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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Bemrist Breezhaler

indacaterol / mometasone furoate

Procedure no: EMEA/H/C/005516/P46/002

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of Abbreviations in Text

C1	Concept 1 Breezhaler
FPM	Fine particle mass
GeoMean	Geometric Mean
MAH	Manufacturing Authorisation Holder
PK	Pharmacokinetic
QMF149	Fixed dose combination of indacaterol acetate and mometasone furoate
TH	Twisthaler inhaler

1. Introduction

On 04/10/2022, the MAH submitted a completed paediatric study for QMF149 75/40 µg indacaterol acetate/mometasone furoate fixed dose combination (**Bemrist Breezhaler EMEA/H/C/005516**) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CQMF149G2203 is a study provided in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2.2. Information on the pharmaceutical formulation used in the study

The Twisthaler inhaler (TH) is a multi-dose dry powder inhaler, with all doses pre-loaded in the device. The Concept 1 Breezhaler (C1) device is a unit dose dry powder inhaler, which requires loading of the dose prior to each use. The following medication/devices will be prepared by Novartis and supplied to the Investigator as open labelled medication:

- Treatment A: Mometasone furoate (MF) delivered via Twisthaler inhaler, (MF 100 µg TH)
- Treatment B: Fixed dose combination of 75 µg indacaterol acetate and 40 µg mometasone furoate delivered as powder in hard capsules via Concept1 Breezhaler inhaler (QMF149 75/40 µg C1)

Table 1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
QMF149 75/40 µg	Capsule for Inhalation	Oral inhalation	Open-label blister delivered via C1 device (Breezhaler®)	Sponsor (global)
Mometasone fuorate 110[1] µg	Dry Powder Inhalation	Oral inhalation	Open-label Twisthaler® (metered dose inhaler)	Sponsor (global)

[1] A single dose of the Asmanex Twisthaler® contains 110 µg of mometasone furoate delivering 100 µg of mometasone furoate from the inhaler mouthpiece following single actuation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CQMF149G2203: An open-label, two-period, single-sequence, crossover study to compare the systemic exposure of a single inhaled dose of mometasone furoate (MF) when administered alone via the MF Twisthaler (TH) to a single inhaled dose of QMF149 75/40 µg indacaterol acetate/MF fixed dose combination when administered via the Concept 1 (Breezhaler) device in ≥ 6 to <12 year old asthma patients

The date of completion (last subject last visit) of this study was 11 April 2022.

2.3.2. Clinical study

Study CQMF149G2203

CQMF149G2203 was a Phase 2 open-label, two-period, single-sequence, crossover study to compare the systemic exposure of a single inhaled dose of mometasone furoate (MF) when administered alone via the MF Twisthaler (TH) to a single inhaled dose of QMF149 indacaterol acetate/MF fixed dose combination when administered via the Concept 1 (C1) (Breezhaler) device in ≥ 6 to < 12 year old asthma patients.

A total of 24 subjects were enrolled, all of whom completed both treatment visits. None of the enrolled subjects discontinued. On the first treatment visit (Day 1) subjects received a single inhaled dose of 100 µg MF administered via the TH device followed by a 4-day washout period. On the second treatment visit (Day 6) subjects received a single inhaled dose of 75/40 µg indacaterol acetate/MF (QMF149 75/40 µg) via the C1 device. Subjects were stratified into 2 age groups; ≥ 6 to < 9 years and ≥ 9 to < 12 years (at least 6 subjects in each of the 2 age groups).

The primary objective of this study was to compare the systemic exposure of MF resulting from single orally inhaled doses of QMF149 75/40 µg administered via the C1 unit dose dry powder inhaler versus the 100µg MF TH metered dose dry powder inhaler in paediatric asthma subjects (≥ 6 to < 12 years of age). The PK parameters used for this study were the AUC0-6h and Cmax of MF after single dose administration of QMF149 75/40 µg C1 and 100µg MF TH. The secondary objectives were to evaluate the systemic exposure of indacaterol resulting from a single orally inhaled dose of QMF149 75/40 µg and to evaluate the safety and tolerability of QMF149 75/40 µg after single dose administration in paediatric subjects.

