Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Foster NEXThaler
(and associated names: Alabaster, Combair, Formodual, Fostair, Fostex, Innovair, Inuvair, Inuver, Inuxair, Kantos, Kantos Master) 100 Micrograms/6 micrograms per inhalation, inhalation powder

Beclometasone dipropionate, formoterol fumarate dihydrate

DE/W/0120/pdWS/001

Marketing Authorisation Holder: Chiesi Farmaceutici S.p.A.

Rapporteur:	Germany (DE)
Finalisation procedure (day 120):	18.05.2020

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Foster NEXThaler (and associated names: Alabaster, Combair, Formodual, Fostair, Fostex, Innovair, Inuvair, Inuver, Inuxair, Kantos, Kantos Master)
INN (or common name) of the active substance(s):	beclometasone dipropionate, formoterol fumarate dihydrate
MAH:	Chiesi Farmaceutici S.p.A.
Currently approved Indication(s)	**Asthma** Foster NEXThaler is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate: • patients not adequately controlled with inhaled corticosteroids and '*as needed*' inhaled rapid-acting $beta_2$-agonist or • patients already adequately controlled on both inhaled corticosteroids and long-acting $beta_2$-agonists. **COPD** Symptomatic treatment of patients with severe COPD (FEV_1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.
Pharmaco-therapeutic group (ATC Code):	R03AK08, (Pharmacotherapeutic group: Adrenergics, inhalants: formoterol and other drugs for obstructive airway diseases).
Pharmaceutical form(s) and strength(s):	100 micrograms/6 micrograms per inhalation, inhalation powder

I. EXECUTIVE SUMMARY

Based on the submitted paediatric data, it is concluded that new information should be included in sections 4.2, 4.8, 5.1 and 5.2 of the SmPC of the medicinal product.

II. RECOMMENDATION

In agreement with the MAH, the following statements will be included in sections 4.2, 4.8, 5.1 and 5.2 of the SmPC of Foster NEXThaler to reflect paediatric data obtained with two experimental fixed dose formulations containing the same extrafine active ingredients, but using lower dose strengths (inserted /modified text highlighted in **bold** and *italics*):

Section 4.2 – Posology and method of administration - Dose recommendations for children and adolescents under 18 years

The safety and efficacy of {Trade name} in children and adolescents under 18 years of age have not been established. ***{Trade name} should not be used in children aged 5-11 years because of safety concerns. Available data in this age group are summarised in sections 5.1 and 5.2****. Currently available* ***clinical*** *data in adolescents aged 12 – 17 years are summarised in sections 4.8 and 5.1, but no recommendation on a posology can be made.*

Section 4.8 – Undesirable effects – Paediatric population

Available pharmacokinetic data do not support the safety of {Trade name} in children aged 5-11 years. *There is limited* ***clinical*** *information in adolescents 12-17 years of age (****see sections 4.2, 5.1 and 5.2****). In a 12 weeks randomised clinical trial in adults and adolescents, 162 adolescents aged 12 – 17 years with moderate to severe asthma received {Trade name} or the corresponding pressurised inhalation solution formulation, 1 or 2 inhalations bid; the frequency, type and severity of adverse drug reactions were not different in adolescents compared to adults.*

Section 5.1 – Pharmacodynamic properties – Paediatric population

There are very limited clinical data available on the use of {Trade name} in children aged 5-11 years. Compared with an equivalent dose of licensed free combination products containing beclometasone dipropionate anhydrous (BDP) and formoterol (FF), administration of a single dose of an experimental fixed dose formulation containing the same extrafine active ingredients as {Trade name}, but using a lower dose strength (50µg BDP and 6µg FF), resulted in markedly higher systemic bioavailability for both components (section 5.2). This higher systemic availability was associated with a statistically significant decrease in plasma potassium (point estimate 0.94, 95%CI [0.92; 0.96]) and increase in time-averaged heart rate (point estimate 1.06, 95%CI [1.01; 1.10]). Moreover, a trend towards cortisol suppression and increase in urinary glucose values was observed in children of the test group as compared to the reference treatment.

In adolescents, only limited information was obtained.

