

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

Montelukast sodium

PL/W/0002/pdWS/002

**Marketing Authorisation Holder:
Merck Sharp & Dohme**

Rapporteur:	Poland
Start of the procedure (day 0):	17.01.2011
Date of this report:	25.03.2011
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR)(day 70):	28.03.2011
Deadline for CMS's comments:	12.04.2011
End of procedure (day 90)	17.04.2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Singulair 10 mg film-coated tablet Singulair 5 mg and 4 mg Chewable Tablets Singulair 4 mg granules Singulair AR 10 mg film-coated tablet Singulair AR 5 mg and 4 mg Chewable Tablets
INN (or common name) of the active substance(s):	Montelukast
MAH:	Merck Sharp & Dohme
Currently approved Indication(s)	The treatment of mild to moderate persistent asthma The prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.
Pharmaco-therapeutic group (ATC Code):	R03D C03
Pharmaceutical form(s) and strength(s):	Singulair 10 mg film-coated tablet Singulair 5 mg and 4 mg Chewable Tablets Singulair 4 mg granules Singulair AR 10 mg film-coated tablet Singulair AR 5 mg and 4 mg Chewable Tablets
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I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed

II. RECOMMENDATION¹

No further action required

III. INTRODUCTION

On January 17th 2011 the MAH submitted reports on 3 completed paediatric studies for montelukast, (PN 301, PN 336, PN911) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the Company does not foresee any regulatory procedures as a result of the submitted paediatric studies.

IV. SCIENTIFIC DISCUSSION

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

PN301

Study drug vials contained 7 mg of lyophilized montelukast or placebo, with sodium carbonate as excipient. Montelukast at dose 5.25-mg or matching placebo was administered intravenously as a bolus using 3.3% dextrose and 0.3% sodium chloride diluent over a total of 2 to 5 minutes.

Montelukast is not approved in any region as an i.v. formulation.

PN336

Montelukast - sodium salt dispensed as a 5-mg oral chewable tablet (approved formulation and strength).

PN911

Montelukast - sodium salt dispensed as a 5-mg oral chewable tablet (approved formulation and strength).

¹ The recommendation from section V can be copied in this section

IV.2 Clinical aspects

1. Introduction

The MAH submitted final reports on three clinical trials on montelukast in paediatric patients:

1. Phase 3 trial – “PN301 – A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous Montelukast with Placebo in Pediatric Patients (Aged 6 to 14 Years) with Acute Asthma”
2. Phase 4 trial – “PN336 – A Multicenter, Double-Blind, Placebo Controlled, Randomized, Parallel-Group Study to Evaluate the Clinical Effect of Oral Montelukast Versus Placebo in Persistent Asthma Which is Also Active During Allergy Seasons in Pediatric Patients With Seasonal Aeroallergen Sensitivity”
3. Phase 4 trial – “PN 911 – A Multicenter, Double-Blind, Randomized, Crossover Design Study to Evaluate the Effect of Montelukast vs. Salmeterol on the Inhibition of Exercise-Induced Bronchoconstriction in Asthmatic Patients Aged 6–14 Years”

2. Clinical studies

Prot. No. PN301 – A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous Montelukast with Placebo in Pediatric Patients (Aged 6 to 14 Years) with Acute Asthma

➤ **Description**

➤ **Methods**

- Objective(s)

The primary objective was to compare the clinical efficacy of i.v. montelukast 5.25 mg, compared with placebo, when administered as adjunctive therapy to pediatric patients with acute asthma.

- Study design

A multinational, randomized, double-blind, placebo-controlled, parallel group study.

- Study population /Sample size

Eligible patients were male or female, ages from 6 to 14 years (inclusive), and presented to the study site for treatment of symptoms consistent with an asthma exacerbation. Patients had a history of asthma-like symptoms on at least one occasion, occurring at least 3 months prior to the current episode. Patients had a baseline FEV1 of $\leq 75\%$ of the predicted value (% predicted). Patients had a baseline modified Pulmonary Index (mPI) score of ≥ 5 (comprising 4 items: respiratory rate, wheezing, inspiratory-expiratory ratio, and accessory muscles use; each item was rated on a scale of 0 [best] to 3 [worst], then added to yield a scale of 0–12) measured twice during 60 min. period before montelukast i.v. administration. A total of 276 patients were randomized, and 267 completed the study. Mean age was approximately 9 years in both treatment groups.