Pharmacokinetic results

The subjects in this study received a single dose from single unused (unprimed) C1 and TH devices. Unprimed devices are not coated with the formulation, and therefore may lead to lower fine particle mass (FPM) and delivered dose compared to later doses actuated from the device throughout its use time. Therefore, a correction factor was applied that took into account this first-dose effect.

Table 2 presents the summary statistics for the relevant PK parameters, corrected for first dose effect. Table 3 presents the Statistical analysis of primary MF plasma parameters, corrected for first dose effect. The Cmax of MF was similar between both formulations, as reflected by the geometric mean ratio of 1.09 (90% CI: 0.93, 1.28) (Table 3). Median Tmax of MF from QMF149 75/40 µg C1 (0.56 h) was reached earlier compared to MF TH (1.07 h) (Table 2), suggesting faster absorption of MF from lungs into systemic circulation from QMF149 75/40 µg C1 versus 100 µg MF TH.

The geometric mean ratio of AUC0-6h of MF from QMF149 75/40 µg C1 vs 100 µg MF TH was 0.88 (90%CI: 0.74, 1.06), indicating a similar exposure of MF from the two formulations. For a few subjects where the last PK sample was collected slightly earlier than the planned 6h time point and the exposure profile did not allow for extrapolation of MF exposure to 6h, the AUC0-6h parameter could not be calculated.

QMF149 75/40 µg C1 utilized for the study was stored under special conditions of 5°C ± 3°C, aiming to avoid any equilibration changes of the FPM over the duration of the study. At the target storage conditions of < 25°C, the FPM of MF is expected to increase by approximately 20% compared to the 5°C ± 3°C storage conditions and therefore an increased MF exposure from QMF149 75/40 µg C1 could be expected. The Applicant hypothesises this could bridge the exposure gap of the GeoMean Ratio to be closer to 1.

There were no apparent differences in exposure were observed between the two age groups of ≥ 6 to < 9 years old and ≥ 9 to < 12 years old.

Table 2 Summary Statistics for MF PK parameters – corrected for first-dose effect (PK Analysis Set)

Compound: Mometasone Furoate, Analyte: Mometasone Furoate, Matrix: Plasma, Treatment Sequence: MF 100 µg via Twisthaler (Day 1) // QMF149 75/40 µg via Concept 1 (Day 6)

PK parameter (Unit)	MF 100 µg via Twisthaler (N=24)	QMF149 75/40 µg via Concept 1 (N=24)
Cmax (pg/mL)	51.9 ± 23.5 (45.3) [23]	53.5 ± 16 (30) [24]
AUC0-6h (h*pg/mL)	208 ± 102 (49.2) [18]	176 ± 57.5 (32.6) [23]
Tmax (h)	1.07 (0.5 -3) [23]	0.56 (0.43 -2) [24]

- Statistics are Mean ± SD (CV%) [n].
- [n] = number of observations used for analysis
- CV% = Coefficient of variation (%) = sd/mean*100.
- For Tmax, Statistics are Median (Min-Max) [n].
- Primary PK Parameters were multiplied with the factor FPMprimed (MF) / FPMunprimed (MF) to assess equivalent MF component doses.
- For MF Twisthaler, first-dose effect correction factor is 1.26. For MF Concept 1, first-dose effect correction factor is 1.62.