In a 3 months randomised clinical trial, 162 ***subjects*** *aged 12-17 years with a diagnosis of moderate to severe asthma received either {Trade name} or the corresponding pressurised inhalation solution formulation, 1 or 2 inhalations bid. The change in pre-dose FEV1 at the end of treatment was greater in the adolescents than in adults.*

See also sections 4.2, 4.8 ***and 5.2*** *for information on paediatric use.*

Section 5.2 – Pharmacokinetic properties – Paediatric population

In single dose pharmacokinetic studies in asthmatic children aged 5-11 years, two experimental paediatric fixed-dose formulations containing the same extrafine active ingredients as {Trade name}, but using lower dose strengths (A: 50µg beclometasone dipropionate [BDP] anhydrous and 6µg formoterol fumarate [FF] = 50/6; B: 35µg BDP and 4µg FF = 35/4), were compared with equivalent doses of licensed free combination products containing BDP and FF. Due to the absence of charcoal block, only systemic exposure as a measure of safety was determined.

Compared with the free combination, BDP/FF 50/6 resulted in greater systemic exposure (AUC0-t) and peak concentrations (Cmax) of all three analytes, parent compound BDP, the active metabolite beclometasone-17-monopropionate (B17MP) and formoterol. Subsequent reduction of the dose strength by about 30% to BDP/FF 35/4 still resulted in markedly higher AUC0-t of B17MP (point estimator 152.5, 90%CI [141.1-164.8]) as well as the parent compound BDP (point estimator 188.6, 90%CI [163.8-217.1]). AUC0-t of formoterol was within and Cmax slightly exceeded the bioequivalence range of 80-125%.

III. INTRODUCTION

In accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use, the MAH submitted the results of two paediatric clinical studies which were performed in accordance with the Paediatric Investigation Plan (PIP) agreed with the PDCO in 2010 (latest decision dated 15JUN2018, EMEA-00548-PIP01-09-M08).

While the same strength as approved in adults (i.e., CHF1535 100/6) was intended for the use in an adolescent population, two (2) lower dose strength products (i.e., CHF1535 50/6 and CHF1535 35/4) were developed and investigated for the treatment of asthmatic children aged ≥5 to <12 years. Neither of these two formulations is currently approved.

The initially tested dose strength (CHF1535 **50/6** DPI) resulted in greater systemic exposures to BDP, B17MP and FF and higher peak concentrations when compared with the free combination of non-extrafine BDP (Clenil® Pulvinal® 100µg) and formoterol (Oxis® Turbohaler® 6µg) (**PAEDIATRIC STUDY 4, PAED 4-DPI, CCD-1103-PR-0058, EudraCT n° 2011-001208-36**).

As the PK endpoints were not met, the dose strength of the experimental product (extrafine BDP / formoterol) was further reduced by about 30% **from 50/6 to 35/4** in an attempt to develop a suitable dose strength while achieving comparable exposures for both BDP and formoterol in asthmatic children.

The second clinical trial under evaluation in this assessment report (**PAED4-DPI/R, CCD-01535BB1-01, EudraCT n°2015-005152-10**) was therefore a repetition of the initial study and performed with CHF1535 **35/4** DPI.

A short critical expert overview has also been provided by the MAH.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Kantos NEXThaler 100/6 and that, consequently, no regulatory action is required.

The amendments to the sections of the product information initially proposed by the MAH can be seen from the below table (deleted text is ~~strikethrough~~, added text is in **bold** and in *italics*):

SmPC section	Proposed text
4.2	***Dose recommendations for children and adolescents under 18 years:*** *The safety and efficacy of {Trade name} in children and adolescents under 18 years of age have not yet been established.* ~~*No data are available in children up to 11 years old.*~~ ***There are limited data available on the use of {Trade name} in children aged 6-11 years (see Sections 4.8 and 5.1). The available pharmacokinetic data do not support safety in this age group, therefore such use is not recommended.*** *Currently available data in adolescents aged 12 – 17 years are summarised in sections 4.8 and 5.1, but no recommendation on a posology can be made.*
4.8	***Paediatric population*** ***The safety of {Trade name} in children aged 6-11 years has not been established and therefore such use is not recommended (see Section 5.1).*** *There is* ~~*no information on the safety of {Trade name} in children up to 11 years of age, and only*~~ *limited information in adolescents 12–17 years of age. In a 12 weeks randomised clinical trial in adults and adolescents, 162 adolescents aged 12–17 years with moderate to severe asthma received {Trade name} or the corresponding pressurised inhalation solution formulation, 1 or 2 inhalations bid; the frequency, type and severity of adverse drug reactions were not different in adolescents compared to adults.*
5.1	***Paediatric population*** *The European Medicines Agency has deferred the obligation to submit the results of studies in asthma with {Trade name} in the 5-11 and 12-17 years subsets of the paediatric population.* ~~*At time of writing, there is no clinical experience on {Trade name} in children 5-11 years of age, old.*~~ ***There are limited data available on the use of {Trade name} in children aged 6-11 years*** *and only limited information in adolescents 12–17 years of age.* *In a 3 months randomised clinical trial 162 adolescents aged 12–17 years with a diagnosis of moderate to severe asthma received either {Trade name} or the corresponding pressurised inhalation solution formulation, 1 or 2 inhalations bid. The change in pre-dose FEV1 at the end of treatment was greater in the adolescents than in adults.* *See also sections 4.2 and 4.8 for information on paediatric use.*

