Pharmacokinetics (PK) of single doses of mometasone furoate (MF) delivered via the Breezhaler® (BH) and Twisthaler® (TH) devices in healthy subjects

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Introduction

- QMF149 is being developed as a once-daily fixed-dose combination of the long-acting β_2-agonist (LABA) indacaterol and the inhaled corticosteroid mometasone furoate (MF) for maintenance treatment of asthma and COPD.
- The components of QMF149 are currently approved to be administered via different devices, with indacaterol maleate delivered via a single-dose, dry-powder inhaler (Onbrez® Breezhaler® [BH]) and MF via a multiple-dose, dry-powder inhaler (Asmanex® Twisthaler®* [TH]).
- To identify a dose of MF in the BH device that provides systemic exposure comparable to that from the MF TH 400 µg, we evaluated the pharmacokinetics (PK) of single doses of MF delivered via the two devices.
- Due to its low oral bioavailability,[1] systemic exposure after inhalation of MF primarily reflects the amount of drug delivered to and absorbed from the lung.

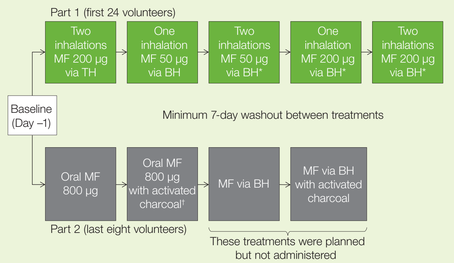
Objectives

- In Part 1 of the study, the objective was to identify a dose of MF in the BH device that provides systemic exposure comparable to that from the MF TH 400 µg, following single-dose, oral inhalation.
- In Part 2, the objective was to determine the relative contributions of pulmonary and gastrointestinal absorption to total systemic exposure of MF following oral inhalation via the BH.

Methods

- This was an open-label, single-dose, two-part study in 32 healthy subjects (24 randomised to Part 1 and eight to Part 2) (Figure 1).

Figure 1. Study design



*Administered only if the predicted AUC_{inf} was <4 x the value for the first MF dose via TH
†Administered only if systemic exposure to MF was measurable after the previous treatment
‡Administered only if complete (≥85%) suppression of MF absorption was observed on oral administration in presence of activated charcoal

- Part 1 had a five-treatment, single-sequence, crossover design.
- Part 2 was completed as a two-treatment, single-sequence, crossover study.
  - As complete suppression (≥85%) of gastrointestinal absorption by charcoal could not be demonstrated, the planned administration of MF via the BH (with or without activated charcoal) was not performed.

*Asmanex® Twisthaler® is a registered trademark of Merck.

Pharmacokinetics

- PK data were obtained from pre-dose up to 72 hours after dosing.
- MF concentrations were determined by a validated liquid plasma chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a limit of quantification of 0.250 pg/mL.
- PK parameters were calculated for each treatment, and included area under the concentration–time curve from time zero to the last quantifiable concentration (AUC_{last}), AUC from time zero to infinity (AUC_{inf}), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}) and apparent terminal elimination half-life ($T_{1/2}$).
- In Part 1, an interim review of PK data (24-hour profiles) was conducted to guide dose escalation for MF BH, following completion of the first two treatments (400 µg via TH and 50 µg via BH), and subsequently following each further treatment.
- For Part 2, the relative oral bioavailability of MF in the presence of activated charcoal was calculated by comparing the AUC parameters following oral administration of MF in the presence (test) and absence (reference) of activated charcoal.

Safety assessments

- In Parts 1 and 2, safety assessments included physical examinations, electrocardiograms, vital signs and laboratory evaluations.

Statistical analysis

- For Part 1, log-transformed AUC or C_{max} parameters were analysed using a linear mixed-effects model.
- BH doses were analysed using a power model on the log scale: $\ln(PK) = \mu + \beta \times \ln(Dose) + subject$, where 'subject' is a random effect.
- Geometric mean and 90% confidence intervals (CI) were calculated for the TH treatment group, and the point at which geometric mean AUC_{last} intercepted the fitted model for the BH was used to estimate the average equivalent dose of MF in the BH.

Results

Disposition and baseline characteristics

- Of the 32 Caucasian males enrolled, eight discontinued before completing the study.
  - All discontinuations were in Part 1 of the study.
  - Seven discontinuations were due to withdrawal of consent and one was due to a protocol violation.
- The mean age of the subjects was 22.8 (range: 20–30) years for Part 1 and 26.4 (21–39) years for Part 2.
- Subjects in Part 1 had a mean weight of 76.4 kg (range: 64.8–93.9 kg), mean height of 181 cm (range: 172–193 cm) and mean body mass index (BMI) of 23.2 kg/m^2 (range: 20.2–27.4 kg/m^2).
- Subjects in Part 2 had a mean weight of 78.7 kg (range: 73.7–84.6 kg), mean height of 183 cm (range: 179–195 cm) and mean BMI of 23.4 kg/m^2 (range: 21.1–26.1 kg/m^2).

PK of inhaled MF (Part 1)

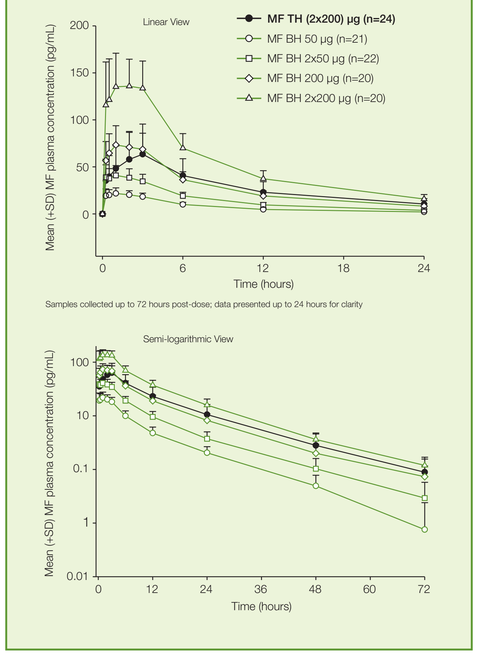
- Dose-normalised AUC_{last} for MF was 1.8–1.9-fold higher when delivered via the BH compared with TH.
- MF was rapidly absorbed following oral inhalation via both devices. Median T_{max} occurred earlier with all doses after inhalation via the BH (0.375–2 hours) compared with the TH (3 hours; Table 1, Figure 2).
- The $T_{1/2}$ of MF was similar after all treatments (11.5–13.2 hours).
- C_{max} and AUC were less variable with the BH (coefficient of variation [CV]: 21.0–26.7%) than with the TH (CV: 48.7–49.8%).

Table 1. Summary of MF PK following inhalation

	AUC_{last} (h·pg/mL)	AUC_{inf} (h·pg/mL)	C_{max} (pg/mL)	T_{max} (hours)	$T_{1/2}$ (hours)
MF TH 400 µg (n=24)	904 (48.7)	924 (48.7)	64.8 (49.8)	3.00 (0.50–3.00)	13.2 (14.5)
MF BH 50 µg (n=21)	217 (25.8)	226 (24.9)	23.4 (24.7)	1.00 (0.25–3.00)	11.5 (28.5)
MF BH 100 µg (n=22)	430 (24.5)	439 (24.7)	44.1 (23.7)	0.375 (0.25–3.00)	12.6 (19.6)
MF BH 200 µg (n=20)	847 (26.4)	862 (26.7)	76.5 (25.5)	1.00 (0.25–3.00)	13.0 (15.5)
MF BH 400 µg (n=20)	1,600 (21.3)	1,630 (21.0)	148 (25.9)	2.00 (0.25–3.00)	12.1 (18.8)

Data are presented as arithmetic mean (CV%), except for T_{max}, which is presented as median (range)

Figure 2. Mean (SD) MF plasma concentration-time profiles: Inhalation via MF TH or BH



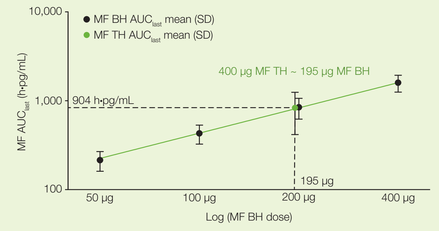
- AUC_{last} and AUC_{inf} increased in a dose proportional manner (Table 2, Figure 3).
  - C_{max} increased in an approximately dose proportional manner (Table 2).
- A linear mixed-effects model with subject as a random effect was fitted to the AUC_{last} data and used to estimate the average equivalent dose of MF in the BH.
  - An estimated average dose of 195 µg (90% CI: 175–215 µg) via the BH is expected to provide systemic exposure equivalent to MF TH 400 µg (see also Figure 3).

Table 2. Statistical analysis of dose proportionality for MF 50–400 µg via the BH

	Dose proportionality for MF BH	
Variable	Slope estimate	90% CI
AUC_{last} (h·pg/mL)	0.98	0.92–1.04
AUC_{inf} (h·pg/mL)	0.97	0.91–1.03
C_{max} (pg/mL)	0.90	0.83–0.96

Statistical dose proportionality was concluded if the 90% CI of the slope estimate included unity

Figure 3. Relationship between AUC_{last} and MF BH dose



PK of orally administered MF (Part 2)

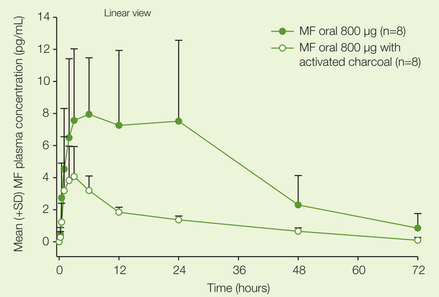
- The PK data for orally administered MF, with and without activated charcoal, are summarised in Table 3 and Figure 4.

Table 3. Summary of MF PK following oral administration

	AUC_{last} (h·pg/mL)	AUC_{inf} (h·pg/mL)	C_{max} (pg/mL)	T_{max} (hours)	$T_{1/2}$ (hours)
MF 800 µg oral (n=8)*	320 (57.3)	386 (50.8)	10.6 (53.2)	9.00 (2.00–24.00)	18.9 (53.6)
MF 800 µg oral with activated charcoal (n=8)*	76.6 (33.7)	96.7 (23.5)	4.85 (65.0)	3.00 (1.00–6.00)	21.5 (22.0)

Data are presented as arithmetic mean (CV%), except for T_{max}, which is presented as median (range)
*n=7 for AUC_{inf} and $T_{1/2}$

Figure 4. Mean (SD) MF plasma concentration-time profiles: Oral administration with or without activated charcoal



- The effectiveness of activated charcoal for reducing oral absorption of MF was estimated as 74% based on AUC_{last}.
- Complete suppression (≥85%) of oral absorption could not be demonstrated. Therefore the planned administration of MF via the BH (with or without activated charcoal) was not performed.
- Relative oral bioavailability of MF (oral versus inhaled via BH) was estimated to be in the range of 9.2–10% based on comparison of dose normalised AUC_{last} for oral administration without charcoal ([0.4 (h·pg/mL)/µg], Part 2 versus inhalation via BH [4–4.34 (h·pg/mL)/µg], Part 1).

Safety

- In Part 1, the overall incidence of adverse events was low and similar across all treatment groups (10–21%), with no evidence of dose-related effects.
  - The most frequent adverse events were headache (three subjects), rash (three subjects) and nasopharyngitis (two subjects); no other individual adverse event occurred in more than one subject.
  - The majority of adverse events were of mild severity and there were no severe events.
  - None of the adverse events were suspected to be related to treatment with no adverse events leading to subject withdrawal.
- Only one adverse event was reported in Part 2 (mild constipation in a subject receiving activated charcoal).

Conclusions

- Systemic exposure to MF via the BH increased in a dose proportional manner over the dose range 50–400 µg.
- An estimated average dose of MF 195 µg in the BH is expected to provide systemic exposure comparable to TH 400 µg.
- Dose-normalised AUC_{last} for MF was 1.8–1.9-fold higher when delivered via the BH, compared with the TH.
- MF via the BH had an acceptable safety profile and was well tolerated in healthy volunteers.

Reference

1. Prescribing information for Dulera®. Available at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed 21 June 2012.

Acknowledgements

The authors wish to thank the subjects and staff at the participating study centre. Also Steve Maton, David Guede and Philippe Remusat (professional statistical and programming support, funded by Novartis) for statistical analysis of data, Paul Hutchin (professional medical writer, funded by Novartis) for assistance with poster preparation, and members of the clinical trial team and project team.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

Poster presented at the European Respiratory Society Annual Congress, 1–5 September 2012, Vienna, Austria.

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