Table 3 Statistical analysis of primary MF plasma PK parameters – corrected for first-dose effect (PK Analysis Set)

Compound: Mometasone Furoate, Analyte: Mometasone Furoate, Matrix: Plasma

				Treatment comparison		
Parameter	Treatment	n*	Adjusted Geo-mean	Comparison	Geo-mean Ratio	(90% CI)
Cmax (pg/mL)	QMF149 C1	24	51.3	QMF149 C1 vs MF TH	1.09	(0.93, 1.28)
	MF TH	23	47.1			
AUC0-6h (h*pg/mL)	QMF149 C1	23	167	QMF149 C1 vs MF TH	0.88	(0.74, 1.06)
	MF TH	18	189			

- QMF149 C1: QMF149 75/40 µg via Concept 1; MF TH: MF 100 µg via Twisthaler.
- Primary PK Parameters were multiplied with the factor FPMprimed (MF) / FPMunprimed (MF) to assess equivalent MF component doses.
- For MF Twisthaler, first-dose effect correction factor is 1.26. For MF Concept 1, first-dose effect correction factor is 1.62.
- n* = number of observations used for analysis.

PK parameter estimation was not carried out for indacaterol. The corrected summary statistics of indacaterol concentration over time are presented below in Table 4. Systemic exposure to indacaterol from QMF149 75/40 µg C1 pre-dose, and at 0.25 h (mean 102 pg/ml; median 87.6 pg/mL) and 1 h (mean 62.3 pg/mL; median 63 pg/mL) post-dose was determined.

Table 4 Summary statistics of indacaterol concentrations (pg/mL) – corrected for first-dose effect (PK Analysis Set)

Compound: QAB149, Analyte: Indacaterol, Matrix: Plasma

Actual Treatment	Profile Day	Scheduled timepoint (h)	n	Mean ± SD (CV%)	Geo-mean (CV%)	Median	Min - Max
QMF149 75/40 µg	Day 6	0H	24	0		0	0
		0.25H	24	102.0 ± 54.9 (54)	89.1 (0.6)	87.6	34.0 – 232.0
		1H	22	62.3 ± 26.2 (42)	57.4 (0.5)	63.0	24.4 – 129.0

- CV% = coefficient of variation (%)=sd/mean*100; CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
- For indacaterol from QMF149 via Concept 1, first-dose effect correction factor is 2.0.

Safety Results

Three subjects (12.5%) experienced treatment-emergent AEs during the 100 µg MF TH treatment period, which are presented in more detail in Table 5. One subject experienced an AE of influenza, which was moderate in severity and was resolved. Two subjects experienced AEs of device failure, which were mild in severity and related to the Twisthaler device that was used for treatment administration on Day 1. None of the observed AEs were suspected to be related to the study drug. No clinically meaningful changes in laboratory parameters, vital signs, or ECGs were observed.

Table 5 Incidence of treatment emergent AEs by primary system organ class and preferred term (Safety Analysis Set)

Primary system organ class Preferred term	MF 100 ug via Twisthaler N=24 n (%)	QMF149 75/40 ug via Concept 1 N=24 n (%)	All Subjects N=24 n (%)
Number of subjects with at least one event	3 (12.5)	0	3 (12.5)
Infections and infestations	1 (4.2)	0	1 (4.2)
Influenza	1 (4.2)	0	1 (4.2)
Product issues	2 (8.3)	0	2 (8.3)
Device failure	2 (8.3)	0	2 (8.3)

- n = number of subjects in the respective treatment period.
- MedDRA version 25.0.

2.3.3. Discussion on clinical aspects

The design and methodology for Study CQMF149G2203 are acceptable. No participants were excluded from analysis sets and missing data points that could not be extrapolated were adequately described.

This study shows that the systemic exposure of MF from single orally inhaled doses of both the QMF149 75/40 µg C1 and 100 µg MF TH preparations are broadly comparable in paediatric asthma subjects. There were no apparent differences in exposure between the two age groups.

QMF149 75/40 µg C1 was well tolerated following single dose administration in paediatric subjects – no AEs were reported.

3. CHMP overall conclusion and recommendation

No changes to the current EU SmPC are required based on the results of this study.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Not Applicable