- Treatments

Prestudy period (60 min.): patients received standard therapy for acute asthma i.e. nebulized β -agonist or inhaled equivalent, oxygen therapy, and inhaled or nebulized ipratropium.

Screening period (60 min., Period I): patients received standard therapy as needed (nebulized β -agonist or inhaled equivalent, oxygen therapy, and inhaled or nebulized ipratropium).

Active treatment period (Period II): patients received i.v. montelukast 5.25 mg or placebo; this phase ended when a disposition decision was made (either discharge home, admit to hospital, or discontinue from study). During Period II, patients also received standard therapy as needed (nebulized β -agonist or inhaled equivalent, oxygen therapy, and inhaled or nebulized ipratropium).

Poststudy period: a telephone or in-person interview was conducted 14–18 days after completion of Period II.

- Outcomes/endpoints

The primary end point was time-weighted average change in Forced Expiratory Volume in 1 second (FEV1) from preallocation baseline over the first 60 minutes after study drug administration.

Additional efficacy endpoints included: the change from baseline in mPI score measured 60 minutes after study drug administration; the percentage of treatment failures, onset of action (time weighted average change in FEV1 over 45, 30, and 15 minutes after study drug administration).

- Statistical Methods

Power analysis:

A sample size of 130 patients in each treatment group provided 90% power to detect an effect size (treatment difference/SD) of 0.4 in the average change in FEV1 from baseline over the first 60 minutes using an alpha of 0.05.

Efficacy

The primary efficacy endpoint as well as other FEV1 endpoints were analyzed using an analysis of covariance (ANCOVA) model with a covariate for baseline FEV1 and factors for treatment and region (US, non-US). Change from baseline in mPI score was analyzed using an ANCOVA model using the baseline mPI as covariate. Percentage of treatment failures was compared using a logistic model with factors for treatment and baseline FEV1.

➤ **Results**

- Recruitment/ Number analysed

A total of 276 patients were randomized; 145 patients received montelukast i.v. at dose 5.25 mg and 131 patients received placebo.

- Baseline data

There were no significant differences between montelukast and placebo treatment groups in the primary and secondary efficacy endpoints.

- Efficacy results

Compared with placebo, montelukast, when administered i.v. at dose 5.25 mg as adjunctive therapy did not significantly improve FEV1 within the first 60 minutes following the end of study drug administration, measured as the Δ FEV1(0–60min) (Least Square [LS] means: 0.08 L versus 0.07 L; $p=0.775$). The change from baseline in mPI was not significantly smaller in the montelukast group than in the placebo group (LS means: -2.95 score versus -2.96 score; $p=0.931$). The percentage of patients in whom treatment failed was similar in the montelukast group and in the placebo group (45.1 % of patients versus 46.1 % of patients, odds ratio = 0.99; $p=0.975$). There were no significant differences between montelukast and placebo groups at the 3 time points assessed: Δ FEV1(0–45 min) (LS means: 0.07 L versus 0.05 L; $p=0.612$), Δ FEV1(0–30 min) (0.06 L versus 0.05 L; $p=0.774$), or Δ FEV1(0–15min) (0.06 L versus 0.01 L; $p=0.173$).

- Safety results

Safety and tolerability were assessed by clinical review of all relevant parameters including clinical adverse experiences and clinical safety parameters. The main safety analyses were based on adverse experience data collected after randomization. No blood samples were required in this study; therefore, no laboratory safety analyses (including laboratory adverse experiences) were performed.

The safety profile of i.v. montelukast was generally comparable to that of placebo. There were no clinically meaningful differences among treatment groups in the number of adverse experiences, serious adverse experiences, drug-related adverse experiences or adverse experiences leading to discontinuation.

Of the 276 randomized patients, clinical adverse experiences were reported by 43 (15.5%) patients; 22 (15.2%) patients were on montelukast treatment and 21 (16.0%) on placebo treatment.