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

As mentioned in the introduction this paediatric work sharing procedure according to article 46 include two pharmaceutical dry powder formulations specifically developed for use in children aged ≥5 to <12 years:

- a dry powder inhalation (DPI) formulation containing 50 µg extrafine beclometasone dipropionate (BDP) and 6 µg formoterol fumarate dihydrate (FF) (CHF1535 **50/6** DPI);
- a DPI formulation containing 35 µg extrafine beclometasone dipropionate (BDP) and 4 µg formoterol fumarate dihydrate (FF) (CHF1535 **35/4** DPI).

Neither of these two formulations is currently approved.

IV.2 Clinical aspects

Overall, the MAH submitted final reports for the following two (2) studies including paediatric asthma patients aged ≥5 to <12 years.

- **PAEDIATRIC STUDY 4 (PAED 4-DPI)**

  Study title. *A single-dose, open-label, randomised, 2-way cross-over, clinical pharmacology study of CHF1535 50/6 NEXT DPI® (fixed combination of beclomethasone dipropionate 50µg plus formoterol fumarate 6µg) versus the free combination of licensed beclomethasone DPI and formoterol DPI in asthmatic children.*

  Sponsor protocol / EudraCT number: CCD-1103-PR-0058 / 2011-001208-36

  Patient population: N=27 children of both gender on regular treatment with ICS or SABA as reliever to control asthma status, aged ≥5 to <12 years, among them N=6 aged 5-8 years (in total N=26 evaluable)

  Treatments

  - TEST: CHF1535 50/6 DPI (four inhalations, total dose: BDP/FF 200/24 µg);
  - REFERENCE: extemporaneous combination of non-extrafine BDP100 (Clenil®) and FF 6 (Oxis®) DPI (total dose: BDP 200mcg + FF 24mcg), two / four inhalations of BDP / FF, respectively)

  Parameters

  - Pharmacokinetics (primarily AUC0-t and Cmax of B17MP, BDP and FF in plasma);
  - Pharmacodynamics (plasma potassium);
  - Safety (8h urinary excretion of cortisol [normalized for creatinine excretion, Ae/Ae_{crea}], glucose concentration in urine, time-averaged heart rate [AUC0-8h/8h]), AEs)

Summary results

In comparison with the reference formulation, CHF1535 50/6 resulted in appreciably greater systemic exposure (AUC0-t) and peak concentration (Cmax) of all three analytes (B17MP, BDP, formoterol) (Figure 1, Table 1).

The supra-bioavailability associated with CHF1535 50/6 was reflected in the pharmacodynamic and safety parameters.

The ratio of least-square means for the AUC0-t of potassium was significantly lower in the test compared with the reference group (point estimator **0.94**, 95%CI [0.92; 0.96]). In the 8-hour post-dose period, more patients in the test group had more potassium values <3.5 meq/L as compared to the reference group (TEST: N=66/85 [77.6%] of potassium values below this threshold in N=21 patients; REFERENCE: N=19/85 [22.4%] in N=12 patients).

For the cortisol/creatinine ratio (Ae/Ae_{crea}), there was a trend towards cortisol suppression in the test group (point estimator **0.85**, 95%CI [0.68; 1.08]) as compared with reference.

The number / percentage of patients with urinary glucose values above the ULN (>30 mg/dL) was higher in the test group (N=25 / 40%) than in the reference group (N=3 / 12%). However, it needs to be taken into consideration that no alimentary restrictions were imposed to the participating children during the 8-hour post-dose period.

