Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

Title of trial:	Safety, tolerability and pharmacokinetics of multiple rising inhalative doses (delivered doses of 23 to 69 µg q.d. and 69 µg b.i.d. for four days) of butylated hydroxytoluene (an excipient novel for inhalation administration) via Respimat® Soft Mist™ Inhaler B (randomised, double-blind, placebo-controlled sub-study 1) and safety, tolerability and pharmacokinetics of multiple rising inhalative doses (fine particle doses of 160 to 1280 µg q.d. for 10 days) of BI 54903 XX via Respimat® Soft Mist™ Inhaler B as randomised, double-blind, placebo-controlled Phase I trial in healthy male volunteers (main study) and comparison of systemic exposure following a single fine particle dose of 640 µg BI 54903 XX via Respimat® Soft Mist™ Inhaler B and of a single fine particle dose of 640 µg Alvesco® (Ciclesonide) via MDI (randomised, open-label, two-way crossover sub-study 2)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	The objective of the study was to investigate safety, tolerability and pharmacokinetics of butylated hydroxytoluene (BHT, sub-study 1) administered via Respimat® Soft Mist™ Inhaler B (SMI B); to assess safety, tolerability and pharmacokinetics of multiple rising doses of BI 54903 XX administered via Respimat® SMI B (main study), and to compare systemic exposure of single dose BI 54903 XX administered via Respimat® SMI B (sub-study 2) with single dose Alvesco® (ciclesonide) administered via HFA-134a propellant metered dose inhaler (MDI).
Methodology:	The sub-study 1 and the main study were randomised, double-blind (within dose group), and placebo-controlled, with repeated-rising doses of BHT and BI 54903 XX. Sub-study 2 was randomised and open-label, with single-dose administrations of BI 54903 XX and Alvesco® (ciclesonide) in a 2-way cross-over design.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 2 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

No. of subjects:	
planned:	56
actual:	entered: 56 <u>Sub-study 1</u> Treatment: Placebo solution containing BHT entered: 18, treated: 18, analysed: 18 Placebo solution without BHT entered: 6, treated: 6, analysed: 6 <u>Main study</u> Treatment: BI 54903 XX entered: 24, treated: 24, analysed: 24 Placebo for BI 54903 XX containing BHT entered: 8, treated: 8, analysed: 8 <u>Sub-study 2</u>* Treatment: BI 54903 XX and Alvesco® entered: 24, treated: 24, analysed: 24 * subjects from main study
Diagnosis and main criteria for inclusion:	Healthy male volunteers aged 21 to 50 years with BMI in the range of 18.5 to 29.9 kg/m^2
Test products:	Inhalation solutions of BHT and BI 54903 XX or matching placebo (for both treatments), and Alvesco® (ciclesonide)

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

doses:	BHT Treatment A: 23 µg (2 actuations of 11.55 µg) q.d. for 4 days Treatment B: 69 µg (6 actuations of 11.55 µg) q.d. for 4 days Treatment C: 69 µg (6+6 actuations of 11.55 µg) b.i.d. for 4 days All doses refer to doses delivered ex mouthpiece. BI 54903 XX Treatment D: 160 µg (2 actuations of 80 µg) q.d. for 10 days Treatment E: 320 µg (4 actuations of 80 µg) q.d. for 10 days Treatment F: 640 µg (2 actuations of 320 µg) q.d. for 10 days Treatment G: 1280 µg (4 actuations of 320 µg) q.d. for 10 days Treatment H: 640 µg (2 actuations of 320 µg), single dose All doses refer to fine particle doses (FPD) delivered ex mouthpiece Alvesco® HFA-MDI (ciclesonide) Treatment I: single fine particle dose of 640 µg (corresponding to 800 µg or 5 doses of 160 µg delivered ex actuator) Alvesco® HFA-MDI.
mode of admin.:	For BHT and BI 54903 XX: Inhalation via the Respimat® SMI B after an overnight fast For Alvesco®: Inhalation via HFA-MDI after an overnight fast
batch no.:	B072000240 (Treatments A-C), B072000253 (Treatments D and E), B072000279 (Treatments F-H), B081000642-GID021E (Treatment I)
Reference therapy:	Placebo
dose:	Actuations similar to the respective active medications
mode of admin.:	Inhalation via the Respimat® SMI B
batch no.:	B072000234 (BHT free placebo), B072000240 (BHT containing placebo)
Duration of treatment:	A-C: Repeated rising doses of BHT for 4 days D-G: Repeated rising doses of BI 54903 XX for 10 days H-I: Single doses of BI 54903 XX and Alvesco® (ciclesonide) for 1 day

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

Criteria for evaluation:

Efficacy / clinical pharmacology:

As far as feasible, the following parameters were calculated for BI 54903 XX and the metabolite CD 1857 XX:

After the first dose: C_{max}, t_{max}, AUC_{0-tz}, AUC_{t1-t2}, $AUC_{\tau,1}$ (=AUC_{0-24}), $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{ih}, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$; additionally for BI 54903 XX only: CL/F, V_z/F.

After the last dose: $C_{max,ss}$, $t_{max,ss}$, $C_{pre,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{ih,ss}$, $Ae_{t1-t2,ss}$, $fe_{t1-t2,ss}$, $CL_{R,t1-t2,ss}$; additionally for BI 54903 XX only: $CL/F_{,ss}$, $V_z/F_{,ss}$.

Accumulation ratio: $R_{A,AUC}$, $R_{A,Cmax}$, and linearity index.

Safety:

The safety and tolerability were assessed by physical examination, vital signs (blood pressure [BP], pulse rate [PR]), 12-lead ECG, body plethysmography, laboratory tests, adverse events and general tolerability.

Statistical methods:

Descriptive statistics was used for safety and pharmacokinetic (PK) endpoints.

<u>Multiple rising dose parts of the trial (sub-study 1 and main study)</u>

A regression model with 95% confidence interval (CI) for the slope was computed for dose proportionality.

Linearity with respect to multiple administration using $AUC_{0-\infty}$ and $AUC_{\tau,ss}$ was addressed by a linear model on the logarithmic scale including 'subject' and 'order' as fixed effects. Both AUCs provided the linearity index including a 2-sided 95% CI.

The trough concentrations at steady state were analysed by a repeated measured linear model with 'time' as a repeated effect and thereafter pairwise comparisons of the differences between all time points were done with t-tests.

<u>Part of the trial comparing systemic exposure: sub-study 2</u>

The Analysis of variance (ANOVA) model on the logarithmic scale was used as the statistical model for the PK parameters in the analysis of relative bioavailability. This model included effects accounting for the following sources of variation: ‘sequence’, ‘subjects within sequences’, ‘period’ and ‘treatment’.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

SUMMARY – CONCLUSIONS:

Safety results:

The inhalation of repeated rising doses of 23 and 69 µg q.d., and 69 µg b.i.d. of BHT in sub-study 1, repeated rising once daily doses of 160-1280 µg of BI 54903 XX in the main study, and single doses of 640 µg BI 54903 XX and 640 µg Alvesco® (ciclesonide) in cross-over, sub-study 2 were well tolerated. The investigator and all subjects assessed the overall tolerability as 'good' in all 3 parts of the study. No SAEs or other significant AEs were reported. No subjects discontinued the trial prematurely due to any AE. In sub-study 1, one subject (4.2%, out of 24 subjects) experienced a mild non drug-related rhinitis after inhalation of 69 µg b.i.d. BHT. In the main study (n=32), among 8 subjects who inhaled the placebo for BI 54903 XX, mild-to-moderate AEs were reported by one subject (12.5%) during the treatment phase (AE-back pain)and by 2 subjects during the washout phase (AEs-pharyngitis and rhinitis). Among subjects (n=24) who inhaled repeated rising doses of BI 54903 XX, one subject each (16.7%) reported mild AEs (cough and oropharyngeal pain) for dose groups 320 µg and 1280 µg during the treatment phase. During the washout phase, 2 subjects who inhaled 160 µg and 320 µg BI 54903 XX during the treatment phase reported AEs (conjunctivitis and nasopharyngitis, vomiting and chills respectively) of moderate intensity. No dose-dependent increase of AEs were observed with the repeated rising doses of BI 54903 XX. Cough, reported by one subject immediately after inhalation of 320 µg BI 54903 XX during the treatment phase and pharyngitis reported by one subject during the washout phase (inhaled the placebo for BI 54903 XX during the treatment phase), were suspected to be drug-related by the investigator. In sub-study 2 (n=24), 2 subjects (8.3%) who inhaled single dose BI 54903 XX reported cough and bronchitis as AEs and 3 subjects (12.5%) who inhaled single dose Alvesco® reported cough and headache as AEs. Cough, reported by one subject immediately after inhalation of both BI 54903 XX and Alvesco® cross-over treatments was suspected to be drug-related by the investigator. This was the same subject who reported cough assessed to be drug-related by the investigator during the main study. The evaluation of laboratory parameters, ECG, vital signs (BP, PR), and lung function (assessed as R_{aw}) did not suggest any notable adverse effect induced under any treatment

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

Efficacy / clinical pharmacology results:

Pharmacokinetics of BHT:

No treatment related BHT plasma and urine concentrations above the limit of quantification were observed.

Pharmacokinetics of BI 54903 XX:

After single and multiple inhalations of 160-1280 µg BI 54903 XX, maximum plasma concentrations were observed at the first measured time point (t_{max} ≈5 min). Concentrations thereafter declined in a multi-exponential manner with a very rapid initial decline within the first 4 h. Since with the increasing doses, and also after multiple doses, plasma concentrations of BI 54903 XX could be measured over longer time periods, PK parameters dependent on log-linear regression over the data ($t_{½(,ss)}$, $AUC_{0-\infty}$, $CL/F_{(,ss)}$, $V_z/F_{(,ss)}$) are not directly comparable between the different dose groups, or between single and multiple inhalations.

The half-life calculated based on data points within 2-4 h after inhalation was 0.52–0.73 hours (gMean values; gCV: 8.42–27.8%). The gMean terminal half-life as calculated from concentration data up to 24 h amounted to 14 h (gCV: 26.1%).

Systemic exposure to BI 54903 XX in the dose range of 160–1280 µg increased in a manner that was more than dose-proportional after single inhalation, but in proportion with the dose after multiple inhalations.

Steady state upon multiple once daily inhalations was achieved at the latest by day 8.

Accumulation of BI 54903 XX in plasma based on C_{max} and AUC values accounted for a factor of 0.67–1.3.

The linearity index ranged between 0.80 and 1.3, suggesting time-independent PK of BI 59403 XX upon once daily dosing for 10 days.

No BI 54903 XX could be detected in urine, indicating negligible urinary excretion of the unchanged drug.

Pharmacokinetics of the metabolite CD 1857 XX:

Maximum plasma concentrations of CD 1857 XX after single and multiple inhalations of 160−1280 µg BI 54903 XX were observed at 0.200–1.14 hours,

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

with no systematic difference between the dose groups or between day 1 and day 10. Concentrations declined thereafter in a manner that was at least bi-exponential, with an initial phase up to ~12 h and a second phase thereafter.

With the increasing doses of BI 54903 XX and upon multiple inhalations, plasma concentrations of CD 1857 XX could be measured over longer time periods. Half-lives for the different dose groups, and on day 1 and day 10, respectively, were therefore calculated from different phases of the plasma-concentration profiles, and ranged from 3.37–9.91 h (gCV: 8.68–54.2%).

Systemic exposure to CD 1857 XX increased dose-proportionally after single and multiple inhalations of 160–1280 µg BI 54903 XX.

Steady state concentrations of CD 1857 XX upon multiple inhalations of BI 54903 XX were reached on day 3 or latest by day 8.

Accumulation of CD 1857 XX in plasma based on C_{max} and AUC values accounted for a factor of 0.98–1.3.

The linearity index in the dose groups treated with 160−1280 µg BI 54903 XX was approximately 1.1, suggesting time-independent PK of CD 1857 XX upon once daily dosing of BI 54903 XX for 10 days.

Urinary excretion of CD 1857 XX was found to be less than 0.005% of the BI 54903 XX dose, hence was negligible.

Systemic exposure to BI 54903 XX and CD 1857 XX after inhalation via Respimat® SMI B compared to inhalation of Alvesco® HFA-MDI (Sub-study 2)

Based on AUC values, systemic exposure to BI 54903 XX after single inhalation of 640 µg BI 54903 XX via the Respimat® SMI B was equivalent to the systemic exposure after inhalation of 640 µg Alvesco® via HFA-MDI. C_{max} values were slightly lower (95%) after inhalation via the Respimat® SMI B than after inhalation of Alvesco®.

The systemic exposure to CD 1857 XX as assessed based on AUC and C_{max} values after inhalation of 640 µg BI 54903 XX via Respimat® SMI B, was approximately 14–22% lower when compared to the systemic exposure after inhalation of Alvesco® via HFA-MDI.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-003168-23	
Name of active ingredient: BI 54903 XX		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 June 2009	**Trial No. / U No.:** 1256.1 / U09-1537-01	**Dates of trial:** 16 JUN 2008 – 12 SEP 2008	**Date of revision** (if applicable)**:**

Conclusions:	The inhalation of repeated rising doses of BHT and BI 54903 XX was safe and well tolerated by healthy male volunteers. No AEs or drug-related effects were reported that could be of any safety concern. No BHT plasma and urine concentrations above the limit of quantification were observed after multiple inhalations of BHT via the Respimat® SMI B. Systemic exposure to BI 54903 XX and CD 1857 XX upon multiple inhalations of BI 54903 XX via the Respimat® SMI B increased in proportion with the dose. The systemic exposure to BI 54903 XX after inhalation of 640 µg was comparable to the exposure after inhalation of 640 µg Alvesco® (ciclesonide). The systemic exposure to CD 1857 XX after inhalation of 640 µg BI 54903 XX was approximately 14–22% lower when compared to the exposure after inhalation of 640 µg Alvesco®. Urinary excretion of BI 54903 XX and CD 1857 XX was negligible.