Prot. No. PN336 – A Multicenter, Double-Blind, Placebo Controlled, Randomized, Parallel-Group Study to Evaluate the Clinical Effect of Oral Montelukast Versus Placebo in Persistent Asthma Which is Also Active During Allergy Seasons in Pediatric Patients With Seasonal Aeroallergen Sensitivity”

➤ **Description**

➤ **Methods**

- Objective(s)

The primary objective was to compare the clinical efficacy of montelukast 5 mg chewable tablets versus placebo in paediatric asthmatic patients with seasonal aeroallergen sensitivity.

- Study design

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

- Study population /Sample size

Eligible patients were male or female, ages from 6 to 14 years (inclusive), and had at least a 1-year history of persistent asthma that was also active during allergy season. Patients had baseline FEV1 between 60% and 85% of predicted (inclusive), evidence of reversible airway obstruction ($\geq 12\%$), and skin test sensitivity demonstrated to at least 2 relevant seasonal aeroallergens. Patients on a stable dose of inhaled corticosteroid (ICS) monotherapy were allowed to continue during the study. To be randomized, patients had to have both a weekly sum of daytime symptoms score of at least 11, and a weekly average of day time and night time SABA use of at least one puff/day during the placebo run in period. A total of 421 patients were randomized; 203 patients were randomized to montelukast and 218 patients to placebo. Mean age of patients in both groups were 10,6 and 10,7 years respectively.

- Treatments

The study consisted of a 1-week single-blind placebo run-in period for demonstration of active asthma at baseline, followed by a 3-week double-blind treatment period during which patients received either montelukast or placebo. Patients were permitted to use inhaled short-acting β -agonist (salbutamol) “as-needed” during the study.

- Outcomes/endpoints

The Primary Endpoint was a percent-change from baseline in FEV1. The Secondary Endpoint was a percent-change from baseline in average daily “as-needed” SABA use.

- Statistical Methods

The percent-change from baseline in FEV1 measured at Week 3 was analyzed using an Analysis of Variance (ANOVA) model which included factors for treatment, season and ICS use at entry (yes/no). Due to non-normal distribution of the secondary endpoint, this variable was analyzed using a nonparametric method: an ANOVA model on the Tukey’s normalized ranks. Efficacy analyses used the FAS population, which included all patients who had baseline and at least one on-treatment measurement.

➤ Results

- Recruitment/ Number analysed

A total of 421 patients were randomized; 203 patients were randomized to montelukast and 218 patients to placebo group.

- Baseline data

Baseline characteristics of enrolled patients were consistent with mild to moderate persistent asthma, no significant differences between montelukast and placebo treatment groups were observed. Mean FEV1 values were 77.4 %-predicted and 77.7 %-predicted for montelukast and placebo groups respectively; and the mean daily “as-needed” SABA use (puffs/day) was 3.01 puffs/day and 2.72 puffs/day for montelukast and placebo groups respectively.

- Efficacy results

No significant differences were shown between montelukast and placebo treatment groups in the primary and secondary efficacy endpoints. Montelukast did not significantly improve the percent-change from baseline in FEV1, compared with placebo (9.53 %-change vs. 9.15 %-change; p-value=0.810). Also the percent-change from baseline in average daily “as-needed” SABA use was not significantly decreased in the montelukast group compared with the placebo group (median values: –18.9 %-change versus –12.4 %-change; p-value=0.173). These results were confirmed by a parametric analysis on the change from baseline.

- Safety results

Safety and tolerability were assessed by clinical review of all relevant parameters including clinical and laboratory adverse experiences and clinical safety parameters. The main safety analyses were based on adverse experience data collected after randomization. For safety analyses, the APaT population was used; one patient was randomized but never received treatment and therefore was excluded from safety analyses. The safety profile of montelukast 5-mg Chewable Tablets in this study was generally comparable to that of placebo. There were no clinically meaningful differences between treatment groups in the number of adverse experiences, serious adverse experiences, drug-related adverse experiences or adverse experiences leading to discontinuation. No laboratory adverse experiences were reported. Of the 420 patients in the APaT population, clinical adverse experiences were reported in 40 (9.5%) patients; 17 (8.4%) patients were on montelukast treatment and 23 (10.6%) on placebo treatment.

