0-6, FVC AUC0-4, and peak FVC (change from test-day baseline in liters) on test days 1, 29, 57, and 85 - FAS_PFT

Endpoint	Treatment comparison	Test Day	Mean (SE) (liters)	P-value	95% CI (liters)
AUC 0-4	CVT R 20/100 - CVTCFC36/206	1	-0.014 (0.022)	0.5125	(-0.057, 0.028)
		29	-0.007 (0.021)	0.7324	(-0.049, 0.034)
		57	-0.019 (0.021)	0.3723	(-0.060, 0.022)
		85	0.000 (0.021)	0.9876	(-0.040, 0.041)
	CVT R 20/100 - IB R 20	1	0.112 (0.022)	<.0001	(0.069, 0.154)
		29	0.090 (0.021)	<.0001	(0.049, 0.132)
		57	0.097 (0.021)	<.0001	(0.056, 0.138)
		85	0.094 (0.021)	<.0001	(0.054, 0.135)
AUC 0-6	CVT R 20/100 - CVTCFC36/206	1	-0.017 (0.021)	0.4167	(-0.058, 0.024)
		29	-0.019 (0.020)	0.3505	(-0.059, 0.021)
		57	-0.019 (0.020)	0.3499	(-0.058, 0.021)
		85	-0.004 (0.020)	0.8288	(-0.044, 0.035)
	CVT R 20/100 - IB R 20	1	0.088 (0.021)	<.0001	(0.046, 0.129)
		29	0.054 (0.020)	0.0079	(0.014, 0.094)
		57	0.064 (0.020)	0.0014	(0.025, 0.104)
		85	0.060 (0.020)	0.0032	(0.020, 0.100)
Peak 0-2	CVT R 20/100 - CVTCFC36/206	1	-0.011 (0.023)	0.6244	(-0.057, 0.034)
		29	0.004 (0.023)	0.8730	(-0.041, 0.049)
		57	-0.015 (0.023)	0.5294	(-0.060, 0.031)
		85	0.013 (0.023)	0.5630	(-0.032, 0.058)
	CVT R 20/100 - IB R 20	1	0.121 (0.024)	<.0001	(0.075, 0.167)
		29	0.129 (0.023)	<.0001	(0.084, 0.174)
		57	0.118 (0.023)	<.0001	(0.072, 0.163)
		85	0.126 (0.023)	<.0001	(0.081, 0.171)

The treatment baseline is 2.604 (0.022) liters.
Means (SE) adjusted for treatment baseline and pooled centre (fixed).
A separate ANCOVA was fitted for each time point and test day.
Test days entirely missing were imputed by carrying the last test day forward.
Missing data within a test day were imputed by carrying either the lowest or last value forward depending on why the data were missing.
Analysis set: 1012.56 FAS_PFT (N= 1424)
Source data: Appendix 16.1.9.2, Statdoc 6.5.3, 6.5.4, 6.5.6 stat\fvc.sas 15JUL2008

Table 15.2.7: 2 Mean of the weekly mean morning pre-dose PEFR (liters/minute) per day by weeks on treatment - FAS_DRY

	CVT R 20/100 (N=441) Mean (SE) (L/min)	CVTCFC36/206 (N=444) Mean (SE) (L/min)	IB R 20 (N=426) Mean (SE) (L/min)
Week 1	194.84(1.238)	194.67(1.251)	193.27(1.272)
Week 2	192.48(1.379)	191.74(1.394)	190.55(1.417)
Week 3	191.31(1.573)	192.18(1.589)	189.81(1.615)
Week 4	190.93(1.653)	190.90(1.671)	188.74(1.699)
Week 5	192.20(1.696)	190.83(1.714)	188.76(1.742)
Week 6	192.83(1.824)	189.63(1.843)	188.84(1.874)
Week 7	191.15(1.846)	189.04(1.865)	188.73(1.896)
Week 8	191.16(1.853)	187.69(1.872)	188.40(1.903)
Week 9	192.29(1.988)	188.42(2.009)	190.00(2.042)
Week 10	190.55(1.976)	188.32(1.996)	188.21(2.029)
Week 11	190.14(2.014)	187.05(2.035)	187.34(2.069)
Week 12	189.73(2.063)	186.70(2.085)	185.82(2.119)
Week 1-12	191.95(1.510)	190.29(1.526)	189.51(1.551)

The treatment baseline is 196.7 (2.241) units.
Means(SE) adjusted for treatment baseline and pooled center(fixed).A separate ANCOVA was fitted for each week.
In order to be able to include the same patients each week, missing weeks were imputed by carrying the last week forward.
Weeks 1-12 is the mean of all non-missing on-treatment,non-clinic days for each patient.Only observed data were included in this mean.
Analysis set: 1012.56 FAS_DRY (N=1399).

Table 15.2.6: 3 Mean of daily night-time symptom scores per week for 12 weeks on treatment - FAS_DRY

	CVT R 20/100 (N=471) Mean (SE) (score)	CVTCFC36/206 (N=467) Mean (SE) (score)	IB R 20 (N=454) Mean (SE) (score)
Week 1	0.826(0.023)	0.825(0.023)	0.777(0.023)
Week 2	0.897(0.025)	0.895(0.025)	0.855(0.026)
Week 3	0.920(0.027)	0.903(0.027)	0.836(0.028)
Week 4	0.886(0.028)	0.948(0.029)	0.860(0.029)
Week 5	0.884(0.029)	0.905(0.029)	0.867(0.030)
Week 6	0.940(0.030)	0.951(0.031)	0.892(0.031)
Week 7	0.950(0.031)	0.955(0.031)	0.881(0.032)
Week 8	0.943(0.032)	0.955(0.032)	0.873(0.033)
Week 9	0.942(0.031)	0.916(0.032)	0.872(0.032)
Week 10	0.995(0.033)	0.969(0.033)	0.869(0.034)
Week 11	0.980(0.032)	0.941(0.032)	0.886(0.033)
Week 12	0.990(0.033)	0.978(0.034)	0.901(0.034)
Week 1-12	0.922(0.023)	0.914(0.024)	0.857(0.024)

The treatment baseline is 0.846 (0.023) units.
Means(SE) adjusted for treatment baseline and pooled center(fixed).A separate ANCOVA was fitted for each week.
In order to be able to include the same patients each week, missing weeks were imputed by carrying the last week forward.
Weeks 1-12 is the mean of all non-missing on-treatment,non-clinic days for each patient.Only observed data were included in this mean.
Analysis set: 1012.56 FAS_DRY (N=1399).
Night-time COPD symptoms: 0=none 1=some - slept well 2=woke once 3=woke several times 4=woke most of night

Source data: Appendix 16.1.9.2, Statdoc 6.11.1, Appendix 16.2, Listing 6.3.4 stat\typ15_eet7.sas 30JUN2008

Table 15.2.6: 4 Mean of daily daytime symptom scores per week for 12 weeks on treatment - FAS_DRY

	CVT R 20/100 (N=452) Mean (SE) (score)	CVTCFC36/206 (N=456) Mean (SE) (score)	IB R 20 (N=437) Mean (SE) (score)
Week 1	0.932(0.021)	0.962(0.021)	0.965(0.022)
Week 2	0.982(0.023)	0.990(0.023)	0.999(0.024)
Week 3	1.004(0.025)	0.994(0.025)	0.979(0.025)
Week 4	0.996(0.026)	1.025(0.026)	1.017(0.027)
Week 5	1.021(0.027)	0.975(0.027)	0.986(0.028)
Week 6	1.022(0.028)	1.024(0.028)	1.020(0.029)
Week 7	1.039(0.029)	1.039(0.029)	1.022(0.029)
Week 8	1.059(0.030)	1.045(0.030)	1.024(0.031)
Week 9	1.050(0.029)	1.007(0.029)	1.004(0.030)
Week 10	1.075(0.031)	1.028(0.031)	1.029(0.031)
Week 11	1.058(0.030)	1.044(0.030)	1.032(0.031)
Week 12	1.055(0.031)	1.051(0.031)	1.016(0.031)
Week 1-12	1.015(0.022)	1.002(0.022)	0.999(0.022)

The treatment baseline is 1.025 (0.024) units.
Means(SE) adjusted for treatment baseline and pooled center(fixed).A separate ANCOVA was fitted for each week.
In order to be able to include the same patients each week, missing weeks were imputed by carrying the last week forward.
Weeks 1-12 is the mean of all non-missing on-treatment,non-clinic days for each patient.Only observed data were included in this mean.
Analysis set: 1012.56 FAS_DRY (N=1399).
Daytime COPD symptoms: 0=none 1=occasional 2=frequent, no interference with activities 3=most of day, interference with activities 4=prevent working and activities

Source data: Appendix 16.1.9.2, Statdoc 6.12.1, Appendix 16.2, Listing 6.3.5 stat\typ15_eet7.sas 30JUN2008