The mean increase in heart rate (AUC0-8h/8h) was also significantly greater in group test compared with reference (point estimator **1.06**, 95%CI [1.01; 1.10]; range: +19.5bpm to +24.3bpm versus +11.5bpm to 16.6bpm).

On the positive side, no AE attributable to the administered IMPs were reported.

Figure 1: Mean (±SEM) plasma concentration of B17MP (left) and formoterol (right) versus time (linear scale, PK/PD set)

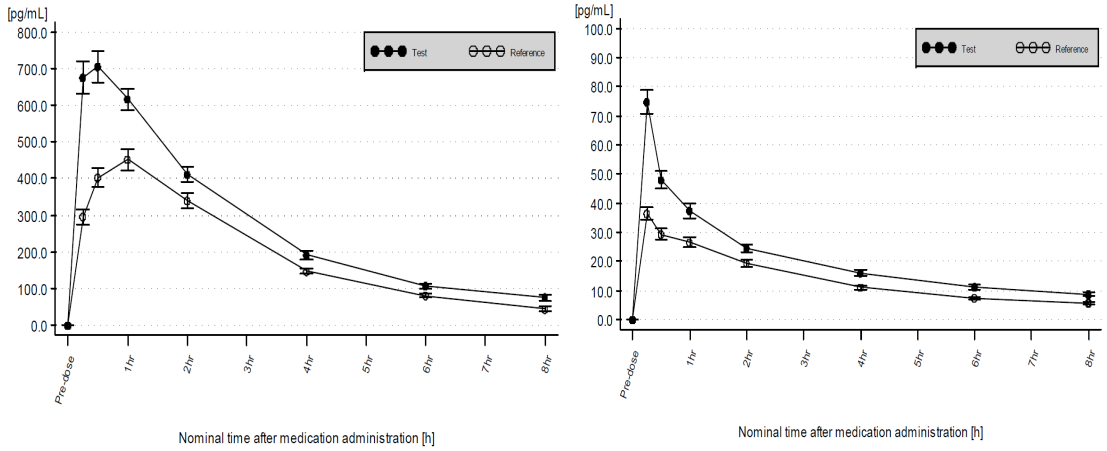


Table 1: Statistical comparison of PK parameters between TEST and REFERENCE (above: B17MP; below: formoterol)

B17MP

Variable	Test[1]	Reference[1]	Ratio (Test / Reference)[1]	90% CI for ratio of means	Within-subject CV%
AUC_{0-t} (h*pg/mL)	2104.2	1448.2	1.4530	(1.31 - 1.62)	22.3
AUC_{0-inf} (h*pg/mL)	2416.0	1706.1	1.4161	(1.29 - 1.55)	19.2
C_{max} (ng/mL)	705.1	451.9	1.5605	(1.40 - 1.74)	22.8
$t_{1/2}$ (h)	2.5	2.4	1.0587	(0.98 - 1.15)	16.7

Formoterol

Variable	Test[1]	Reference[1]	Ratio (Test / Reference)[1]	90% CI for the ratio of means	Within-subject CV%
AUC_{0-t} (h*pg/mL)	156.5	106.8	1.4662	(1.31 - 1.64)	23.8
AUC_{0-inf} (h*pg/mL)	200.1	133.8	1.4958	(1.33 - 1.68)	24.5
C_{max} (ng/mL)	72.1	37.7	1.9112	(1.68 - 2.17)	27.4
$t_{1/2}$ (h)	3.5	3.3	1.0768	(0.99 - 1.18)	18.6

- **PAEDIATRIC STUDY 4 repeat (PAED 4-DPI/R)**

Study title: *A single-dose, open-label, randomized, 2-way cross-over, clinical pharmacology study of **CHF 1535 35/4** NEXThaler® (DPI fixed combination of beclometasone dipropionate (BDP) 35 µg plus formoterol fumarate (FF) 4 µg versus the free combination of licensed BDP DPI and FF DPI in asthmatic children.*

Sponsor protocol / EudraCT number: CCD-01535BB1-01 / 2015-005152-10

Patient population: N=26 children of both gender on regular treatment with ICS or SABA as reliever to control asthma status, aged ≥5 to <12 years, among them N=12 patients aged 5 to 8 years and N=14 patients aged 9 to 11 years (in total N=26 evaluable)

Treatments

- TEST: CHF1535 35/4 DPI (four inhalations, total dose: BDP/FF 140/16 µg);
- REFERENCE: extemporaneous combination of non-extrafine BDP100 (Clenil®) and FF 6 (Oxis®) DPI (total dose: BDP 200mcg + FF 24mcg), two / four inhalations of BDP / FF, respectively)

Parameters (including, but not limited to)

- Pharmacokinetics: B17MP (AUC0-t) as primary variable; B17MP (AUC0-inf, Cmax, tmax, t1/2); BDP and formoterol (AUC0-t, AUC0-inf, Cmax, tmax, t1/2) as secondary variables;
- Pharmacodynamic variables (peak expiratory flow, plasma potassium)
- Saferty (urinary excretion of cortisol, creatinine excretion; concentrations of glucose, cortisol and creatinine in urine; vital signs including pulse rate; adverse events).

Statistical Methods

Inferential analysis for log transformed PK parameters (AUC0-t, AUC0-inf, Cmax, t1/2) were performed by a fixed effects ANOVA model with fixed terms for sequence, patient-within-sequence, period and treatment. Treatment population geometric means were estimated from the exponential of the Least Squared (LS) Means. Ratios of estimated treatment population geometric means and their associated 90% confidence intervals were calculated from the exponential of the LS Means difference and the corresponding 90% Confidence Interval (CI).

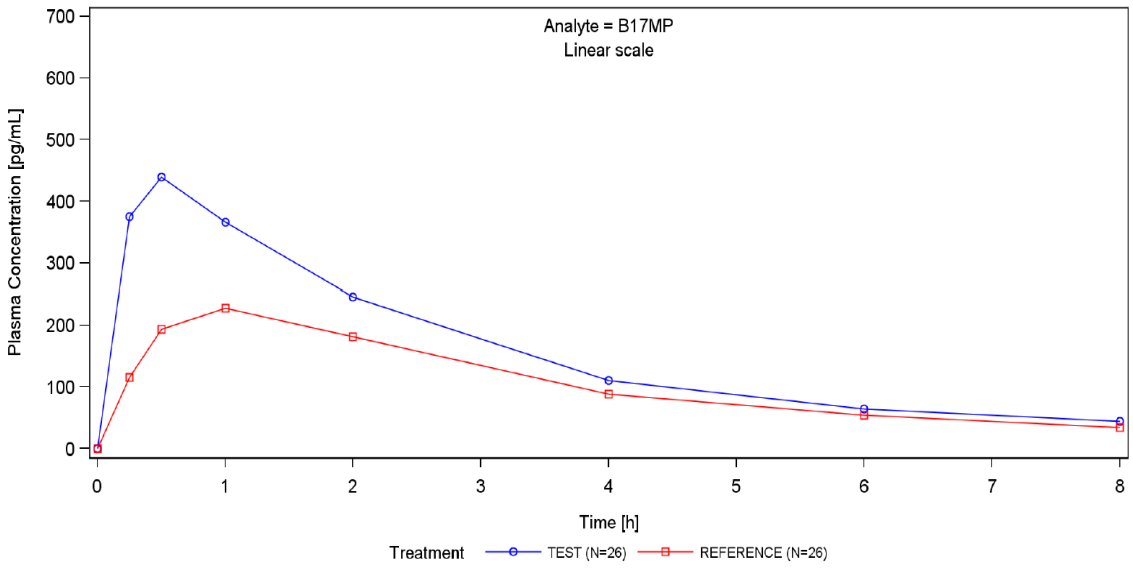
The pharmacokinetic and pharmacodynamic calculations were performed using Phoenix WinNonlin 6.4 (Pharsight Corporation, Palo Alto, CA, USA).

Summary results

Pharmacokinetic results demonstrated that the administration of CHF1535 35/4 (**total dose: 140 µg extrafine BDP and 16 µg formoterol**) resulted in higher total systemic exposure (AUC0-t) for both active metabolite B17MP (point estimator 152.5, 90%CI [141.1-164.8]) and parent compound BDP (point estimator 188.6, 90%CI [163.8-217.1]) as compared with the free combination (**total dose: 200 µg non-extrafine BDP and 16 µg formoterol).**

Analysis by age subgroup showed that the total systemic exposure to B17MP from CHF1535 in the age group 5-8 years was almost two third higher compared with the reference treatment (point estimator 158.6, 90%CI [139.2-180.7]), while it was somewhat lower in the age group 9-11 years (point estimator 146.4, 90%CI [132.0-162.3]) (Figure 2).

Figure 2: Mean plasma concentration of B17MP versus time (linear scale, PK population)



Total systemic exposure to the parent compound BDP was almost twice that observed with the reference treatment with no relevant differences based on the age subgroup. Peak concentrations (Cmax) of both B17MP and BDP were also markedly increased.

Test and reference product resulted in comparable total systemic exposure to the LABA component (point estimator for formoterol 91.5, 90%CI [84.0-99.7]). However, following

administration of the test product, the upper 90%CI for peak exposure (Cmax) slightly exceeded the bioequivalence range of 80-125% (point estimator 114.6, 90%CI [99.8-131.5]).

Reportedly, plasma AUC0-t and Cmin values were comparable for the both treatments (TEST and REFERENCE). A number of '*aberrant*' hyperkalaemic blood results were (repeatedly) observed in five (5) out of 26 subjects enrolled (19.2%). Therefore, the respective AUC0-t results were neither included in the calculation of descriptive statistics nor the inferential statistical calculations. In view of the relatively frequent recurrence of '*aberrant*' hyperkalaemic results, uncertainties remained whether the analyses presented by the applicant for the minimum potassium levels following test or reference treatment were reliable.

Reportedly, no between-treatment differences were observed for systemic effects such as

- glucose concentration in urine from 0-8h post-dose (qualitative assessment; no pre-dose results available for any of the subjects);
- cortisol and creatinine concentration in urine;
- excretion of cortisol and creatinine in urine from 0-8h post-dose;
- 8h urinary excretion of cortisol, normalized for 8h creatinine excretion;
- vital signs (PR via pulse oximetry, SBP, DBP, AUC0-8h for PR).

A total of 2 (7.7%) patients reported a total of 3 TEAEs. None of them was severe, led to treatment discontinuation or was serious.

Glucosuria was reported twice in one patient of the lower age subgroup (5-8 years of age), once during treatment with CHF1535, and a second time while receiving the free combination reference treatment. Both AEs were considered by the investigator to be treatment-related.

Discussion on clinical aspects. Although results of both clinical trials (PAED4 and PAED4-DPI/R) have been obtained with an investigational (not approved) medicinal product and lower dose strength (CHF1535 50/6 or CHF1535 35/4), inclusion of these data in the SmPC of Foster® NEXThaler (CHF1535 100/6) was deemed necessary by the RMS, based on CMDh requests in comparable circumstances.

Both trials resulted in evidence that single, supratherapeutic doses of experimental CHF1535 50/6 or CHF1535 35/4 resulted in higher systemic exposures as compared with equivalent doses of the approved, non-extrafine free combination comparator, thereby failing to demonstrate bioequivalence.

Even with the lower dose strength product (**CHF1535 35/4**, corresponding to a further 30% reduction of both BDP and formoterol in comparison with CHF1535 50/6), total systemic exposure (as based on AUC0-t) and Cmax to B17MP (primary variable) and BDP (secondary variable) were still higher in comparison with inhalation of the chosen reference products. Based on point estimators, exposure to the corticoid component (B17MP and BDP) was higher by a **factor 1.5** and **1.9**, respectively. Total exposure (AUC0-t) to the LABA component (formoterol) was within the bioequivalence range while Cmax was not (upper 90%CI=131.5, thus exceeding the upper limit of the bioequivalence range).

Overall, no significant pharmacodynamic or safety findings were reported in this single-dose study. Observed effects on potassium levels (and their decrease) need to be interpreted with caution as a number of '*aberrant*' hyperkalaemic results point towards methodological issues with blood sampling and/or sample processing.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Based on the data presented with two lower-dose experimental formulations (CHF1535 50/6 and CHF1535 35/4), the RMS was of the opinion that **no suitable and safe posology of Foster (CHF1535 100/6)** in children aged 5 to 11 years can currently be defined. From the submitted evidence and data, it could be deducted that the administration of CHF1535 100/6 in children aged 5-11 years of age carries a risk of (markedly) increased systemic exposure to beclometasone, but also formoterol.

In order to make clear that Foster NEXThaler (CHF1535 100/6) is not suitable for treatment of asthma in this age group, the following mention was proposed by the RMS to be included in section 4.2 of the SmPC:

«*{Trade name} should not be used in children aged 5-11 years because of safety concerns.*»

Alternative products and presentations are available for treatment of asthma in children of this age group.

Commenting member states were in agreement with the above.

In addition, related amendments / changes of sections 4.8, 5.1 and 5.2 of the SmPC were agreed with the MAH to adequately reflect the results of the two paediatric trials PAED4 and PAED4-DPI/R. The detailed amendments / changes proposed for inclusion in the SmPC sections 4.2, 4.8, 5.1 and 5.2 are as follows (inserted / modified text highlighted in **bold** and *italics*):

Section 4.2 – Posology and method of administration - Dose recommendations for children and adolescents under 18 years

> *The safety and efficacy of {Trade name} in children and adolescents under 18 years of age have not been established.* ***{Trade name} should not be used in children aged 5-11 years because of safety concerns. Available data in this age group are summarised in sections 5.1 and 5.2****. Currently available* ***clinical*** *data in adolescents aged 12 – 17 years are summarised in sections 4.8 and 5.1, but no recommendation on a posology can be made.*

Section 4.8 – Undesirable effects – Paediatric population

> ***Available pharmacokinetic data do not support the safety of {Trade name} in children aged 5-11 years.*** *There is limited* ***clinical*** *information in adolescents 12-17 years of age (****see sections 4.2, 5.1 and 5.2****). In a 12 weeks randomised clinical trial in adults and adolescents, 162 adolescents aged 12 – 17 years with moderate to severe asthma received {Trade name} or the corresponding pressurised inhalation solution formulation, 1 or 2 inhalations bid; the frequency, type and severity of adverse drug reactions were not different in adolescents compared to adults.*

Section 5.1 – Pharmacodynamic properties – Paediatric population

> ***There are very limited clinical data available on the use of {Trade name} in children aged 5-11 years. Compared with an equivalent dose of licensed free combination products containing beclometasone dipropionate anhydrous (BDP) and formoterol (FF), administration of a single dose of an experimental fixed dose formulation containing the same extrafine active ingredients as {Trade name}, but using a lower dose strength (50µg BDP and 6µg FF), resulted in markedly higher systemic bioavailability for both components (section 5.2). This higher systemic availability was associated with a statistically significant decrease in plasma potassium (point estimate 0.94, 95%CI [0.92; 0.96]) and increase in time-averaged heart rate (point estimate 1.06, 95%CI [1.01; 1.10]). Moreover, a trend towards cortisol suppression***

and increase in urinary glucose values was observed in children of the test group as compared to the reference treatment.

In adolescents, only limited information was obtained.

In a 3 months randomised clinical trial, 162 ***subjects*** *aged 12-17 years with a diagnosis of moderate to severe asthma received either {Trade name} or the corresponding pressurised inhalation solution formulation, 1 or 2 inhalations bid. The change in pre-dose FEV1 at the end of treatment was greater in the adolescents than in adults.*

See also sections 4.2, 4.8 ***and 5.2*** *for information on paediatric use.*

Section 5.2 – Pharmacokinetic properties – Paediatric population

In single dose pharmacokinetic studies in asthmatic children aged 5-11 years, two experimental paediatric fixed-dose formulations containing the same extrafine active ingredients as {Trade name}, but using lower dose strengths (A: 50µg beclometasone dipropionate [BDP] anhydrous and 6µg formoterol fumarate [FF] = 50/6; B: 35µg BDP and 4µg FF = 35/4), were compared with equivalent doses of licensed free combination products containing BDP and FF. Due to the absence of charcoal block, only systemic exposure as a measure of safety was determined.

Compared with the free combination, BDP/FF 50/6 resulted in greater systemic exposure (AUC0-t) and peak concentrations (Cmax) of all three analytes, parent compound BDP, the active metabolite beclometasone-17-monopropionate (B17MP) and formoterol. Subsequent reduction of the dose strength by about 30% to BDP/FF 35/4 still resulted in markedly higher AUC0-t of B17MP (point estimator 152.5, 90%CI [141.1-164.8]) as well as the parent compound BDP (point estimator 188.6, 90%CI [163.8-217.1]). AUC0-t of formoterol was within and Cmax slightly exceeded the bioequivalence range of 80-125%.

The most recently submitted version of the SmPC (**V9.3, issue date 05/2020**) was approved. No further action from the MAH was required.

The MAH was asked to submit a type IB variation (as usual within 30 days after the end of the procedure) in order to update the SmPC with the inserted / modified text in sections 4.2, 4.8, 5.1 and 5.2.