Prot. No. PN 911 – A Multicenter, Double-Blind, Randomized, Crossover Design Study to Evaluate the Effect of Montelukast vs. Salmeterol on the Inhibition of Exercise-Induced Bronchoconstriction in Asthmatic Patients Aged 6–14 Years.

➤ **Description**

➤ **Methods**

- Objective(s)

The primary objective was to compare the clinical efficacy of montelukast 5 mg chewable tablets versus the effect versus salmeterol, when administered concomitantly with fluticasone, on protection against exercise-induced bronchoconstriction (EIB) in paediatric patients aged 6 to 14 years.

- Study design

A multicenter, randomized, double-blind, double-dummy, active-controlled, 2-period crossover study.

- Study population /Sample size

Eligible patients were male or female, ages from 6 to 14 years (inclusive), and had a clinical history of asthma for at least 12 months. Patients were regular users of inhaled corticosteroids (ICS) (defined as not missing more than 1 of 7 days per week of ICS in the 8

weeks before Visit 1). To be randomized, patients fulfilled the following at both Visit 1 and Visit 2:

(1) stable lung function prior to exercise challenge: FEV1 of $\geq 70\%$ predicted value while withholding SABA for at least six hours; and

(2) documented EIB while on ICS: defined as a $\geq 15\%$ decline from pre-exercise FEV1. (A protocol amendment decreased the required decline from $\geq 20\%$ to $\geq 15\%$). A total of 154 patients were randomized, 78 of them received montelukast/salmeterol and 76 received salmeterol/montelukast. Mean age of patients in both groups were 10,2 and 9,8 years respectively.

- Treatments

All patients received oral montelukast (5-mg chewable tablet) or inhaled salmeterol (50-mcg inhalation suspension twice daily); matching-placebo double-dummy controls were used to maintain blinding. All patients received concurrent open-label inhaled fluticasone (100-mcg inhalation suspension twice daily) throughout the study. Patients were allowed to use SABA “as-needed” throughout the study; however, SABA was withheld ≥ 6 hours prior to an exercise challenge. EIB was measured as the responses to an exercise challenge (a 6-minute run on a treadmill) performed at Visits 1 (before run-in), 2 (after 2 weeks of run-in), 4 and 6 (at end of each 4 weeks double-blind treatment period).

- Outcomes/endpoints

The Primary Endpoint was a maximum percent-fall (relative to pre-exercise baseline) in FEV1, as measured over the 20 minutes post-exercise and before the SABA rescue (given at 20 minutes postexercise). The Secondary Endpoints were:

- (1) Area Under the Curve for percent-change in FEV1 during the 0–20 minutes postexercise (AUC0-20min),
- (2) Time to recovery to within 5% of the pre-exercise level of FEV1,
- (3) Maximum FEV1 %-predicted post-SABA rescue,
- (4) Average percent-change (relative to pre-exercise) in FEV1 post-SABA rescue. a percent-change from baseline in FEV1..

- Statistical Methods

The maximum percent-fall in FEV1 (primary endpoint) was analyzed using an ANOVA model with factors for patient, treatment, and period effect. The primary hypothesis was assessed using the p-value for the adequate contrast from within the ANOVA model comparing montelukast versus salmeterol. Estimates of the treatment effects with 95% CIs were obtained from the ANOVA model. The estimated LS mean was provided for each treatment group, together with the 95% CI. The secondary endpoints were analyzed using a similar ANOVA model as for the primary endpoint. The maximum FEV1 %-predicted post-SABA was analyzed by an ANCOVA model with factors for patient, treatment, and period; and using a covariate of FEV1 %-predicted at pre-exercise baseline. Average percent-change in FEV1 post-SABA was analyzed using a similar ANCOVA model. Time to recovery was analyzed using a marginal models approach; the treatment effect was estimated using a Cox proportional hazard model with factors for treatment and period. Efficacy analyses used the FAS population, which included all patients who took at least one dose of post-randomization study drug and had at least one measurement available for analysis in both treatment periods of the crossover design.

➤ Results

- Recruitment/ Number analysed

A total of 154 patients were randomized; 78 of them received montelukast/salmeterol and 76 received salmeterol/montelukast.

- Baseline data

The mean (SD) maximum %-fall in FEV1 after exercise for the two pre-randomization challenges was 25.09 (9.65) %-fall.

- Efficacy results

Significant improvements in protection against EIB were shown for montelukast, compared with salmeterol, in the primary efficacy endpoint and in each of the secondary efficacy endpoints. Compared with salmeterol, montelukast significantly reduced the maximum percent-fall in FEV1 after exercise and before SABA use (LS means: 10.57 %-fall versus 13.82 %-fall; $p=0.009$). Analysis of secondary endpoint have shown that the AUC0-20min was significantly smaller for montelukast than for salmeterol (LS means: 116.04 %•min versus 168.75 %•min; $p=0.006$), time to recovery was significantly shorter for montelukast than for salmeterol (median values: 5.9 min versus 11.1 min; $p=0.035$), maximum FEV1 %-predicted post-SABA rescue was significantly greater for montelukast than for salmeterol (LS means: 104.03 %-predicted versus 99.92 %-predicted; $p<0.001$) and average percent-change in FEV1 post-SABA rescue was significantly greater for montelukast than for salmeterol (LS means: 6.51 %-change versus 2.72 %-change; $p<0.001$).

- Safety results

Safety and tolerability were assessed by clinical review of all relevant parameters including clinical and laboratory adverse experiences and clinical safety parameters. The main safety analyses were based on adverse experience data collected after randomization. For safety analyses, the APaT population was used. Among the 154 randomized patients in this crossover study, 150 patients received montelukast treatment and 150 patients received salmeterol treatment. In the APaT population in this crossover study clinical adverse experiences were reported by 28 (18.7%) patients on montelukast and 22 (14.7%) on salmeterol. There were no drug-related adverse experiences, no discontinuations due to adverse experiences and only one serious adverse experience on each treatment (both serious adverse experiences were overdoses). No laboratory adverse experiences were reported after randomization.

3. Discussion on clinical aspects

The MAH stated that the study PN 301 was part of the clinical development program for an intravenous formulation of montelukast which was stopped by the MAH based on the clinical study results of this investigational formulation . The obtained results fully support this decision. Montelukast i.v. at dose 5.25 mg, given as a single-dose of adjunctive therapy to standard therapy for acute asthma in patients aged 6 to 14 years with acute asthma, does not significantly improve any investigated marker of asthma severity. This clearly indicates that there are no benefits of adjuvant intravenous montelukast therapy to paediatric patients with acute asthma.

Montelukast i.v. 5.25 mg, given as a single-dose of adjunctive therapy has a safety and tolerability profile comparable with that of placebo.

Results of the study PN336 have shown that montelukast 5 mg, given orally once daily for 3 weeks, was generally well-tolerated in this placebo-controlled study in children aged 6 to 14 years with allergic asthma, and has a safety and tolerability profile comparable with that of placebo. However no significant differences were shown between montelukast and placebo treatment groups in the primary and secondary efficacy endpoints.

Results of the study PN911 have shown that montelukast 5 mg, given orally once daily for 4 weeks to patients aged 6 to 14 years with persistent asthma and documented EIB, provides greater protection against EIB than inhaled salmeterol 50-mcg twice-daily, as measured by maximum percent-fall in FEV1 (relative to pre-exercise baseline and before SABA use). Montelukast, compared with salmeterol, is more effective in reducing the extent and duration of EIB, as measured by the AUC0-20min and time to recovery.

Montelukast, compared with salmeterol, is also more effective in maximizing the beneficial effect of SABA that is given as a rescue therapy post-exercise. Montelukast 5 mg, given orally once daily for 4 weeks, was generally well-tolerated in this active-controlled study in children aged 6 to 14 years with EIB, and has a favorable safety profile.

In conclusion results of PN 301, PN336 and PN911 studies do not alter our knowledge about the risk/benefit profile of montelukast for acute asthma, for treatment of mild to moderate persistent asthma and for prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The results of the submitted paediatric studies (PN 301, PN 336, PN 911) do not alter the risk/benefit profile of montelukast. No SmPC and PL changes are required.

➤ Recommendation

No further action required

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable